DEDICATED TO PROFESSOR D. SEEBACH ON HIS 65TH BIRTHDAY

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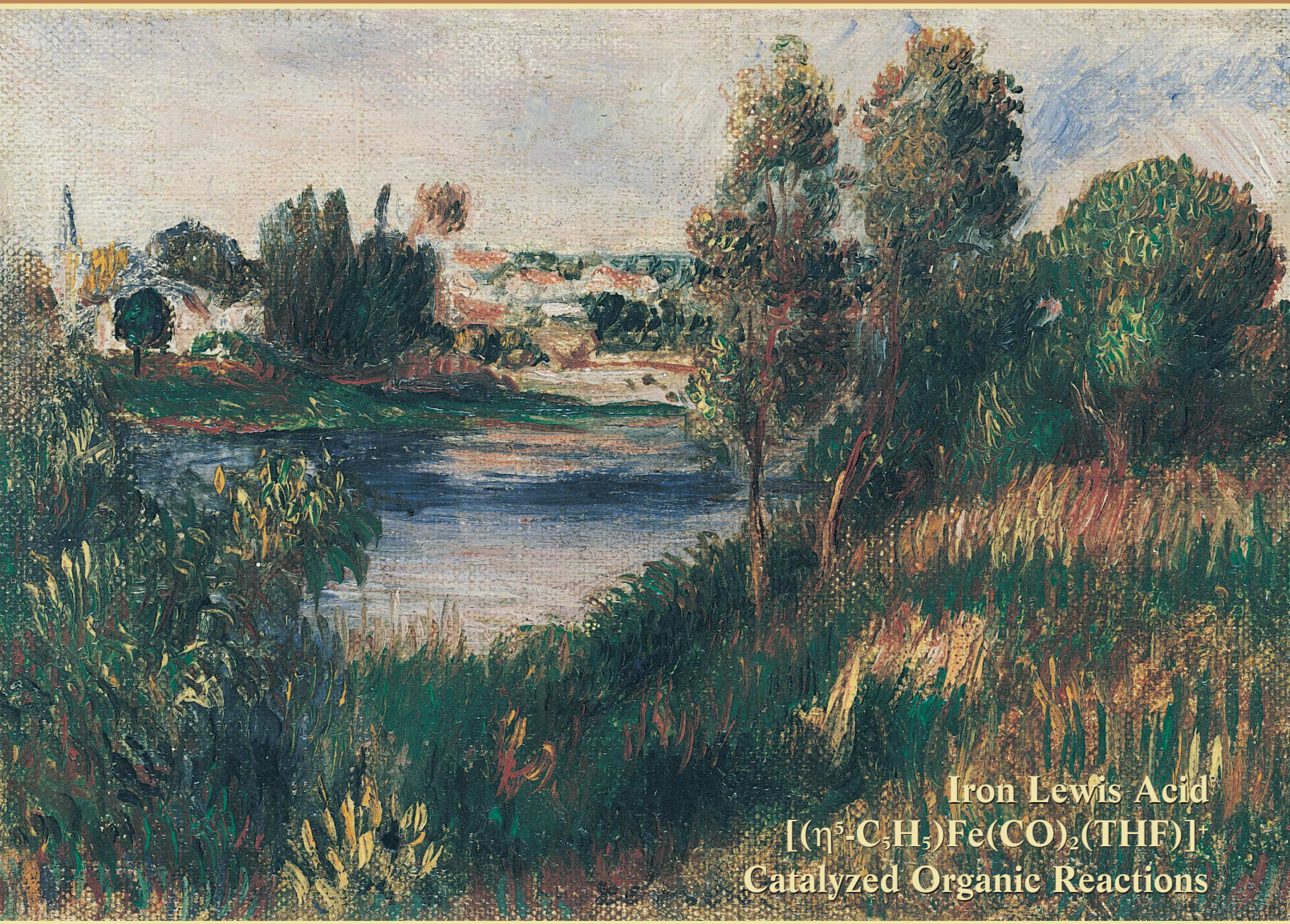
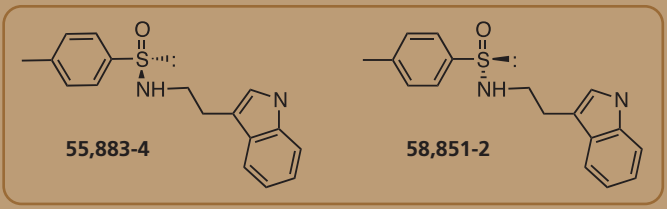


Iron Lewis Acid $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]^+$ Catalyzed Organic Reactions

Applications of Dialkylaminopyridine (DMAP) Catalysts in Organic Synthesis

new products



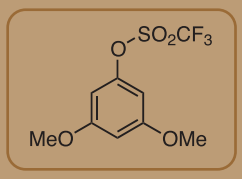
55,883-4 (*R*)-(+)-*N*-*p*-Tolylsulfinyltryptamine, 97%

58,851-2 (*S*)-(–)-*N*-*p*-Tolylsulfinyltryptamine, 97%

These chiral tryptamine-derived sulfinamines can be condensed with aldehydes to form *N*-sulfinyliminium ions with high diastereomeric ratios. These ions undergo Picket–Spengler cyclization to generate biologically active tetrahydro-β-carbolines.

Gremmen, C. et al. *Org. Lett.* **2000**, 2, 1955.

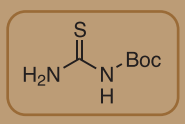
57,926-2 3,5-Dimethoxyphenol trifluoromethanesulfonate, 97%



This triflate-activated dimethoxyphenol readily undergoes Suzuki cross-couplings under mild conditions. It has been utilized in the synthesis of naturally occurring 5-alkylresorcinols[1] and Δ^8-tetrahydrocannabinol analogs.[2]

(1) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (2) Crocker, P. J. et al. *Tetrahedron* **1999**, *55*, 13907.

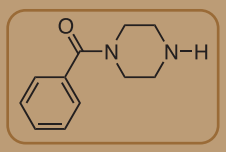
59,276-5 *N*-Boc-thiourea



This monoprotected thiourea has been used in the synthesis of 2-aminothiazole intermediates for the study of marine metabolites.

Schiavi, B. et al. *Synth. Commun.* **2002**, *32*, 1671.

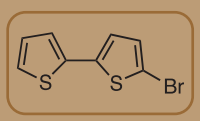
57,108-3 1-Benzoylpiperazine, 97%



Employed in the synthesis of various biologically active compounds such as nitric oxide donors,[1] pyruvate dehydrogenase kinase inhibitors,[2] and serine protease factor Xa inhibitors.[3]

(1) Mu, L. et al. *Chem. Pharm. Bull.* **2000**, *48*, 808. (2) Aicher, T. D. et al. *J. Med. Chem.* **2000**, *43*, 236. (3) Jones, S. D. et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 733.

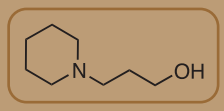
52,285-6 5-Bromo-2,2′-bithiophene, 96%



Building block for the synthesis of soluble thiophene oligomers possessing electronic and electro-optical properties.

Sotgiu, G. et al. *Tetrahedron* **2002**, *58*, 2245.

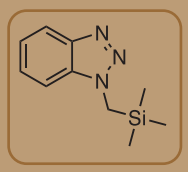
15,293-5, 1-Piperidinepropanol, 97%



Employed in the preparation of new nonimidazole histamine H_3 receptor ligands designed to increase histaminergic neurotransmission.

Apelt, J. et al. *J. Med. Chem.* **2002**, *45*, 1128.

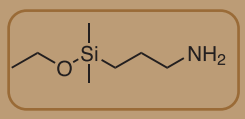
58,928-4 1-[(Trimethylsilyl)methyl]benzotriazole, 99%



Reagent for the one-carbon homologation of acyl chlorides to the corresponding acids or esters.

Katritzky, A. R. et al. *J. Org. Chem.* **2001**, *66*, 5606. Katritzky, A. R. et al. *ibid.* **2002**, *67*, 7526.

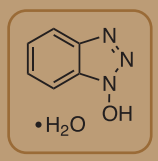
58,885-7 3-(Ethoxydimethylsilyl)propylamine, 97%



Was utilized to develop surface tension arrays for the synthesis of oligonucleotide arrays on glass surfaces.

Butler, J. H. et al. *J. Am. Chem. Soc.* **2001**, *123*, 8887.

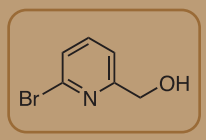
57,896-7 1-Hydroxybenzotriazole hydrate, 15 wt. % solution in dimethylfomamide



A key reagent for peptide[1] and polyamide[2] synthesis.

(1) *Encyclopedia of Reagents for Organic Synthesis;* Paquette, L. A., Ed.; Wiley: West Sussex, U.K., 1995; pp 2752–2755. (2) Xiao, J. et al. *J. Org. Chem.* **2000**, *65*, 5506.

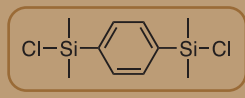
55,414-6 (6-Bromopyridin-2-yl)methanol, 96%



Has been used in the synthesis of oligopyridine-functionalized aza-crown ethers[1] and 4-pyridyl-1,4-dihydropyridines.[2]

(1) Tsukube, H. et al. *J. Org. Chem.* **1993**, *58*, 4389. (2) Ashimori, A. et al. *Chem. Pharm. Bull.* **1990**, *38*, 2446.

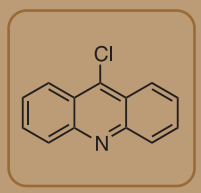
54,944-5 1,4-Phenylenebis(chlorodimethylsilane), 95%



This organosilane was utilized in the synthesis of zirconocene polymers and macrocycles.

Mao, S. S. H. et al. *J. Am. Chem. Soc.* **1998**, *120*, 1193.

15,942-5 9-Chloroacridine



A main building block for many biologically active compounds such as anti-inflammatory,[1] antibacterial,[1] and antimalarial[2] substances.

(1) Yeh-Long, C. et al. *J. Med. Chem.* **2002**, *45*, 4689. (2) Kimura, M.; Okabayashi, I. *J. Heterocycl. Chem.* **1986**, *23*, 965.

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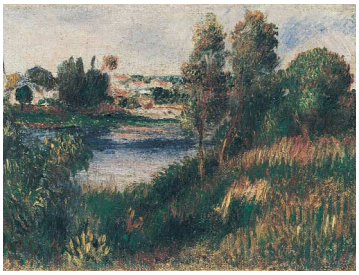
About Our Cover

Landscape at Vétheuil (oil on canvas, 115 x 165 cm) was painted by the French impressionist painter Auguste Renoir around 1890. Vétheuil, on the river Seine northwest of Paris, was chosen by Renoir's fellow impressionist Claude Monet as a location sufficiently distant from Paris to avoid urban distractions and allow concentration on painting. The landscape around Vétheuil, like that near Argenteuil and other popular boating and picnicking spots along the Seine, was an important source of inspiration for a number of these artists.



Photograph © Board of Trustees, National Gallery of Art, Washington.

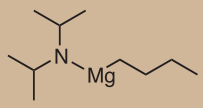
The impressionists were not actually a homogeneous group united by clearly defined principles. Some can be called impressionists only at certain times during their careers, and among the group there is considerable ideological and stylistic variety. Generally speaking, however, they were unhappy with academic training, rejected the notion central to romanticism that a work of art should convey emotional content, and were uninterested in the message of social realism. They felt that the proper purpose of a work of art is not to be a vehicle for the artist's imagination or to represent historical or literary subjects, but to record dispassionately the actuality of nature and contemporary life.

Renoir's *Landscape at Vétheuil* is characteristic of impressionist paintings in the artist's rejection of a balanced and contrived composition in favor of what might be called a snapshot view, and in his use of a loose technique of small strokes of paint to convey the immediacy of visual experience. The irony is that this quasiscientific approach is often misinterpreted by modern viewers, who see in impressionism a romantic and idealized vision of the world, rather than the direct record of experience it was meant to be.

This painting is in the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.

"Please Bother Us."

Joe Porwoll, President



Professor Philip Eaton of the Department of Chemistry at The University of Chicago kindly suggested that we market a solution of butylmagnesium diisopropylamide. This thermally stable reagent deprotonates cyclopropane carboxamides and weak CH acids stoichiometrically and regioselectively.

Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169.

59,045-2
Butylmagnesium diisopropylamide,
1.0*M* solution in tetrahydrofuran

Naturally, we made this valuable reagent. It was no bother at all, just a pleasure to be able to help.

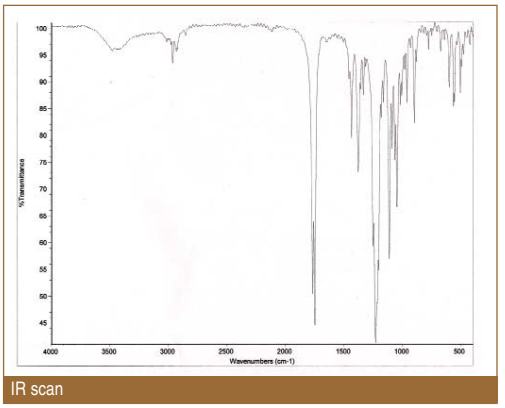
Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

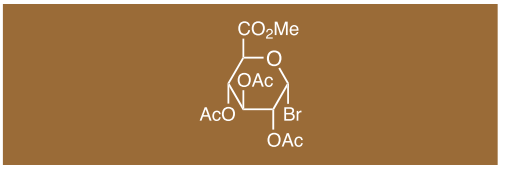
Lab Notes

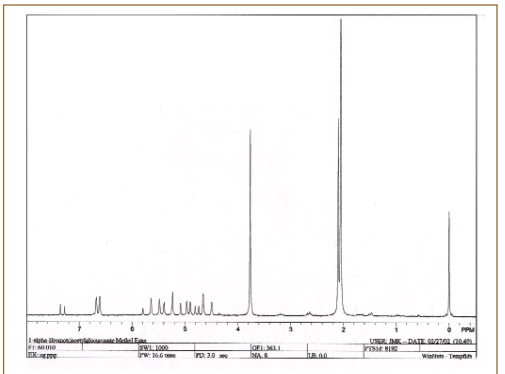
Purification of 1α-Bromotriacetylglucuronate Methyl Ester

Glycoside linkages are most commonly synthesized by the Koenigs–Knorr reaction,[1] through coupling of an acetylated 1-bromosugar with an alcohol or phenol group in the presence of a salt such as silver carbonate. The key to the success of this reaction is the purity of the bromosugar, which is prepared by reacting the fully acetylated and esterified sugar with an acetic acid solution of hydrobromic acid. The original method for preparing 1α-bromotriacetylglucuronate methyl ester recommended recrystallizing the product from absolute alcohol.[2] Over the years, observations in our labs have led us to the realization that residual alcohol in the purified bromosugar generates hydrobromic acid and causes the rapid degradation of the crystals.[3] In fact, after just a few hours at room temperature, the material rapidly turns brown. After 1–3 days, the material is definitely degraded, turning an oily black, and must be recrystallized before it can be used. This degradation is so rapid that the material is not widely available commercially.[4] Even when stored under anhydrous conditions in the freezer, the material has a relatively short life span.



IR scan





NMR scan

Difficulties with maintaining large quantities of the pure bromosugar have led us to search for a better recrystallization solvent. The requisite solvent(s) must be anhydrous and not contain reactive groups such as hydroxyls. We found that benzene–hexane or, preferably, toluene–hexane meets these requirements. The crude bromosugar is dissolved in warm (not boiling) toluene and briefly treated with decolorizing charcoal. The solution is filtered while warm through a sintered glass funnel (do not use filter paper) containing a Celite® pad, and hexane is added with stirring to the colorless filtrate until it begins to turn cloudy. The white crystals, which form after refrigeration overnight, are collected on a sintered glass funnel and thoroughly dried under high vacuum at room temperature. Material prepared in this fashion may be stored under anhydrous conditions in the freezer for an indefinite period, and is even stable at room temperature under anhydrous conditions or under vacuum for several days.

Purity can be readily determined visually (white to off-white) or by odor, since HBr can be easily detected in the decomposed material. The melting point must be carefully determined. When rapidly heated, the material melts at 82–83 °C, but, if allowed to cool and resolidify and is then heated slowly, the sample melts with decomposition at 102–104 °C. A slowly heated sample also melts with decomposition at 102–104 °C. Infrared and NMR analyses are also useful for purity determination. The IR (KBr) spectrum has two sharp carbonyl absorptions at 1767 and 1748 cm^{-1} and a set of C–O absorptions centered at 1229 cm^{-1}. The ^1H NMR ($CDCl_3$, 60 MHz) spectrum consists of overlapping acetate methyls centered at 2.05 ppm (9 H), the ester methoxy at 3.77 ppm (3 H), the C-2, C-3, C-4, and C-5 ring hydrogens between 4.5 and 5.8 ppm (4 H), and the C-1 hydrogen centered at 6.65 ppm (1 H, doublet).[5]

References and Notes: (1) Conrow, R. B.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 863. (2) Bollenback, G. N.; Long, J. W.; Benjamin, D. G.; Lindquist, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 3310. (3) Hadd, H. E.; Slikker, W., Jr.; Helton, E. D. *J. Steroid Biochem.* **1980**, *13*, 1107. (4) 1α-Bromotriacetylglucuronate methyl ester (CAS Registry Number℠ 21085-72-3) is currently available from a very small number of companies, including the Sigma (cat. no. A8292) and Fluka (cat. no. 00533F) brands of Sigma-Aldrich Corp., and is shipped in dry ice. (5) The resonances at 7.27 and 7.37 ppm arise from a trace of $CHCl_3$ (from $CDCl_3$) and benzene (recrystallization solvent), respectively. While it is difficult to pump off all of the aromatic solvent, it should not affect further use of the material in the Koenigs–Knorr reaction, since this reaction is most often carried out in benzene or toluene.

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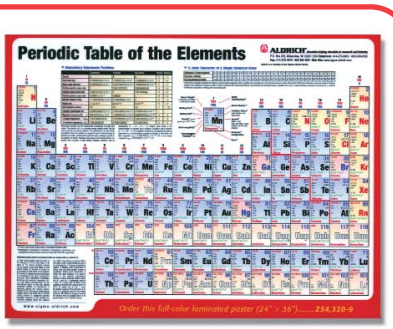

Iron Lewis Acid $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]^+$ Catalyzed Organic Reactions

*Mark D. Redlich[†], Michael F. Mayer[‡], and M. Mahmun Hossain**
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1. Introduction

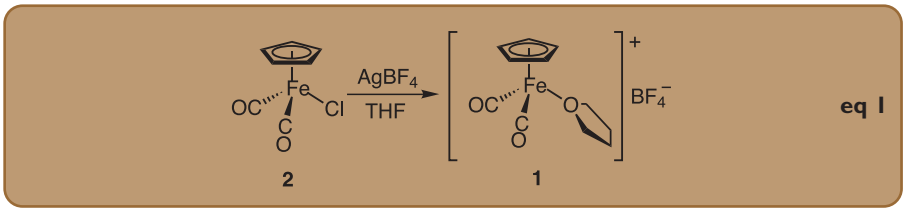
Iron is abundant, inexpensive, and relatively nontoxic in comparison to other transition metals, thus making it an ideal choice for the study of transition-metal-based organometallic compounds. Since the synthesis and discovery of ferrocene in 1951,[1] iron complexes have been central to the discipline of organometallic chemistry. Thus, it is surprising, considering its role in the ascent of modern organometallic chemistry, that iron is relatively under-represented in catalysis, despite its advantages over other transition metals. Ferrocene and related "piano stool" complexes have been studied extensively because of their unique properties, stability, and ease of characterization. A related fragment, $[(\eta^5\text{-}C_5H_5)(CO)_2Fe]$, has been incorporated into so many compounds that it is now commonly represented as Fp.[2]

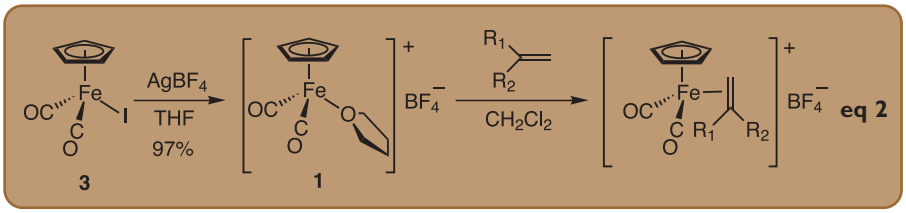
The Fp cation, $[(\eta^5\text{-}C_5H_5)(CO)_2Fe]^+$, a 16-electron complex, is a relatively mild Lewis acid.[3] It was first mentioned in the literature in 1955,[4] and has since been widely studied by various research groups. Many of the early publications came from Rosenblum's group,[5] whose pioneering efforts used Fp^+ as a stoichiometric auxiliary in a variety of transformations to obtain unique organoiron products. However, it wasn't until 1982 that the preparation of a *singular* Fp complex for the purpose of catalysis was reported by Rosenblum and Scheck.[6]

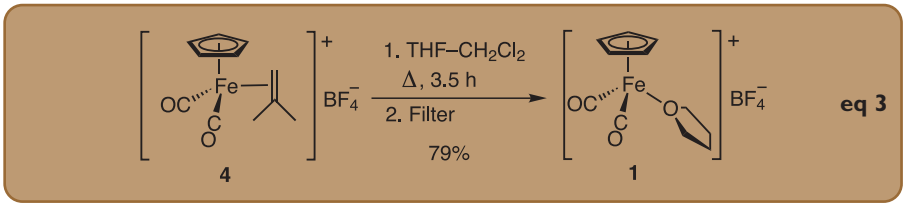
In the past decade, one particular Fp complex $[(\eta^5\text{-}C_5H_5)(CO)_2Fe(THF)]^+[BF_4]^-$, **1**, has been extensively utilized as an easily handled, stable reagent for the synthesis of a variety of compounds. Many publications have reported the use of stoichiometric quantities of **1** in ligand substitution reactions to create new organometallic complexes.[7] Although several of these reactions are interesting examples of organometallic synthesis, they don't fall within the scope of this review. Instead, we have chosen to focus on the catalytic transformations facilitated by the Fp cation, which is generated from adduct **1**. These transformations often yield unique products or achieve selectivities that are different from those of other transition-metal catalysts.

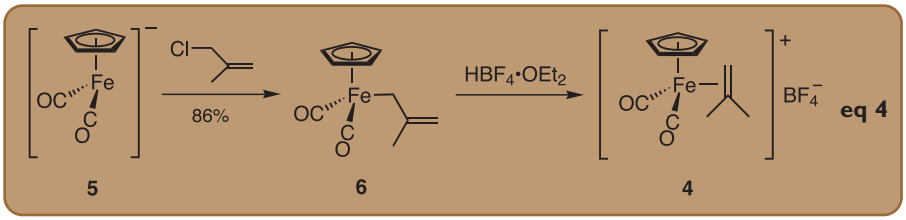
2. Synthetic Routes to the Iron Lewis Acid–THF Adduct 1

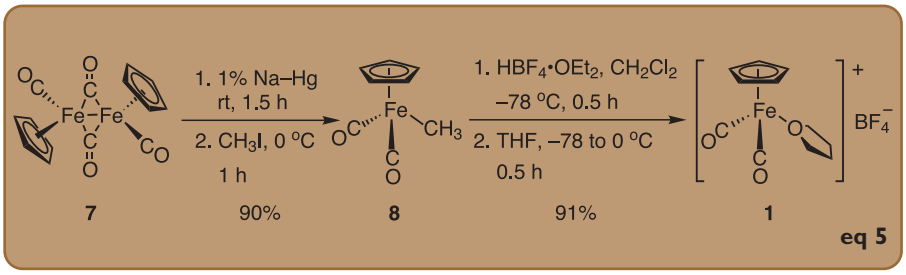
The first synthesis of adduct **1** was reported in 1971 by Giering and Rosenblum.[8] It was prepared by treating $(\eta^5\text{-}C_5H_5)\text{-}Fe(CO)_2Cl$ (**2**) with $AgBF_4$ in THF (**eq 1**). However, the focus of that particular report was not the preparation of this iron Lewis acid complex, but rather analogous olefin

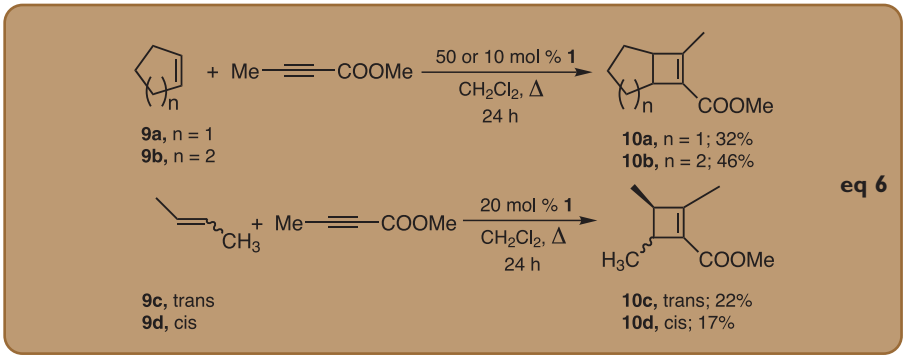












complexes of the type $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(\eta^2\text{-olefin})]^+ BF_4^-$. There was no mention of any workup or yield of complex **1**, and any knowledge regarding its utility was not reported.

Reger and Coleman reported the second synthesis of **1** in 1977.[9] They followed a similar route: the iodo complex, $(\eta^5\text{-}C_5H_5)Fe(CO)_2I$ (**3**), was reacted with $AgBF_4$ in THF to provide **1** in 97% yield. Lewis acid adduct **1** was then used as a precursor to olefin complexes (**eq 2**).

However, there is a potential problem with the use of $AgBF_4$ as a reagent in the synthesis of **1**. Any remaining Ag^+ impurities could cast doubt on the catalytic effect of **1**, as Ag^+ is also a weak Lewis acid. Worse yet, these impurities could interfere with the selectivity of the catalyst, especially when working with an asymmetric variant of **1**.

In 1982, Rosenblum and Scheck[6] reported a "more convenient and less expensive method" to prepare **1** by heating $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(\text{isobutylene})]^+ BF_4^-$ (**4**) in THF–CH_2Cl_2 for 3.5 h and filtering the reaction mixture to provide **1** in 79% yield (**eq 3**). However, the isobutylene complex, **4**, itself was synthesized by treating methallyl complex **6** with tetrafluoroboric acid. Methallyl complex **6**, in turn, was prepared from the Fp anion (**5**) and methallyl chloride (**eq 4**).[10] For these reasons, Reger and Coleman's route remained the more widely used method, due in part to its simplicity, high yield, and commercial availability of the iodo complex **3**.

In 1998, Mahmood and Hossain reported a new synthetic route to **1** using inexpensive, commercially available starting materials (**eq 5**).[11a] Importantly, the route does not introduce a competing silver Lewis acid species. Starting from the dicarbonyl dimer **7**, the ferrate was formed by reduction with Na–Hg amalgam and trapped using methyl iodide.[11b] The resulting known complex **8** was protonated by tetrafluoroboric acid–diethyl ether, and precipitated by addition of THF. The resulting adduct was repeatedly precipitated and washed with CH_2Cl_2 and THF to remove residual HBF_4 impurities. This method produces **1** in an 80–85% overall yield, and has been the preferred method for preparing this catalyst in Hossain's subsequent work.

3. Homogeneous Catalyses

3.1. [2+2] Cycloaddition

Rosenblum and Scheck reported the first use of **1** as a catalyst.[6] In their 1982 paper, **1** catalyzed a [2+2] cycloaddition of alkenes **9** with methyl tetrolate (**eq 6**). Catalytic amounts (10–50%) of **1** were reported in only a few of the examples, and the product yields were modest (17–46%) for all the examples. However, this report established that **1** could be used in catalytic quantities to activate functional groups toward reaction.

3.2. Diels–Alder Reaction

The next report of the use of **1** as a catalyst was published by Hersh and co-workers seven years later.[12] Hersh's group screened a number of organometallic complexes as catalysts for the Diels–Alder reaction. Several common dienophiles were found to form adducts with dienes **11** in

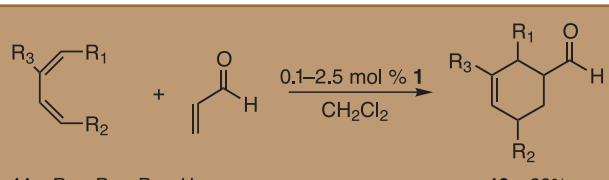
varying yields. In particular, **1** was found to give unexpectedly good results (**eq 7**). The surprise was due to the fact that the product yields did not appear to correlate with the relative strength of the Lewis acid catalyst. Hersh noted "the complete failure of the expected correlation of reactivity with acidity for $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]^+$ BF_4^- raised the serious possibility that catalysis in this case was the result of adventitious impurities." After a series of control experiments, Hersh and co-workers concluded that the nature of the catalytic impurity was unknown, and suggested that "the best evidence that these materials are the true catalysts will be the demonstration that a chiral analogue is capable of induction of asymmetric Diels–Alder reactions." This evidence was provided in 1994 by Kündig and co-workers, who prepared chiral catalysts **13** (**Figure 1**) and found them to catalyze the Diels–Alder reaction with very high enantioselectivities (**eq 8**).[13]

3.3. Cyclopropanation

During the 1990s, Hossain and various co-workers have reported several transformations employing **1** as catalyst. The first such application was the catalytic cyclopropanation of alkenes **14a–c** using ethyl diazoacetate (EDA) (**eq 9**), in which a preference for the formation of the more sterically crowded cis cyclopropanes was observed for the first time.[14] Yields were good for the olefins studied, and selectivity was good for styrene, but decreased for other olefins.

In order to establish that **1**, and not other acidic impurities, was truly the catalyst in this cyclopropanation, the proton-trapping agent, 2,6-di-*tert*-butylpyridine (**16**), was added in one case.[14b] Hersh had reported that the Diels–Alder reaction was inhibited by addition of **16**,[12] whereas Hossain observed no appreciable difference in the yield or selectivity of the cyclopropanation in the presence of **16** (**eq 10**).

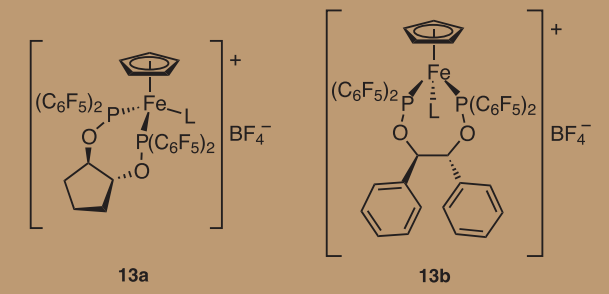
The proposed mechanism for the cyclopropanation involves formation of the reactive iron carbenoid **18** from the Fp cation (**17**) and EDA, and subsequent reaction of **18** with the alkene (**Scheme 1**). Although the iron carbenoid species was not observed, the presence of carbene dimers, diethyl maleate and fumarate, in the product mixture, along with the preference for the cis isomer, are consistent with the formation of a carbenoid species. These observations are also consistent with the cyclopropanation mechanism proposed by Casey[15] and Brookhart[16] based on their investigations of the stoichiometric formation of cyclopropanes from isolable iron carbenes. Moreover, a catalytic cycle



11a, $R_1 = R_2 = R_3 = H$
11b, $R_1 = R_2 = H$, $R_3 = Me$
11c, $R_1 = Me$, $R_2 = R_3 = H$
11d, $R_1,R_2 = -CH_2-$, $R_3 = H$

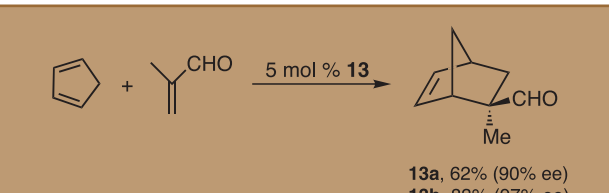
12a, 38%
12b, 86%
12c, 89%
12d, 83%

eq 7



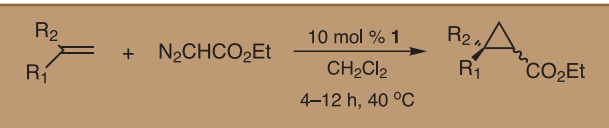
13a **13b**

Figure 1. Chiral Catalysts Analogous to **1**.



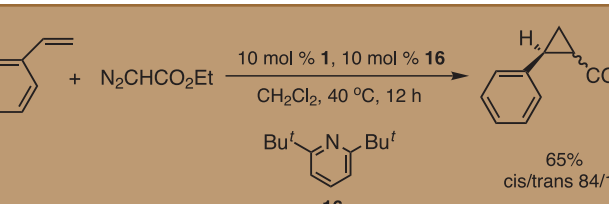
13a, 62% (90% ee)
13b, 83% (97% ee)

eq 8



		cis/trans
14a; R_1 = Ph, R_2 = H	**15a,** 68%	85/15
14b; R_1 = *p*-MeC_6H_4, R_2 = H	**15b,** 66%	60/40
14c; R_1 = Ph, R_2 = Me	**15c,** 60%	60/40
14d; R_1 = OMe, R_2 = Me	**15d,** 66%	55/45
14e; R_1 = OEt, R_2 = H	**15e,** 68%	45/55

eq 9



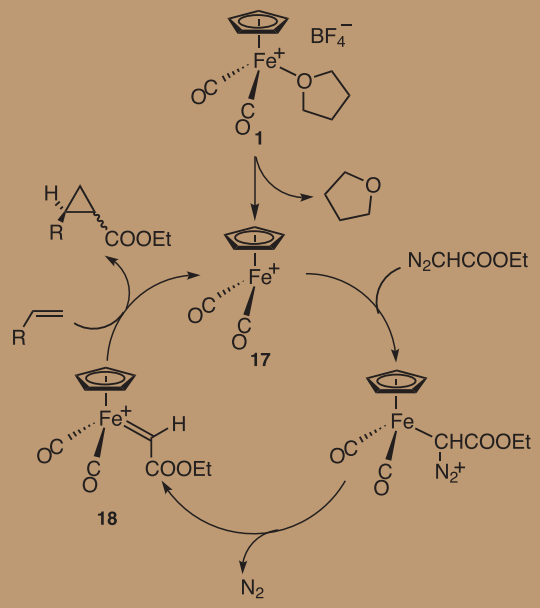
16

65%
cis/trans 84/16

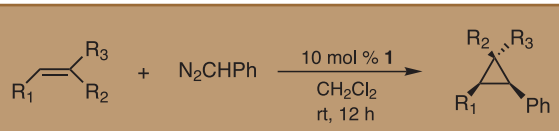
eq 10

wherein the olefin initially complexes with the Fp cation followed by subsequent attack by EDA is improbable due to the observed inhibition of the reaction by higher concentrations of the olefin.

Hossain's group broadened the scope of the reaction by using phenyldiazomethane (PDM) and olefins **19** (**eq 11**).[17] This cyclopropanation resulted in excellent cis/trans selectivities (≥96% cis in all reported cases), and, contrary to the cyclopropanation with EDA, showed tolerance for aliphatic olefins. Here too, the presence of carbene dimers (stilbenes) and the cis selectivity imply the presence of a carbenoid intermediate.

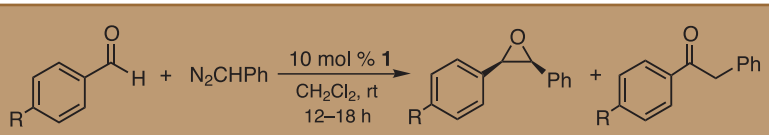


Scheme 1. Proposed Mechanism of the Catalytic Cyclopropanation Reaction.



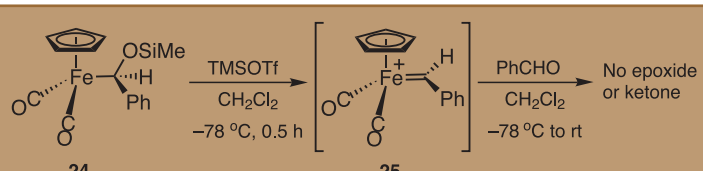
		cis/trans
19a; R_1 = Ph, R_2 = R_3 = H	**20a**, 80%	96/04
19b; R_1 = *p*-$CH_3C_6H_4$, R_2 = R_3 = H	**20b**, 51%	all cis
19c; R_1 = OAc, R_2 = R_3 = H	**20c**, 51%	all cis
19d; R_1,R_2 = -$(CH_2)_3$-, R_3 = H	**20d**, 25%	97/03 (endo/exo)
19e; R_1 = R_2 = R_3 = CH_3	**20e**, 20%	all cis

eq 11



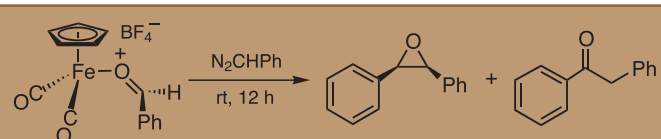
21a, R = H	**22a**, 30%	**23a**, 55%
21b, R = Cl	**22b**, 36%	**23b**, 50%
21c, R = NO_2	**22c**, 42%	**23c**, 43%
21d, R = CF_3	**22d**, 42%	**23d**, 44%
21e, R = CH_3	**22e**, trace	**23e**, 52%
21f, R = OCH_3	**22f**, 0%	**23f**, 55%

eq 12



24 **25**

eq 13



26 39% 61%

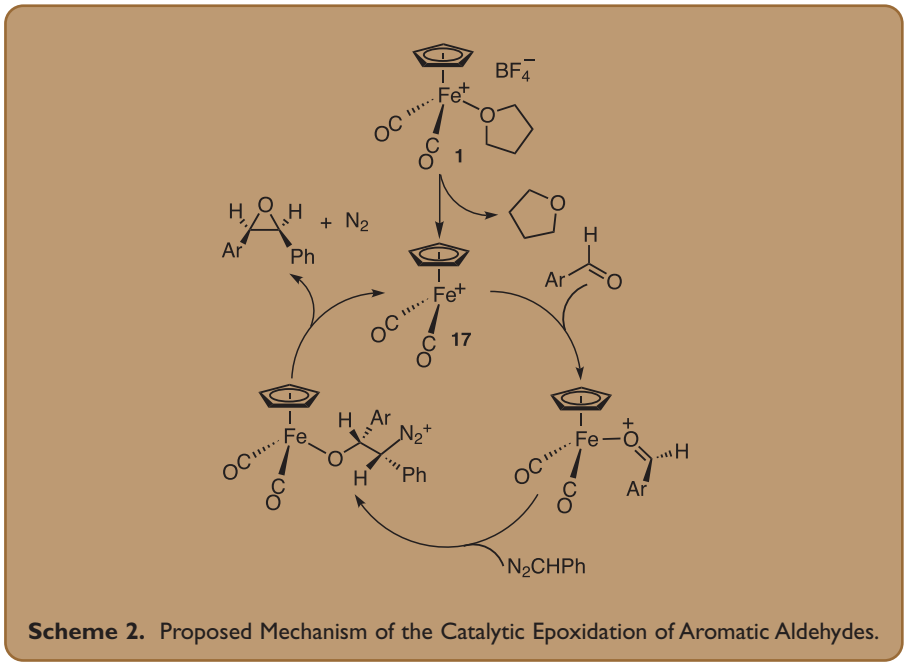
eq 14

3.4. Epoxidation of Aromatic Aldehydes

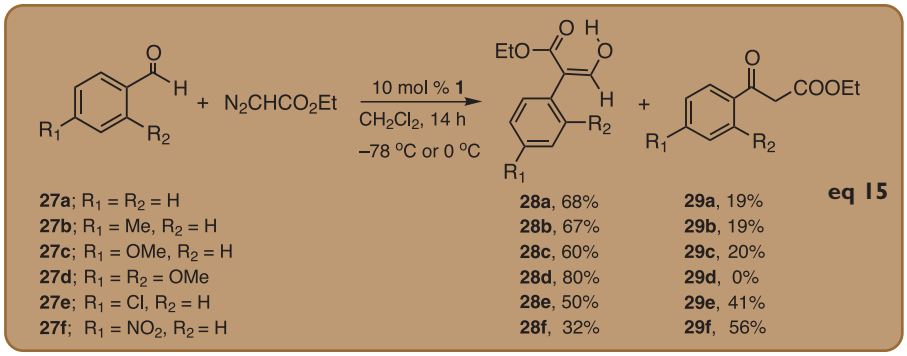
Iron Lewis acid **1** also proved useful in the epoxidation of aromatic aldehydes, **21**, by PDM (**eq 12**).[18] This reaction exhibited cis selectivity, in contrast to other previously reported catalytic methods that favor the trans epoxides. Homologated ketones **23** were also found in the crude reaction mixtures, accounting for the bulk of the nonepoxide products (~50%). The yields of the cis epoxides were moderate and increased slightly when electron-withdrawing groups were present on the aromatic ring. In contrast, little or no epoxide was observed when the ring bore electron-donating groups.

To gain insight into the mechanism of this reaction, the iron benzylidene complex **25** was prepared (**eq 13**) from **24** and trimethylsilyltriflate.[18] When **25** was treated with benzaldehyde, no epoxide product was formed. However, when iron σ-benzaldehyde complex **26** was treated with PDM (**eq 14**), the reaction proceeded to give roughly the same product distribution of epoxide and ketone as was seen in the catalytic reaction with **1**.

On the basis of these observations, a mechanism was proposed in which the key intermediate is the σ-bonded aldehyde complex, rather than the iron carbenoid that was postulated for the cyclopropanation reaction (**Scheme 2**).[18]



Scheme 2. Proposed Mechanism of the Catalytic Epoxidation of Aromatic Aldehydes.



27a; $R_1 = R_2 = H$	**28a**, 68%	**29a**, 19%	**eq 15**
27b; R_1 = Me, $R_2 = H$	**28b**, 67%	**29b**, 19%	
27c; R_1 = OMe, $R_2 = H$	**28c**, 60%	**29c**, 20%	
27d; $R_1 = R_2$ = OMe	**28d**, 80%	**29d**, 0%	
27e; R_1 = Cl, $R_2 = H$	**28e**, 50%	**29e**, 41%	
27f; $R_1 = NO_2$, $R_2 = H$	**28f**, 32%	**29f**, 56%	

3.5. Arylacrylate Formation

In contrast to PDM, EDA reacted with aromatic aldehydes **27** in the presence of **1** to give as the major products, not the expected epoxides, but β-hydroxy-α-arylacrylates **28** and β-keto esters **29** as the major byproducts (**eq 15**). The yields of acrylates, unlike those of epoxides **22**, were lower when electron-withdrawing groups were present in the aldehyde, and the same or higher when electron-donating groups were present. To explain these results, a catalytic cycle was proposed that also proceeds through an iron σ-bonded aldehyde complex, which leads to complex **30** upon addition of EDA. An unusual 1,2-aryl migration and loss of N_2 lead from complex **30** to the initial product **31**, which tautomerizes to the observed acrylate (**Scheme 3**).[11a]

The formation of acrylates was taken advantage of in a three-step synthesis of the naproxen precursor 2-(6-methoxy-2-naphthyl)propenoic acid (**33**) (**Scheme 4**).[19] The one-step reduction of the acrylate to form propenoic acid ester **32** was unprecedented.

3.6. Isomerization of Aryl Epoxides

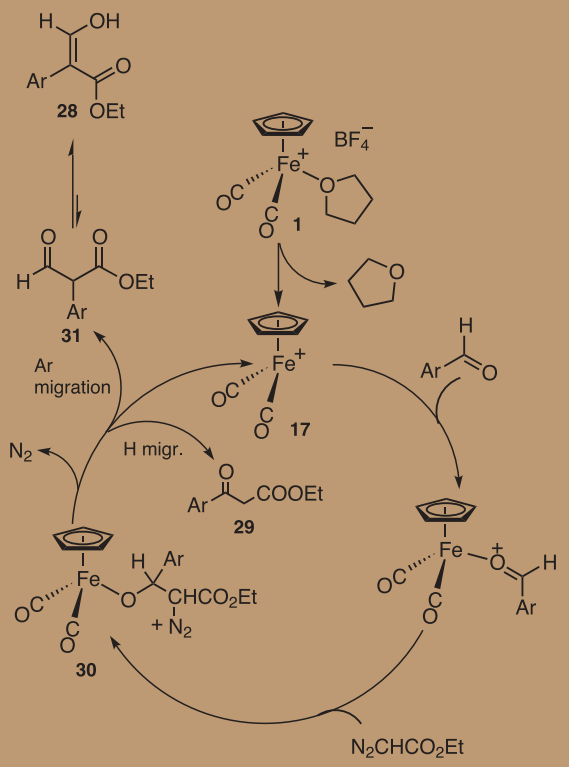
Iron Lewis acid complex **1** also facilitates the isomerization of aryl epoxides **34** to the corresponding aldehydes, **35,** in excellent yields (≥ 86%) (**eq 16**).[20] This is the first reported case of a metal-catalyzed, *selective* rearrangement of aryl epoxides to form aldehydes exclusively. The proposed catalytic cycle for the isomerization involves coordination of the epoxide to the Fp cation, followed by ring-opening to produce the benzylic carbocation **36** (**Scheme 5**). A selective 1,2 migration of the R group forms the aldehyde and regenerates the active catalyst **17**.

3.7. Aziridination

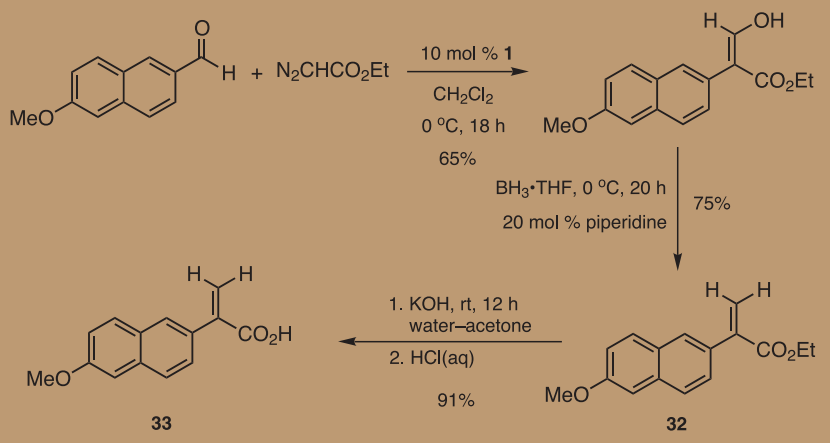
Complex **1** catalyzed equally well the reaction of EDA with aryl imines **37** to form aziridines **38 (eq 17**). The cis aziridine was the major isomer in all but one case when EDA was used. Yields were moderate to good, with the major byproducts being β-amino-α,β-unsaturated esters **39** and **40** (10–40%).[21]

In analogy to the epoxidation of aromatic aldehydes (Section 3.4, Scheme 2), the mechanism of aziridine formation is believed to proceed through an activated iminium ion intermediate, **41**, rather than an iron carbenoid similar to **25**. Support for this mechanism comes from the observation that no aziridine is formed when imine **37a** is added to iron carbene **25**. In contrast, when treated with EDA, the prepared and isolated iminium ion complex **41** forms the corresponding aziridine (**Scheme 6**). This mechanism also explains the formation of byproducts **39** and **40**, which arise from intermediate **42** by either a 1,2-aryl migration or a hydride shift, respectively.

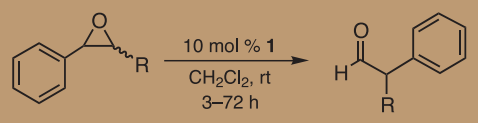
Upon further investigation, it was discovered that the catalytic reaction initially forms both the cis and trans aziridines.[22] However, once the imine is nearly completely consumed, the trans isomer, **43**, undergoes either catalytic decomposition or isomerization to form byproducts **39** and **40** or cis aziridine **38**, respectively.



Scheme 3. Postulated Catalytic Cycle for the Formation of Acrylates **28**.



Scheme 4. Three-Step Synthesis of Naproxen Precursor **33**.



34a, R = Ph (cis)
34b, R = Ph (trans)
34c, R = H
34d, R = *p*-ClC_6H_4
34e, R = *p*-$CH_3C_6H_4$

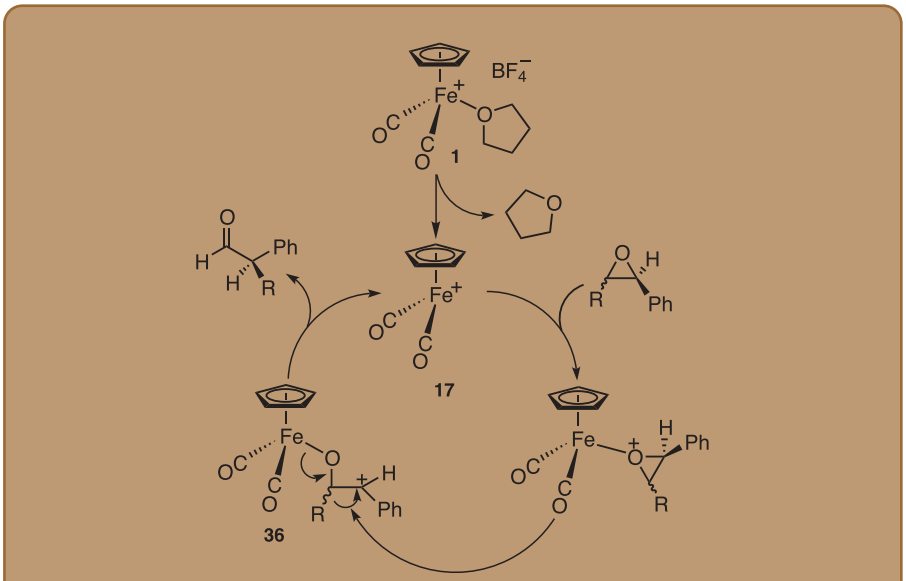
35a, 93%
35b, 91%
35c, 86%
35d, 95%
35e, 95%

eq 16

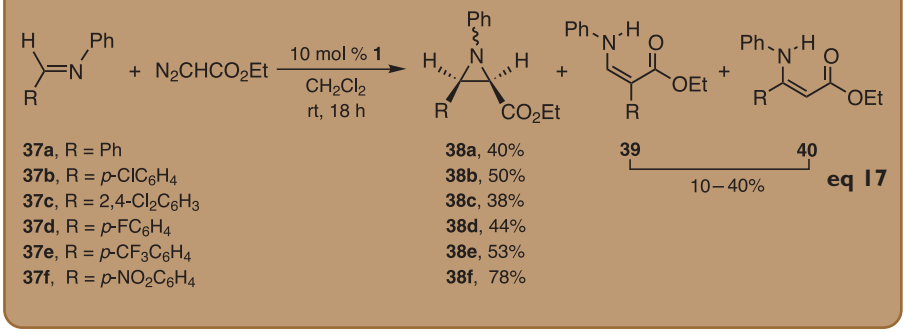
The isomerization of **43** to **38** appears to be unique to the iron Lewis acid **1**: BF_3 produced a variety of byproducts (including an α,β-unsaturated ester) when added to a dichloromethane solution of pure trans aziridine **43**. It thus appears that selective decomposition may be at work in the case of other Lewis acid catalyzed aziridinations.

Gratifyingly, when PDM was reacted with imines **37a**,**f** and **44**, the yields of aziridines **45** increased dramatically (72–95%) and cis specificity was observed in all instances (**eq 18**).[21] However, no byproducts analogous to the ones obtained with EDA were observed. Furthermore, the reaction proved to be more general due to its tolerance of *N*-benzyl and *N*-alkyl groups on the imine.

Very recently, we have reported the aziridination of olefins **46** using **1**.[23] The reactions were performed with *N*-(*p*-tosyl)iminophenyliodinane (PhI=NTs) as the nitrenoid precursor and the limiting reagent (**eq 19**). PhI=NTs was consumed entirely to provide aziridines **47** with retention of stereochemistry (i.e., *cis*-stilbene produced the cis aziridine). Yields were markedly lower when trans olefins were employed, indicating a sensitivity of the reaction to geometric modifications. A plausible catalytic cycle is shown in **Scheme 7**, and features the generation of the transient nitrenoid intermediate **48**. In order to explain the observed stereoselectivity, ring closure of carbocation **49** is presumed to occur significantly faster than bond rotation around C_α–C_β.



Scheme 5. Proposed Catalytic Cycle for the Isomerization of Aryl Epoxides.

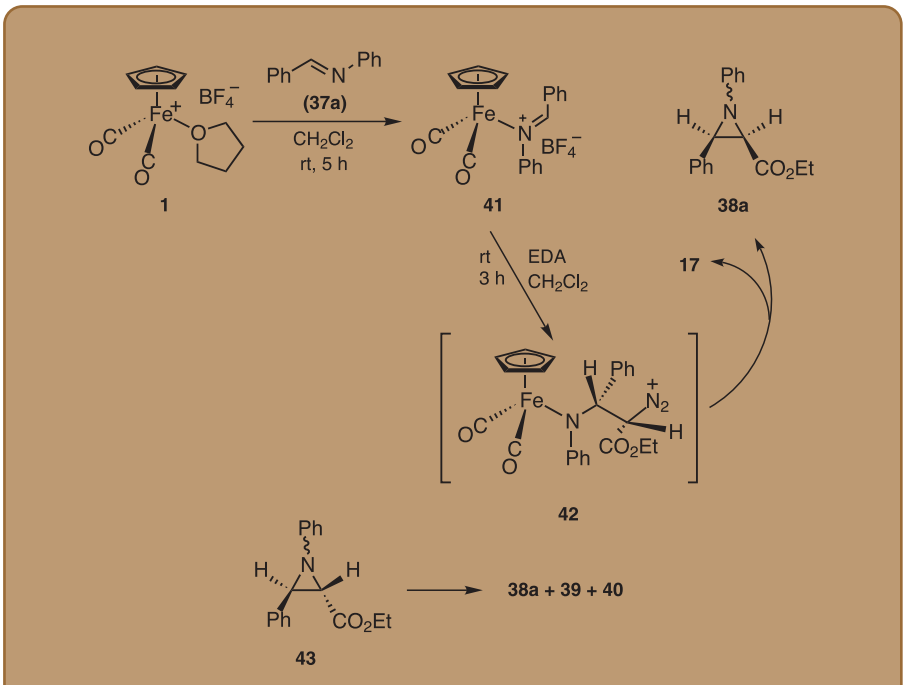


4. Heterogeneous Catalyses

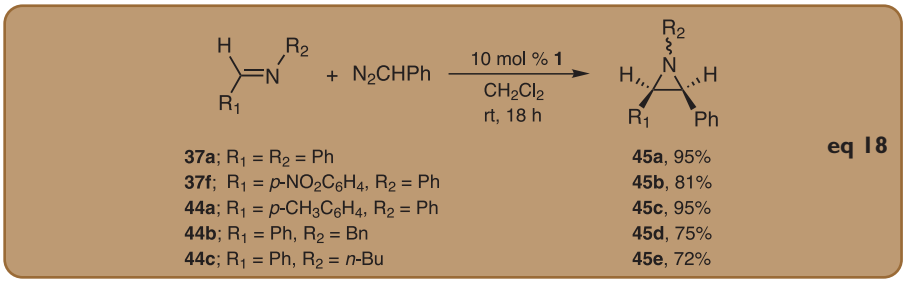
4.1. Divinylbenzene Polymer Bound Iron Lewis Acid

Iron Lewis acid **1** has been supported on two different systems for use in a few heterogeneous catalyses, the first of which was published in 1993.[24] Starting from the monomer (η^5-vinylcyclopentadienyl)$(CO)_2FeCH_3$ (**50**), the polymer-bound catalyst was prepared in two steps. First, **50** was copolymerized with divinylbenzene using AIBN as initiator. The resulting copolymer **51** was then treated with trimethylsilyl triflate, followed by THF, to yield the polymer-bound Lewis acid **52** (**Scheme 8**). The reactive site of **52** differs from **1** only in its counterion, which is triflate as compared to the usual tetrafluoroborate.

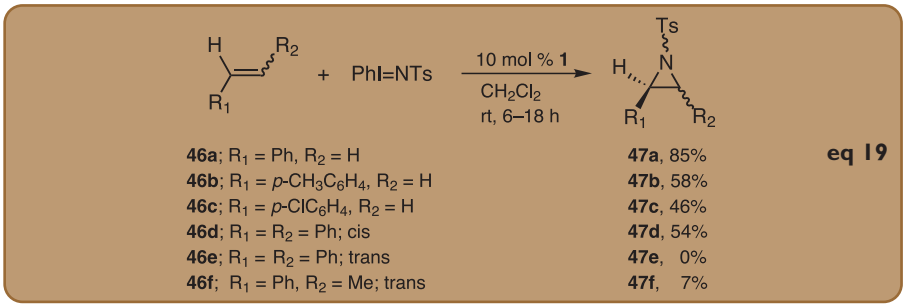
The effectiveness of **52** as a polymer-bound Lewis acid catalyst was tested in the Diels–Alder reaction (**eq 20**). 25 wt. % of **52** (relative to aldehyde **54**) was typically employed, as opposed to 10 mol % of the homogeneous monomeric catalyst **1**. Catalyst **52** was filtered from the reaction



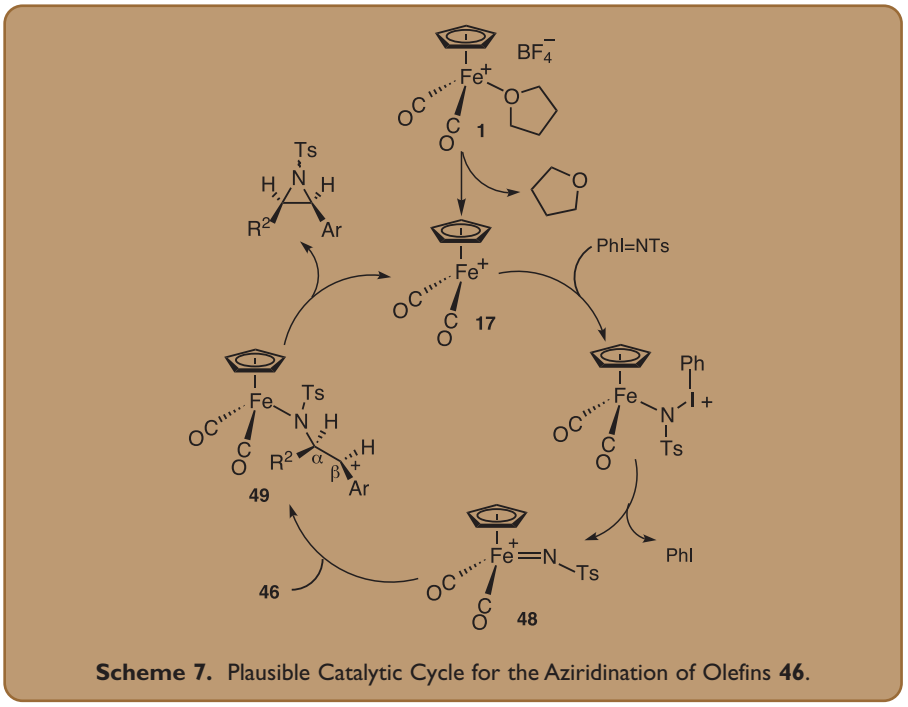
Scheme 6. Proposed Pathway for the Aziridination of Aryl Imines.



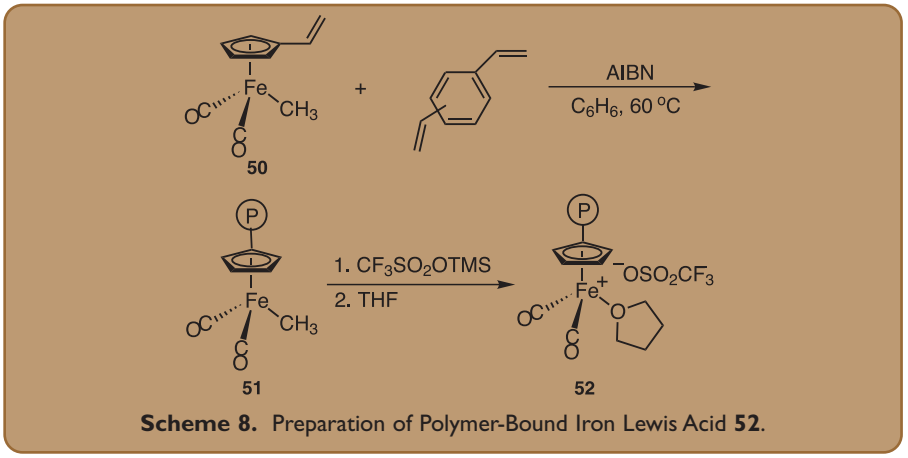
eq 18



eq 19



Scheme 7. Plausible Catalytic Cycle for the Aziridination of Olefins **46**.



Scheme 8. Preparation of Polymer-Bound Iron Lewis Acid **52**.

mixture and washed with CH_2Cl_2 before its next use. There was some loss in activity as evidenced by a decrease in yield in the subsequent reaction, but no apparent loss in selectivity.

4.2. Silica-Supported Iron Lewis Acid

Recently, the adsorption of adduct **1** onto silica and its utilization in several reaction sequences have been described.[25] Preparation of the silica-supported catalyst, SS-**1**, was notably straightforward: it required merely stirring silica gel with **1** in dichloromethane for 5 min at room temperature, followed by decanting of the supernatant liquid and drying of the solid under vacuum. IR analysis showed the presence of the carbonyls and THF. The ^{1}H NMR spectrum of the supernatant solution verified the absence of either unsupported **1** or displaced THF. Elemental analysis of the solid indicated 1.36% iron by mass (calculated: 1.41%). Therefore, it is postulated that no ligands are displaced in the adsorption of **1** onto silica, but rather that the catalyst is supported by electrostatic interactions.

4.2.1. Arylacrylate Formation

The effectiveness of SS-**1** as a Lewis acid catalyst was tested first in the reaction of 2,4-dimethoxybenzaldehyde (**27d**) with EDA.[25] The initial yield of β-hydroxy-α-arylacrylate **28d** was comparable to its yield from the same reaction using unsupported **1** (72% vs 80%). The reaction mixture was decanted from SS-**1** and the latter was washed several times with CH_2Cl_2 and reused. Although the yield of **28d** diminished somewhat with each subsequent run (72% to 53% after 6 runs) and longer reaction times were required for later runs, SS-**1** showed a practical duration of activity, remaining active for at least 52 days.

4.2.2. Cyclopropanation

The effectiveness of SS-**1** was also demonstrated in the reaction of styrene (**14a**) with EDA.[25] As was observed in the reaction of EDA with 2,4-dimethoxybenzaldehyde (**27d**), the initial yield of cyclopropane **15a** was comparable to the one obtained in the reaction using unsupported **1** (61% vs 68%). Similarly, the yield of **15a** diminished slightly with each subsequent run using recycled SS-**1** (45% yield from run 5). However, in contrast to the observed preference for *cis*-**15a** by **1**, SS-**1** showed a preference for *trans*-**15a** (cis/trans = 1:1.2–2.0). This reversal in cis–trans selectivity is reminiscent of the decrease in

selectivity for the trans isomer observed in the Cu-catalyzed cyclopropanation of styrene under heterogeneous vs homogeneous conditions.[26]

4.2.3. Aziridination

The third test of the effectiveness of SS-**1** involved catalysis of the reaction of *N*-benzylideneaniline (**37a**) with PDM.[25] The yields of aziridine **45a** from the first two runs were in excellent agreement (92% and 90%) with the corresponding yield (95%) from the same reaction with unsupported **1**. However, the activity of SS-**1** fell off sharply after the second cycle. This dramatic drop (only 25% yield of **45a** in run 5) stands in contrast to the slight-to-moderate decrease in yield observed in the cyclopropanation and the arylacrylate-forming reactions. Accounting for the decrease in yield of **45a** with successive runs using recycled SS-**1** was a corresponding increase in yield of two byproducts: *cis*-stilbene and diphenylazine.

5. Conclusions

The Fp–THF adduct **1** is a useful Lewis acid catalyst of several organic transformations. It is an inexpensive and nontoxic alternative to many of the transition-metal catalysts currently available to the chemist, often leads to unique products and stereoselectivities, and its scope of applications continues to grow. **Table 1** summarizes the types of results obtained with **1** and contrasts them with those obtained with other Lewis acids under comparable reaction conditions.[27–31]

6. References and Notes

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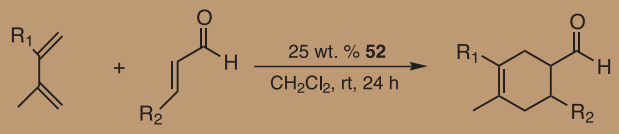
About the Authors

Mark Redlich was born in 1973 in Milwaukee, WI. He received a Bachelor of Science degree in 1995 from Marquette University in Milwaukee. He completed his doctoral studies in 2002 at the University of Wisconsin-Milwaukee (UWM) working under the supervision of Professor Hossain. His doctoral work included the synthesis of novel asymmetric iron Lewis acids and their applications in the reactions of imines and diazo compounds. Since receiving his Ph.D. degree, he has been working as the product line specialist for general and fine organics at Aldrich Chemical Company. He enjoys spending time with his wife, Tracy, and writing music in his free time.

Michael Mayer was born in 1971 in Milwaukee, WI. He received a B.S. degree in chemistry from the University of Wisconsin-Oshkosh (1994), and a Ph.D. degree from UWM (2000) under the supervision of Professor Hossain for "Studies Directed Toward an Asymmetric Synthesis of Aziridines with an Iron Lewis Acid Catalyst". He is currently an NIH postdoctoral research fellow at the University of Illinois at Urbana-Champaign, carrying out research with Professor S. C. Zimmerman in the areas of dendrimer chemistry and supramolecular self-assembly of hydrogen-bonding arrays.

M. Mahmun Hossain was born in Bogra, Bangladesh. He received his M.Sc. degree in chemistry from Dhaka University, Bangladesh. In 1985, he received his Ph.D. from the University of South Carolina, where he worked under the direction of Professor Robert S. Bly. After about 3 years of postdoctoral study with Professor Jack



53a, R_1 = H
53b, R_1 = Me
53c, R_1 = Me
53d, CpH

54a, R_2 = H
54b, R_2 = H
54c, R_2 = Me
54d, R_2 = Me

55a, 60%
55b, 97% (70%)*
55c, 90% (55%)*
55d, 60% (84/16 endo/exo)
(50%)(84/16 endo/exo)*

* Yields in parentheses are from a second run using recycled **52**.

eq 20

Table 1. Representative Results Obtained with 1 vs Those Obtained with Other Lewis Acids

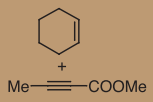
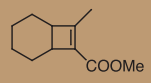
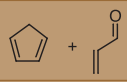
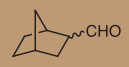
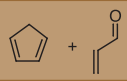
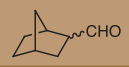
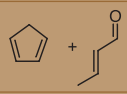
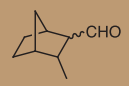
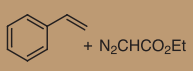
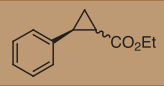
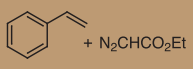
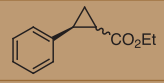
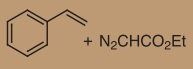
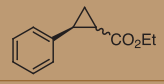
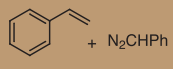
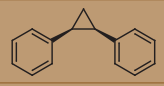
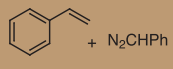
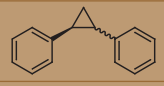
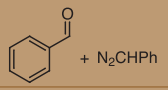
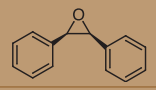
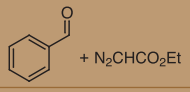
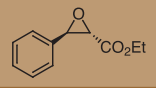
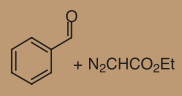
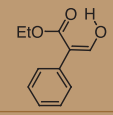
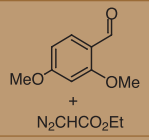
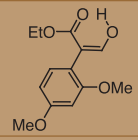
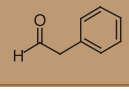
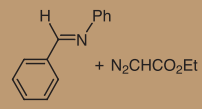
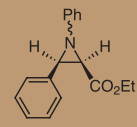
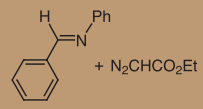
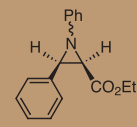
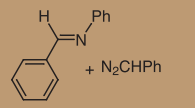
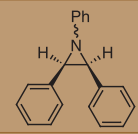
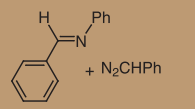
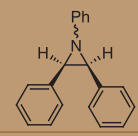
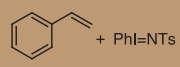
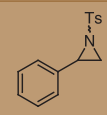
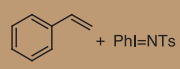
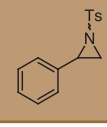
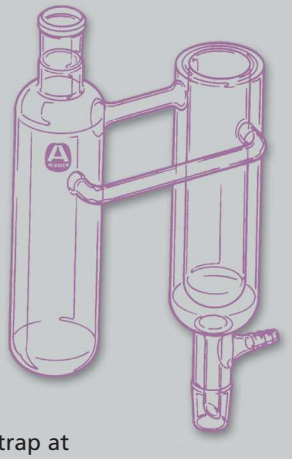
Entry	*Rxn Type*	*Starting Materials*	*Catalyst*	*Major Product*	*Yield*	*Cis/Trans*	*Ref.*
1	[2+2] cycloaddition		**1**		46%	N/A	6
2	Diels–Alder		**1**		83%	92/8 (endo/exo)	12
3	Diels–Alder		**[Cp(CO)$_3$W(THF)]$^+$ PF$_6^-$**		76%	80/20 (endo/exo)	12
4	Diels–Alder		**52**		60%	84/16 (endo/exo)	24
5	Cyclopropanation		**1**		68%	85/15	14
6	Cyclopropanation		**Rh$_2$(OAc)$_4$**		93%	38/62	27
7	Cyclopropanation		SS-**1**		61%	45/55	25
8	Cyclopropanation		**1**		80%	96/4	17
9	Cyclopropanation		**Rh$_2$(OAc)$_4$**		38%	77/33	28
10	Epoxidation		**1**		30%	all cis	18
11	Epoxidation		**CH$_3$ReO$_3$ (MTO)**		79%	all trans	29
12	Acrylate Formation		**1**		68%	N/A	11a
13	Acrylate Formation		SS-**1**		72%	N/A	25
14	Epoxide–Aldehyde Isomerization		**1**		86%	N/A	20

Table 1. Representative Results Obtained with 1 vs Those Obtained with Other Lewis Acids (cont.)

Entry	Rxn Type	Starting Materials	Catalyst	Major Product	Yield	Cis/Trans	Ref.
15	Aziridination		**1**		40%	all cis	21
16	Aziridination		**BF_3** **$AlCl_3$** **$TiCl_4$**		93% 56% 62%	93/7 98/2 89/11	30
17	Aziridination		**1**		95%	all cis	21
18	Aziridination		SS-**1**		92%	all cis	25
19	Aziridination		**1**		85%	N/A	23
20	Aziridination		**$CuClO_4$** **$Cu(OTf)_2$**		90% 92%	N/A	31

Halpern at the University of Chicago, he joined the Department of Chemistry at UWM as an assistant professor in 1988. In 1994, he was promoted to associate professor, and received a research award from the UWM Foundation for his outstanding research and creativity. He is an author of nearly 50 publications and has presented more than 75 seminars, posters, and papers at various meetings and at universities and colleges. He has supervised 8 Ph.D., 4 M.S., and nearly 25 B.S. students. Currently, he is working in the area of asymmetric synthesis catalyzed by chiral metal complexes. He and his wife, Farida, who is also a chemist, have two sons, Tanim and Aunim, and one daughter, Anita.

The Aldrich Mini Diazald® Apparatus



This unit is designed for the preparation of 1 to 50 mmol of diazomethane from 25 wt. % solution of Diazald® in 2-methoxyethyl ether (diglyme), and consists of a reaction vessel and condenser in one compact piece (with ⅋19/22 Clear-Seal® joints). The only additional equipment needed consists of an addition funnel and receiver (both of which must have Clear-Seal® joints). The major feature of this apparatus is the cold-finger in place of a water-jacketed condenser. When filled with dry ice/isopropanol slush, the condenser very efficiently prevents diazomethane/ether vapor from escaping into the atmosphere. A typical experimental procedure employing this apparatus follows.

Procedure for an Alcohol-Containing Ethereal Solution

Fill the condenser with dry ice, then add isopropanol slowly until the cold-finger is about one-third full. Add ethanol (95%, 10 mL) to a solution of potassium hydroxide (5 g) in water (8 mL) in the reaction vessel. Attach a 100-mL receiving flask (with Clear-Seal® joint) to the condenser and cool the flask in a dry ice/isopropanol bath. Provide an ether trap at the side arm (the glass tube must have firepolished ends). The trap should be cooled in a dry ice/isopropanol bath.

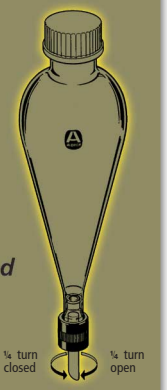
Place a separatory funnel (with Clear-Seal® joint) over the reaction vessel and charge the funnel with 20 mL of 25 wt % Diazald® in diglyme (5 g, 23.3 mmol) and 30 mL of ether. Warm the reaction vessel to 65 °C with a water bath and add the Diazald® solution over a period of 20 minutes to the KOH/EtOH–H_2O solution. The rate of distillation should approximate the rate of addition. Replenish the cold-finger with dry ice as necessary. When all the Diazald® has been used up, slowly add 10 mL of ether and continue the distillation until the distillate is colorless. If the distillate is still yellow, add another 10 mL of ether and continue the distillation. The ether will contain about 900 mg (21.4 mmol) of diazomethane.

Diazald®, 25 wt. % solution in 2-methoxyethyl ether **59,514-4**

Apparatus

With ⅋ 19/22 Clear-Seal® joints	**Z10,889-8**	**Separatory funnel**, 125mL	**Z10,038-2**
With ⅋ 19/26 Clear-Seal® joints	**Z20,250-9**	**Round-bottom flask**, 100mL	**Z10,035-8**

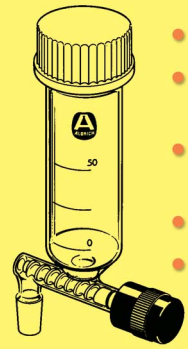
Squibb Separatory Funnels



- *Leakproof screw thread closure cap with PTFE-faced silicone liner*
- *Precision all-PTFE valve and drip-tip*

Cap. (mL)	Cap size (mm)	Valve size (mm)	Cat. No.
60	32	2	**Z41,819-6**
125	45	2	**Z41,821-8**
250	45	4	**Z41,822-6**
500	45	4	**Z41,823-4**
1,000	45	4	**Z41,824-2**
2,000	45	6	**Z41,825-0**
4,000	45	8	**Z41,826-9**
6,000	45	8	**Z41,827-7**

Powder Addition Funnels



- *Large 45mm top opening with threaded cap*
- *Removable PTFE auger for easy cleaning, designed for vacuum applications*
- *Delivers free-flowing granular material to reactions by turning the auger feed*
- *Continuous delivery or a single charge*
- *500mL size has a clean-out, side-arm port*

Cap. (mL)	Approx. H (mm)	Bottom ⅋ joint	Cat. No.
50	180	14/20	**Z41,813-7**
125	250	24/40	**Z41,814-5**
500	300	24/40	**Z41,815-3**

Carbon Nanotubes

Carbon nanotubes (CNTs) were first isolated and characterized by Iijima in 1991.[1] Since then, dozens of research articles have been published, and new applications for CNTs have been proposed. The unique physical and chemical properties of CNTs, such as structural rigidity[2] and flexibility continue to generate considerable interest. Additionally, CNTs are extremely strong, about 100 times stronger (stress-resistant) than steel at one-sixth the weight. CNTs can also act as either conductors or semiconductors depending on their chirality,[3-5] possess an intrinsic superconductivity,[6] are ideal thermal conductors,[7] and can also behave as field emitters.[8]

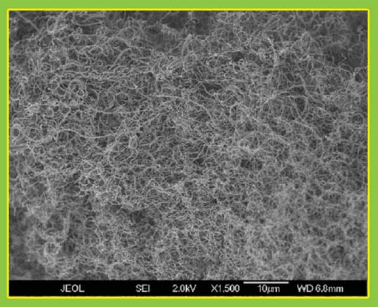


Fig. 1. Low-resolution SEM of a typical sample of 57,680-8 multiwall carbon nanotube.

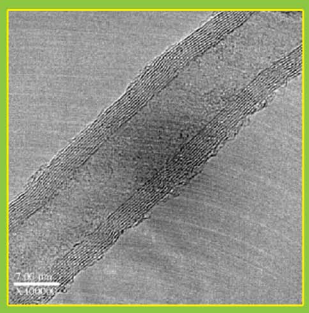


Fig. 2. High-resolution TEM of a typical multiwall carbon nanotube (57,680-8) showing the spacing between the graphene layers.

Images reprinted with permission from NanoLab, Inc.

NEW!

57,680-8 **Multiwall carbon nanotube,** 95+%, diam = 20–50 nm, length = 5–20 micron

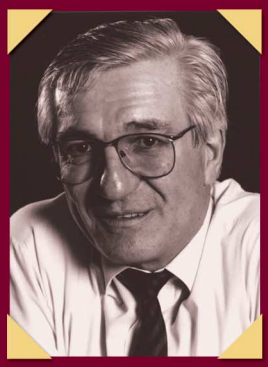
51,930-8 **Carbon nanotubes, single-walled, CarboLex AP-grade,** diam = 12–15 Å

41,298-8 **Bucky tubes, as-produced cylinders**

40,607-4 **Bucky tubes, powdered cylinder cores**

(1) Iijima, S. *Nature* **1991**, *354*, 56. (2) Overney, G. et al. *Z. Phys. D* **1993**, *27*, 93. (3) Mintmire, J.W. et al. *Phys. Rev. Lett.* **1992**, *68*, 631. (4) Hamada, N. et al. *ibid.* **1992**, *68*, 1579. (5) Saito, R. et al. *Phys. Rev. B* **1992**, *46*, 1804. (6) Kociak, C. et al. *Phys. Rev. Lett.* **2001**, *86*, 2416. (7) Berber, S. et al. *ibid.* **2000**, *84*, 4613. (8) Rinzler, A.G. et al. *Science* **1995**, *296*, 1550.

Honoring Professor Dieter Seebach on His 65th Birthday



Prof. Dr. Seebach was born in 1937 in Karlsruhe, Germany, and studied chemistry under R. Criegee at the University of Karlsruhe, where he completed his doctoral research on small rings and peroxides in 1964. After about two years at Harvard University as a lecturer and a postdoctoral fellow working for Professor E. J. Corey, he returned to Karlsruhe and earned his "Habilitation" in 1969. In 1971, he joined the faculty of Justus Liebig University in Giessen, and, in 1977, the faculty of the Swiss Federal Institute of Technology (ETH) in Zürich, where he is currently professor of organic chemistry.

Professor Seebach has received numerous honors and awards for his achievements in chemical research. Among these, are an honorary doctorate from the University of Montpellier (1989), the Fluka "Reagent of the Year" Prize (1987), and the ACS Award for Creative Work in Synthetic Organic Chemistry (1992). He has been a visiting professor at several universities and institutions, and is a member of the Deutsche Akademie der Naturforscher, Leopoldina, the Schweizerischen Akademie der Technischen Wissenschaften, and the Mexican Academy of Sciences. He is also a corresponding member of the Akademie der Wissenschaften und Literatur in Mainz.

Professor Seebach's research activity has focused on the development of new synthetic methods, the preparation and secondary structure investigations of β-peptides, the synthesis and applications of oligomers of (*R*)-3-hydroxybutyric acid and of the biopolymer PHB, the synthesis of chiral dendrimers, and the applications of chiral titanates in organic synthesis. In recent years, he has been preoccupied primarily with the chemistry of TADDOLs and TADDOL derivatives.

Editor's Note: The chemistry journal *Synthesis* has recently published a more extensive account of Professor Seebach's professional career and has dedicated a whole issue to him. See *Synthesis* **2002**, Issue 14 (October 7).

Happy 65th Birthday Professor Seebach!

Congratulations!

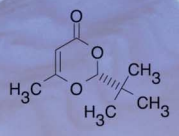
Fluka congratulates Professor Dieter Seebach on his 65th birthday, and would like to highlight a few of his many outstanding and lasting contributions to organic synthesis. Please take a look at our **New 2003/04 Fluka Catalogue** (for subscription, please visit www.sigma-aldrich.com/iceberg) to identify the large number of reagents and building blocks developed by Professor Seebach and his coworkers. A comprehensive survey of his work is found in *Synthesis*, **2002**, Issue 14 (October 7).

Chiral Building Blocks

Fluka product number **20264** has been awarded to Dieter Seebach as **"Fluka Reagent of the Year 1987"**. As chiral building block, this derivative of acetoacetate undergoes various stereoselective reactions with nucleophiles and electrophiles.

Seebach, D. et al. *J. Am. Chem. Soc.* **1988**, *110*, 4763; Seebach, D. et al. *Chem. Ber.* **1991**, *124*, 1845; Lange, G. L.; Organ, M. G. *Tetrahedron Lett.* **1993**, *34*, 1425.

20264 **(*R*)-2-*tert*-Butyl-6-methyl-1,3-dioxin-4-one**
puriss., ≥ 99.0% (HPLC, sum of enantiomers),
mp 60–62°C, $[\alpha]_{546}^{20}$ -267 ± 3°, $[\alpha]_{D}^{20}$ -219 ± 3° (c = 1 in chloroform)
$C_9H_{14}O_3$ M_r 170.21 [107289-20-3] 250mg; 1g



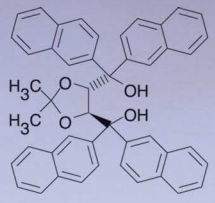
Chiral Auxiliaries

DINOLs for enantioselective reactions: as stoichiometric chiral reagents or auxiliaries in Lewis acid mediated transformations and for many other stereocontrolled processes.

Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem.* **2001**, *113*, 97; *Angew. Chem., Int. Ed.* **2001**, *40*, 93.

59488 **(+)-2,3-*O*-Isopropylidene-1,1,4,4-tetra(2-naphthyl)-D-threitol, (+)-DINOL**
(4*S*,5*S*)-2,2-Dimethyl-α,α,α′,α′-tetra(2-naphthyl)dioxolane-4,5-dimethanol
purum, ≥ 98.0% (HPLC, sum of enantiomers); mp 213–216 °C
ee ≥ 99.5% (HPLC), $[\alpha]_{546}^{20}$ +141 ± 2°, $[\alpha]_{D}^{20}$ +116 ± 2° (c = 1 in ethyl acetate)
$C_{47}H_{38}O_4$ M_r 666.82 [137365-16-3] 1g; 5g

59490 **(–)-2,3-*O*-Isopropylidene-1,1,4,4-tetra(2-naphthyl)-L-threitol, (–)-DINOL**
(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetra(2-naphthyl)dioxolane-4,5-dimethanol
purum, ≥ 99.0% (HPLC, sum of enantiomers); mp 213–216 °C
ee ≥ 99.5% (HPLC), $[\alpha]_{546}^{20}$ -141 ± 2°, $[\alpha]_{D}^{20}$ -116 ± 2° (c = 1 in ethyl acetate)
$C_{47}H_{38}O_4$ M_r 666.82 [137365-09-4] 1g; 5g



59488

Chiral Ligands

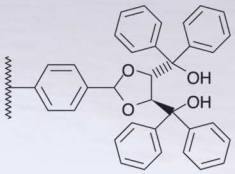
TADDOLs are a novel class of ligands, employed for the synthesis of enantiomerically pure compounds by highly stereoselective transformations.

Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem.* **2001**, *113*, 97.

40876 NEW! **(+)-2,3-*O*-Benzylidene-1,1,4,4-tetraphenyl-D-threitol, polymer-bound**
(4*S*,5*S*)-2,α,α,α′,α′-Pentaphenyldioxolane-4,5-dimethanol, polymer-bound
(*S*,*S*)-Taddol (phenyl), polymer-bound, capacity ~ 0.4 mmol/g 250mg

40875 NEW! **(–)-2,3-*O*-Benzylidene-1,1,4,4-tetraphenyl-L-threitol, polymer-bound**
(4*R*,5*R*)-2,α,α,α′,α′-Pentaphenyldioxolane-4,5-dimethanol, polymer-bound
(*R*,*R*)-Taddol (phenyl), polymer-bound, capacity ~ 0.4 mmol/g 250mg

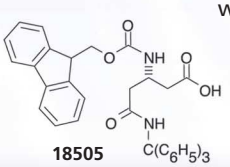
59532 **(–)-2,3-*O*-Isopropylidene-1,1,4,4-tetraphenyl-L-threitol**
(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
purum, ≥ 97.0% (HPLC, sum of enantiomers)
$[\alpha]_{546}^{20}$ -79 ± 2°, $[\alpha]_{D}^{20}$ -67 ± 2° (c = 1 in chloroform)
$C_{31}H_{30}O_4$ M_r 466.6 [93379-48-7] 250mg; 1g



40876

β-Peptides

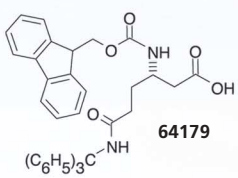
These are "homologs" of natural α-peptides and proteins, exhibiting remarkable biological activity together with an extraordinary biological stability, e.g., to common peptidases. Fluka offers a broad range of Fmoc- and Boc-protected unnatural β-amino acids for medicinal chemistry. For a complete overview, please visit our website, ask your local Sigma-Aldrich office for a copy of *ChemFiles (Vol. 2, No. 4): Unnatural Amino Acids II*, or take a look at www.sigma-aldrich.com/chemfiles.



18505

18505 NEW! **Fmoc-β-Gln(Trt)-OH**, Fmoc-β-Homoasn(Trt)-OH
purum, ≥ 97.0% (HPLC) $C_{39}H_{34}N_2O_5$ M_r 610.7 [283160-20-3] 250mg; 1g

64179 NEW! **Fmoc-β-Homogln(Trt)-OH**
purum, ≥ 97.0% (HPLC) $C_{40}H_{36}N_2O_5$ M_r 624.7 – 250mg; 1g



64179

Soon to come: In the second quarter of 2003, Sigma-Aldrich will introduce a ChemFile about our *Chiral Building Blocks and Intermediates*! Ask for it at your local Sigma-Aldrich office or take a look at **www.sigma-aldrich.com/chemfiles** for regular updates.

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FINE CHEMICALS

Isotope Labeling as a Tool in Structural Genomics and Proteome Analysis

Proteomics, the study of structure and function of proteins, is key to modern life science and medicine. Recent advances in the field of proteomics have been made possible by modern NMR, MS, genomic engineering, and stable isotope chemistry. Dr. Kurt Wüthrich—of the Swiss Federal Institute of Technology (Zürich) and The Scripps Research Institute (La Jolla, CA), and the co-recipient of the 2002 Nobel Prize in Chemistry—has recently used isotopically labeled proteins in TROSY and CRINEP studies, thus elevating our understanding of macrobiomolecules (≤900 kDa) to a new level.[1-8]

The production of isotopically labeled proteins has become easily accessible to today's biochemists. A variety of isotope-labeled substrates are readily available for feeding the genetically modified microorganisms, which produce the proteins of interest to research. These growth media components include ^{13}C-labeled glucose; ^{13}C-, ^{13}C,^{15}N-, ^{13}C,D-, and ^{15}N,D-labeled amino acids; ammonium-^{15}N chloride; and even isotope-enriched growth media tailored for specific microorganisms. Alternatively, the proteins can be prepared from isotope-labeled amino acids using cell free synthesis. As a result, scientists can harvest isotopically labeled proteins and other interesting biomolecules for scientific research in a relatively short period of time, a process that was only imagined not long ago

With the help of modern NMR techniques, MS instrumentation, genetic engineering techniques, and a commercial stable-isotope supplier, the possibilities for today's researchers are boundless. It is likely that proteomics will be the most productive biochemistry research field in the near future.

References: (1) Wagner, G. et al. *Eur. J. Biochem.* **1981**, *114*, 375. (2) Wüthrich, K. et al. *J. Mol. Biol.* **1982**, *155*, 311. (3) Wagner, G.; Wüthrich, K. *ibid.* **1982**, *155*, 347. (4) Wider, G. et al. *ibid.* **1982**, *155*, 367. (5) Braun, W. et al. *Biochim. Biophys. Acta* **1981**, *667*, 377. (6) Braun, W. et al. *J. Mol. Biol.* **1983**, *169*, 921. (7) Pervushin, K. et al. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 12366. (8) Riek, R. et al. *ibid.* **1999**, *96*, 4918.

Products for Minimal Media

38,937-4	**D-Glucose-$^{13}C_6$**, 99 atom % ^{13}C
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55,200-3	**D-Glucose-*1,2,3,4,5,6,6*-d_7**, 98 atom % D
61,633-8	**D-Glucose-d_{12}**, 97–99 atom % D
29,925-1	**Ammonium-^{15}N chloride**, 98 atom % ^{15}N
48,801-1	**Ammonium-^{15}N hydroxide** (3*N*), 98 atom % ^{15}N
29,928-6	**Ammonium-^{15}N sulfate**, 98 atom % ^{15}N

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60,681-2	**ISOGRO™ Powder-Growth Medium** (unlabeled)
60,686-3	**ISOGRO™-^{13}C Powder-Growth Medium**, 99 atom % ^{13}C
61,672-9	**ISOGRO™-*D* Powder-Growth Medium**, 97–99 atom % D
60,687-1	**ISOGRO™-^{15}N Powder-Growth Medium**, 98 atom % ^{15}N
60,683-9	**ISOGRO™-^{13}C,^{15}N Powder-Growth Medium**, 99 atom % ^{13}C; 98 atom % ^{15}N
60,830-0	**ISOGRO™-^{15}N,*D* Powder-Growth Medium**, 98 atom % ^{15}N; 97–99 atom % D
60,829-7	**ISOGRO™-^{13}C,^{15}N,*D* Powder-Growth Medium**, 99 atom % ^{13}C; 98 atom % ^{15}N; 97–99 atom % D

α-*Keto Acids*

57,133-4	**2-Keto-3-methyl-^{13}C-butyric-*4*-^{13}C acid, sodium salt**, 99 atom % ^{13}C
60,756-8	**2-Keto-3-methylbutyric acid-$^{13}C_5$-*3*-d_1, sodium salt**, 99 atom % ^{13}C, 98 atom % D
57,134-2	**2-Ketobutyric-*4*-^{13}C acid, sodium salt hydrate**, 99 atom % ^{13}C
60,754-1	**2-Ketobutyric acid-$^{13}C_4$-*3,3*-d_2, sodium salt hydrate**, 99 atom % ^{13}C, 98 atom % D
60,848-3	**Pyruvic-*3*-^{13}C-*3,3,3*-d_3 acid, sodium salt**, 99 atom % ^{13}C, 50–60 atom % D
49,073-3	**Pyruvic-*3*-^{13}C acid, sodium salt**, 99 atom % ^{13}C
60,753-3	**2-Ketobutyric-*4*-^{13}C-*3,3,4,4,4*-d_5 acid, sodium salt hydrate**, 99 atom % ^{13}C, 97–98 atom % CD_2, 50–70 atom % CD_3

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Applications of Dialkylaminopyridine (DMAP) Catalysts in Organic Synthesis

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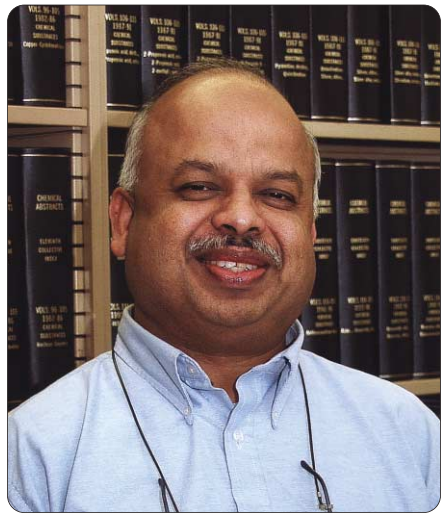
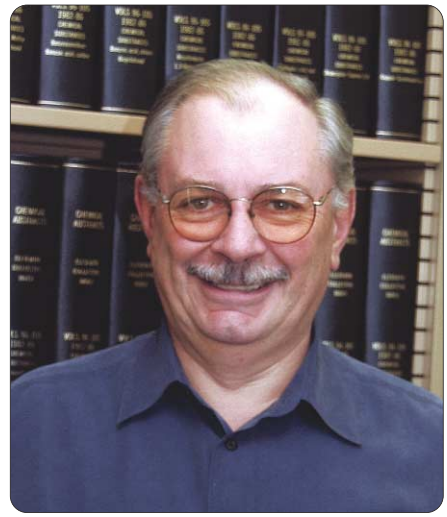
Outline





1. Introduction

In their 1978 review of the applications of 4-dialkylaminopyridines, Helmut Vorbrueggen and colleagues reported dramatic enhancements in yields and rates of acylations of sterically hindered alcohols and less reactive amines upon addition of catalytic amounts of 4-dimethylaminopyridine (DMAP) or 4-pyrrolidinopyridine (PPY).[1] Moreover, Litvinenko and Kirichenko[2] had observed a 10^4-fold rate enhancement in the benzoylation of *m*-chloroaniline when DMAP was used instead of pyridine. As a result of these and many similar observations, DMAP has now become the catalyst of choice for the most difficult acylations. It has also been used to great effect as an acylation catalyst to achieve high regio- and stereoselectivities. As a testament to the importance of DMAP, several reviews of its chemistry and the chemistry of related compounds have appeared since Vorbrueggen's 1978 survey.[3]

The aim of this article is to review current applications of DMAP as a catalyst for acylations and alkylations, the Baylis–Hillman reaction, and nucleophilic substitutions. Successful kinetic resolutions of alcohols and amines with chiral DMAP analogues will also be discussed among other recent developments.

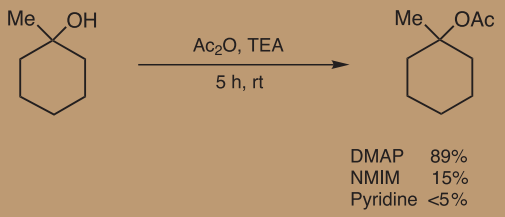
One of the earliest reported acylation reactions catalyzed by DMAP is the acetylation of 1-methylcyclohexanol, a sterically crowded alcohol.[4] We recently studied the use of the acetic anhydride–DMAP (catalytic)–triethylamine (stoichiometric) acetylation system and found it to be clearly superior to *N*-methylimidazole (NMIM) as a catalyst under comparable conditions, as well as to the customary acetic anhydride–pyridine system (**eq 1**).[5]

This superiority of DMAP over other common organic acylation catalysts has been rationalized as depicted in **Scheme 1**.[1,6] Step 1 is more rapid for DMAP as it is a better nucleophile than pyridine. Intermediate **1** is relatively more stable than the pyridine analogue (effect of the dimethylamino group); this leads to a greater concentration of the acylating species and a speeding up of the acylation. Step 2 is fast, promoted by a stoichiometric concentration of added tertiary amine base. Two points are noteworthy in the practical applications of DMAP: DMAP is usually more effective (a) when used with anhydrides rather than with acid chlorides, and (b) when the solvent is nonpolar.

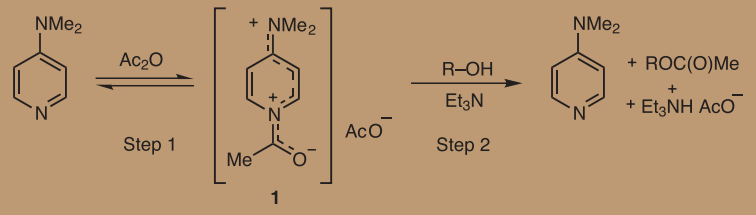
2. Catalysis of Acylations and Alkylations

2.1. Acylation of Tertiary Alcohols

In addition to the acetylation of 1-methylcyclohexanol, there are many other examples of the difficult acylations of tertiary alcohols made easier by using DMAP under mild conditions (**Figure 1**). Formation of acetate **2** in 92% yield from its alcohol precursor is noteworthy as the acid-labile acetal functionality survives the reaction conditions (rt, 30 min).[7] The mild conditions (rt, 7 h) used for acetylation lead to **3** in 95% yield with retention of the original stereochemistry.[8] In the synthesis of



eq 1



Scheme 1. Rationalization of DMAP Catalysis in Acylation Reactions.

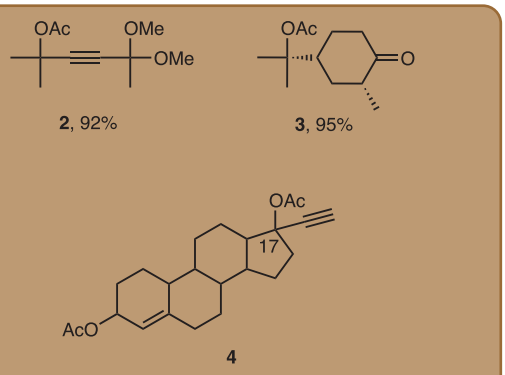
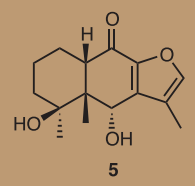
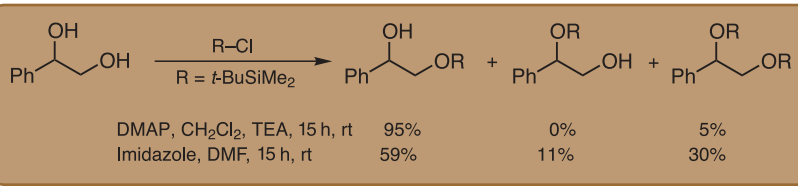
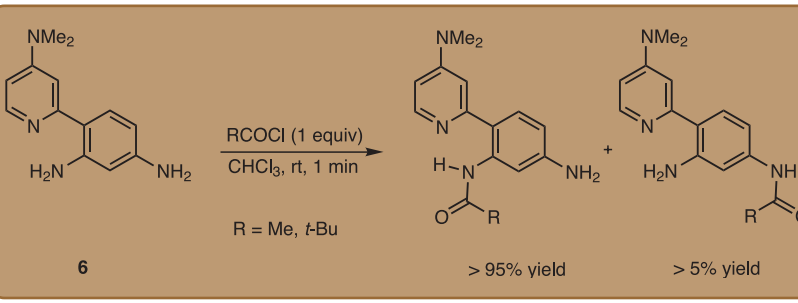


Figure 1. Mild, DMAP-Catalyzed Acetylations of Sterically Hindered Tertiary Alcohols.





eq 2



eq 3

highly active progestational agents, the final step is the acylation of tertiary 17β-OH groups in 17α-ethynyl steroids leading to structures such as **4**. These reactions are performed under mild conditions (24 °C, 24 h) with acetic anhydride, DMAP and TEA.[9]

2.2. Some Highly Regioselective Acylations and Silylations of Alcohols and Amines

In the case of the trans sesquiterpenediol **5**, it is possible to acetylate regiospecifically the secondary hydroxyl group with acetic anhydride/DMAP in the presence of the tertiary hydroxyl group. The corresponding cis diol remains unchanged under the same reaction conditions as a result of strong intramolecular hydrogen bonding between the OH groups.[1]

Silylation of a primary alcohol in the presence of a secondary one often presents a challenge as mixtures are formed, e.g., when using imidazole as catalyst. In contrast, regioselective silylation of the primary hydroxyl group can be easily achieved when DMAP is employed as catalyst (**eq 2**).[10]

Selective monoacylation of a diamine can be accomplished by suitable incorporation of a DMAP fragment within a molecule. Very recently, the regioselective monoacylation of amine **6** was achieved in >95% yield using one equivalent of an acid chloride in chloroform (rt, 1 min) (**eq 3**).[11] The observed regioselectivity is believed to be due to the proximity of the C-2 amino group to the carbonyl carbon of the acylpyridinium ion intermediate.

2.3. Formation of Amides without Racemization

Formation of amide bonds without racemization is an important part of peptide synthesis. Racemization of the chiral centers sometimes occurs under the reaction conditions, thus reducing the purity of the amide or peptide and leading to protracted product purification. Hence, there has always been an interest in amide- or peptide-bond-forming reactions under milder conditions so as not to cause any racemization of any existing chiral centers.

A series of chiral, α-substituted carboxylic acids reacted with sensitive

α-functionalized chiral isocyanates at 0 °C in dichloromethane and in the presence of a catalytic amount of DMAP to form amides in high yields without racemization at either of the chiral centers (**eq 4**).[12a] Similar reactions carried out in pyridine at higher temperatures (> 60 °C) resulted in extensive racemization.[12b]

2.4. Acylation with Activation

The large-scale conversion of carboxylic acid **7** to amide **8** was investigated by Zanka and coworkers.[13] The activation system $SOCl_2$/DMF/DCM[14] gave a low yield (34%) of **8** in the presence of *N*-methylmorpholine. Replacement of *N*-methylmorpholine with TEA gave a good yield, but provided a dark-colored product. In contrast, use of a catalytic amount of DMAP with TEA resulted in an excellent yield of high-quality **8** (**eq 5**).[13]

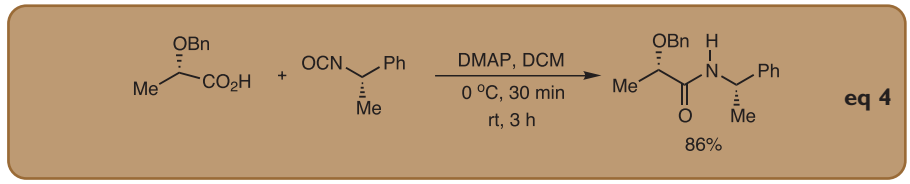
A recent review of the CP molecule labyrinth by Nicolaou and Baran included the report of a successful model study for the one-carbon homologation of aldehydes to nitriles by a cyanohydrin formation–deoxygenation sequence. The mild deoxygenation of the cyanohydrin was achieved by the DMAP-catalyzed acylation of the hydroxyl group with thiocarbonyldiimidazole, followed by reduction with tri-*n*-butyltin hydride (**eq 6**).[15]

Ferrocenyl esters have been synthesized using DCC/DMAP in the ambient-temperature ionic liquids (RTILs) 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and its hexafluorophosphate ([bmim][PF_6]) (**eq 7**). High yields and efficient recycling of the solvent characterized these reactions.[16] It is noteworthy that nonvolatile RTILs can be substituted for DCM in these types of reactions.

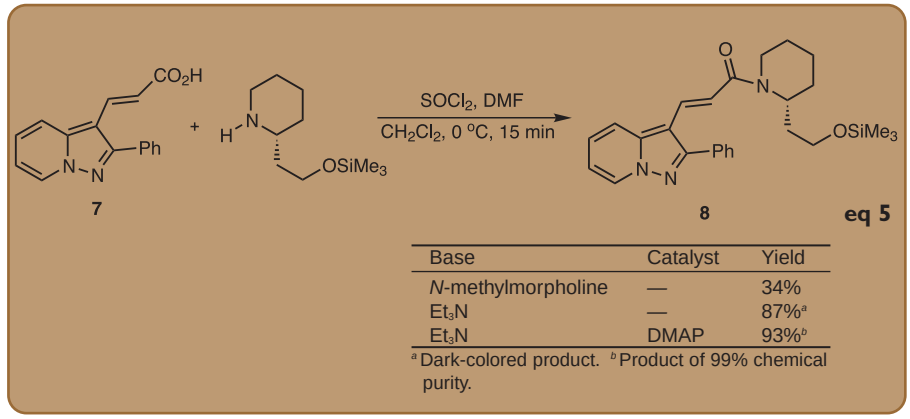
Removal of DMAP from the products of a reaction can present difficulties. In the combinatorial synthesis of acylsulfonamides **9**, 95% of DMAP was removed from the reaction mixture using Amberlyst® A-15 followed by filtration (**eq 8**).[17]

2.5. Transesterification

Transesterification is an equilibrium-controlled process that can be catalyzed most effectively by DMAP. However, in order to achieve a reasonable yield of the product, usually an excess of the alcohol to be acylated is used. In the case of some methyl β-ketocarboxylates, transesterification has been accomplished by using only one equivalent of high-boiling alcohols in the presence of a catalytic amount of DMAP (**eq 9**).[18] This has been achieved by removing the methanol formed as an azeotrope with cyclohexane. This azeotrope is formed in the



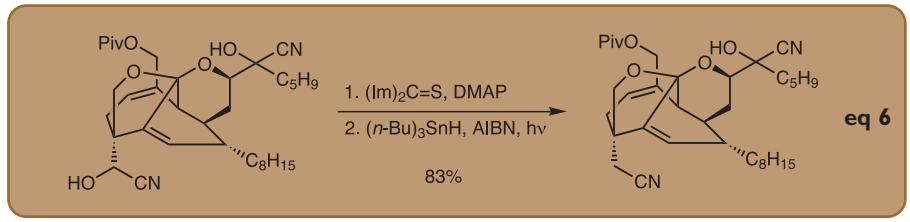
eq 4



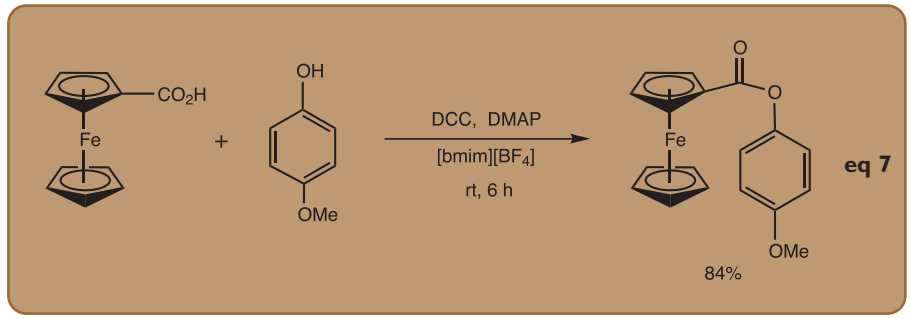
eq 5

Base	Catalyst	Yield
N-methylmorpholine	—	34%
Et_3N	—	87%[a]
Et_3N	DMAP	93%[b]

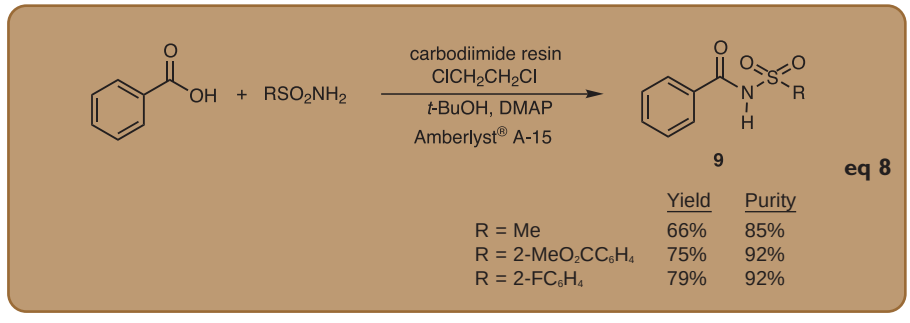
[a] Dark-colored product. [b] Product of 99% chemical purity.



eq 6

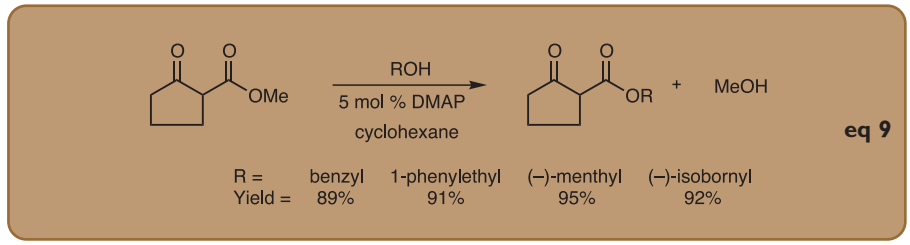


eq 7



eq 8

	Yield	Purity
R = Me	66%	85%
R = 2-$MeO_2CC_6H_4$	75%	92%
R = 2-FC_6H_4	79%	92%



eq 9

R =	benzyl	1-phenylethyl	(–)-menthyl	(–)-isobornyl
Yield =	89%	91%	95%	92%

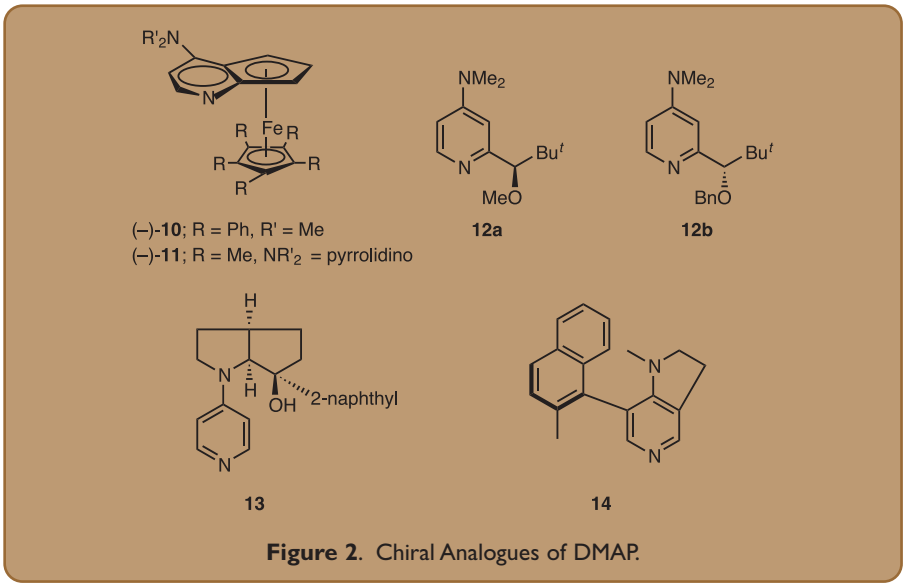
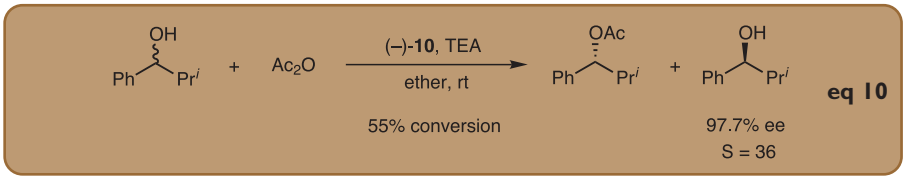
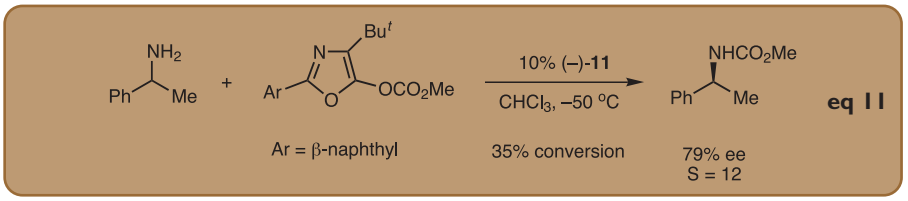
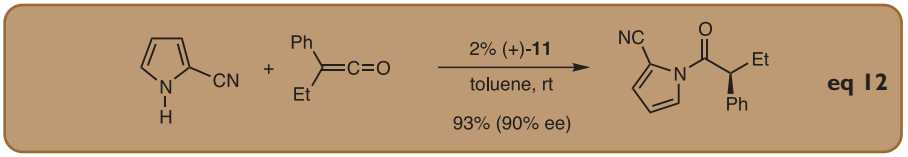
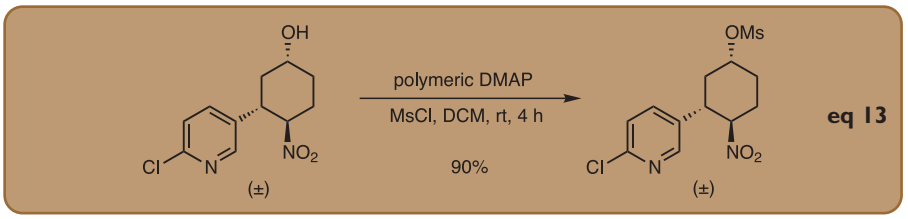


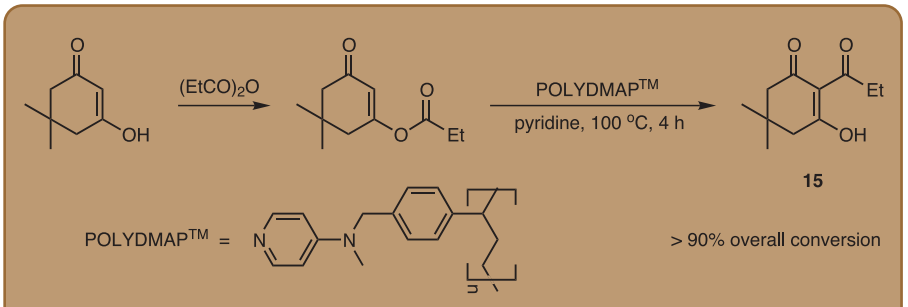
Figure 2. Chiral Analogues of DMAP.











Scheme 2. Synthesis of Model Trione from Dimedone.

vapor phase but its components, cyclohexane and methanol, are not miscible at ambient temperature in the condensed phase.

3. Chiral DMAP Analogues for Kinetic Resolution

3.1. Resolution of Alcohols

Several chiral analogues of DMAP (**Figure 2**) have recently been reported by the groups of Fu (**10**, **11**),[19] Vedejs (**12**),[20] Fuji (**13**),[21] and Spivey (**14**; the chirality of this compound stems from the restricted rotation about the aryl–aryl bond).[22] These analogues have been used for the chiral resolution of alcohols.[23] Fu and co-workers[19] acetylated a series of secondary alcohols using 2 mol % of (–)-**10** and triethylamine in ether at room temperature. They observed a selectivity of S = 36 and an ee of 97.7% for the unreacted alcohol at 55% conversion (**eq 10**).

Quasienantiomeric dimethylaminopyridines **12a** and **12b** can act in an equal but opposite sense just like enantiomers. The different chloroformate derivatives of **12a** and **12b** have been used under stoichiometric conditions in the parallel kinetic resolution of 1-(1-naphthyl)ethanol to give high yields of quasienantiomeric carbonates, which are much easier to separate than racemates.[20,24]

3.2. Resolution of Amines

Fu's group then took on the further challenge of resolving amines using catalyst **11**.[25] Here, they had to overcome the direct easy acylation of the very basic amines without involvement of the chiral catalyst. They had found from previous work[26] an O-acylated azlactone that reacted much more readily with (–)-**11** than with a primary amine. They exploited this azlactone for the kinetic resolution of racemic 1-phenylethylamine (**eq 11**).[25] By conducting the reaction at –50 °C and adding the acylating agent in two batches, the resolution of 1-phenylethylamine was achieved with a selectivity factor of 12. The experiment resulted in 35% conversion of 1-phenylethylamine into the carbamate with a 79% ee, leaving unreacted 1-phenylethylamine with a 42% ee.

The first enantioselective addition of amines to ketenes catalyzed by a planar chiral derivative of 4-(pyrrolidino)pyridine (PPY), (–)-**11**, has been reported by Hodous and Fu.[27] The enantioselective attack has been explained by invoking a possible intervention of a chiral Brønsted acid (protonated form of **11**) catalyst (**eq 12**). The *N*-acylpyrrole products are easily transformed into chiral acids, amides, or esters.

4. Polymeric Dialkylaminopyridines as Catalysts

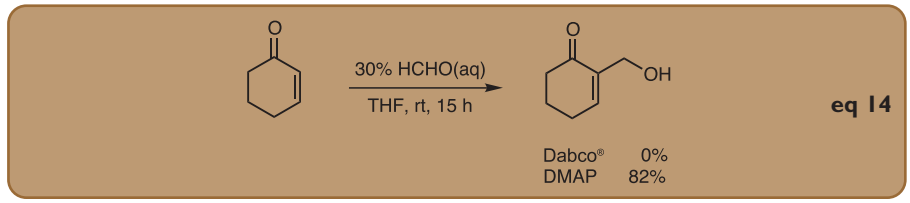
Rhodium supported on polymeric DMAP is an efficient catalytic system in the chemoselective hydrogenation of α,β-unsaturated aldehydes to allylic alcohols with formic acid.[28] Ley and coworkers[29] have synthesized the potent analgesic (±)-epibatidine in ten steps by using a sequence of polymer-supported reagents. One step involves the use of a polymer-supported aminomethylpyridine, an alcohol, and mesyl chloride in DCM to afford a 90% yield of the mesyl derivative of the alcohol (**eq 13**).

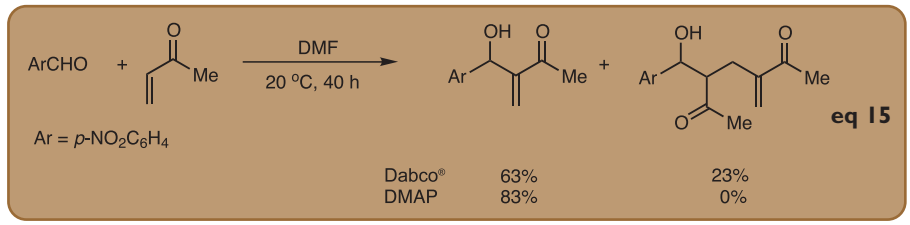
We have studied[30] the acylation (followed by a Fries rearrangement) of dimedone with propionic anhydride. The sequence leads to trione **15**, which is a model for the types of intermediates encountered in the production of trione herbicides.[31] In the absence of DMAP, only a low yield of **15** is obtained; in the presence of DMAP the yield increases to 89%. We have also used POLYDMAP™ for this reaction with great success. A conversion of over 90% of dimedone to **15** has been observed over 20 cycles (10 mol % loading, pyridine, 100 °C, 4 h).[30] However, when the sequence is run in pyridine with no added POLYDMAP™, it stops at the intermediate ester stage (**Scheme 2**).

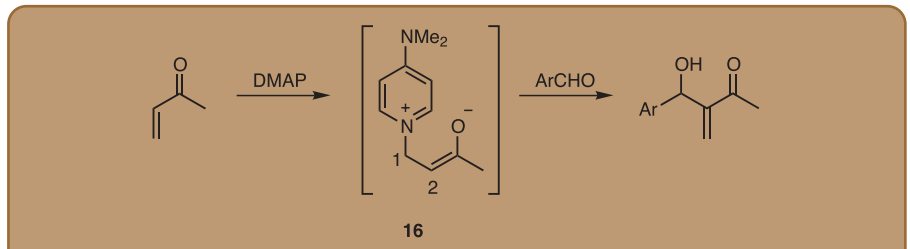
5. Baylis–Hillman Reaction

Baylis and Hillman were the first to report the strong-base-catalyzed reaction of aldehydes with acrylates at C-2.[32] Prior to this report, Morita et al. had observed a similar alkylation using tricyclohexylphosphine as catalyst.[33] The observation by Baylis and Hillman lay dormant in the patent literature for ten years or so. Lately, it has become of interest as an important method for producing highly functionalized acrylates for further synthetic transformations.[34] Until recently, mainly Dabco® and tributylphosphine were favored as catalysts, but now DMAP is starting to be used and it gives contrasting results.

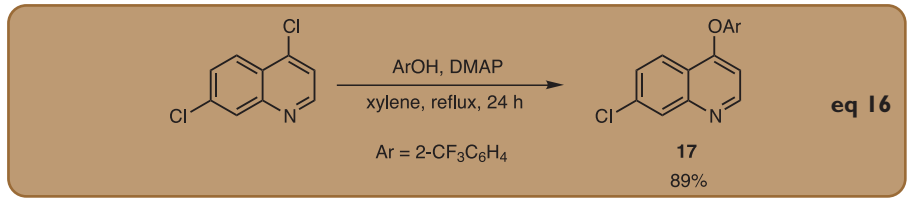
Use of Dabco® as catalyst for the hydroxymethylation of cyclohexenone gave no reaction, however DMAP was found to be a very effective catalyst (**eq 14**).[35] The Dabco®-catalyzed reaction of aryl aldehydes with methyl vinyl ketone gave a diadduct in some cases (**eq 15**).[36] This diadduct was not observed when DMAP was employed, and the yield of the expected product increased. Very recently, DMAP has been compared with Dabco® and several other bases and has been found to be as good a catalyst as Dabco® or PPh_3 in the reaction of arylimines with methyl vinyl ketone to form the normal Baylis–Hillman adducts.[37]

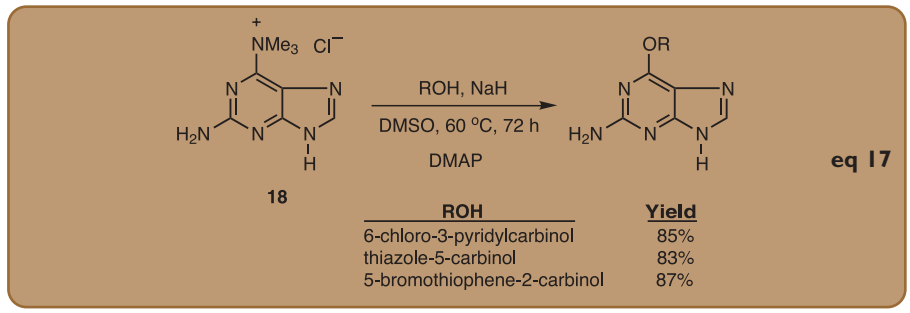






Scheme 3. Postulated Mechanism of the Baylis–Hillman Reaction.





The mechanism of the Baylis–Hillman reaction is believed to involve initial conjugate addition of the catalyst to methyl vinyl ketone to give a dipolar intermediate, **16**, that should be well stabilized in the case of DMAP. This intermediate then undergoes reaction with an aldehyde or imine (**Scheme 3**).[36,37]

6. Nucleophilic Substitutions

DMAP is an effective catalyst for some nucleophilic aromatic substitution reactions. Substituted 4-phenoxyquinolines are valuable plant fungicides and are generally prepared by condensing a substituted 4-haloquinoline with an excess of a substituted phenol, preferably by refluxing in xylene overnight. In order to accelerate the rate of the desired reaction as well as not to use an excess of the phenol, DMAP has been used as an effective catalyst. For example, 4,7-dichloroquinoline undergoes nucleophilic attack at the 4 position to give aryloxyquinoline **17** faster and in better yields, as compared to the uncatalyzed reaction, when the reaction is carried out in the presence of DMAP, PPY, or POLYDMAP™ (**eq 16**).[38]

DMAP also facilitated O^6-substitution in guanines **18**.[39] In this case, the proposed 4-dimethylaminopyridinium intermediate was isolated (**eq 17**).

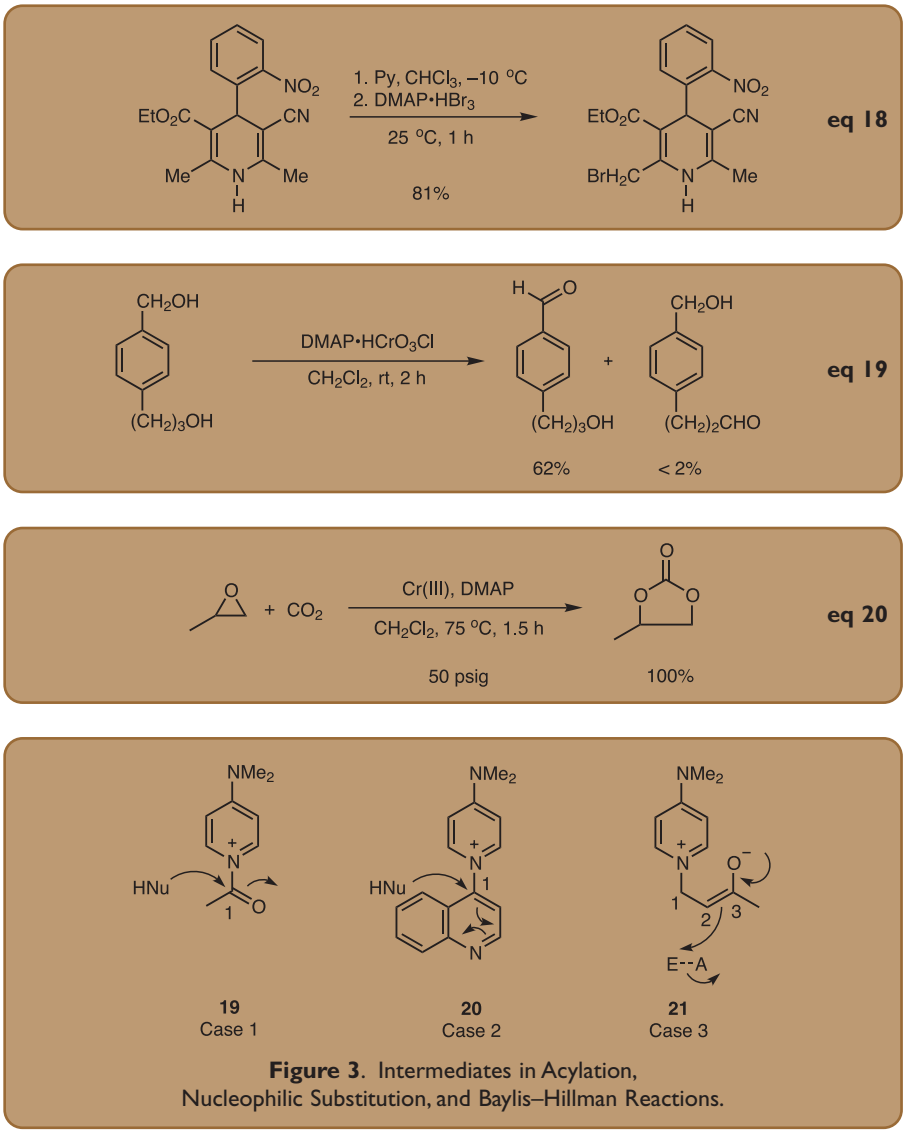


Figure 3. Intermediates in Acylation, Nucleophilic Substitution, and Baylis–Hillman Reactions.

7. Reagents Supported on DMAP

7.1. Halogens

4-Dimethylaminopyridinium bromide perbromide, an orange solid, has been prepared by treating DMAP with HBr and bromine. This reagent has been used in the monobromination of ketones at the α position,[40] as well as in a regioselective bromination of a 1,4-dihydropyridine derivative (**eq 18**).[41]

7.2. Metals

A complex of chromium trioxide with DMAP selectively oxidizes benzylic and allylic alcohols in the presence of other alcohols (**eq 19**).[42] Chromium complexes work better in the presence of DMAP as catalyst in the reaction of epoxides with carbon dioxide to form cyclic carbonates (**eq 20**).[43]

The ionic liquid [bmim]PF_6 has been employed in combination with DMAP in a simple and practical approach for immobilizing OsO_4 as catalyst for olefin dihydroxylation. Both catalyst and ionic liquid were repeatedly recycled and reused in the dihydroxylation of a variety of olefins with minimal loss in catalytic activity.[44]

7.3. Other Reagents

Thionyl chloride supported on DMAP, called 4-(dimethylamino)pyridinium chlorosulfite chloride, has been used in the synthesis of esters and amides from carboxylic acids, in the dehydration of oximes to nitriles, and in the synthesis of chlorosilanes from silanols.[45]

8. Prospects

Several thousand papers and patents that refer to the use of DMAP have appeared since the 1970s. We expect this intense interest to continue, led principally by the use of DMAP in the catalysis of acylation reactions under mild conditions to achieve or maintain regio- and stereochemical integrity. Cleaner reactions through the use of ionic liquids rather than volatile solvents are likely to become more common, and more effective ways to recover and recycle DMAP may be found. Polymeric forms of DMAP are increasingly being used to address recycle and separation concerns and to support metal catalysts.

It is interesting to contrast the reactivities of the DMAP intermediates **19** and **20**, where nucleophilic attack at C-1 is promoted, with **21**, where electrophilic attack at C-2 is promoted (**Figure 3**). Case 1 is representative of a large number of DMAP-catalyzed reactions (Sections 2, 3, and 4 of this review), and its mechanism is discussed in Section 1. Case 2 is ostensibly the promotion of a nucleophilic substitution by DMAP; however, it may be considered a series of (conjugate) addition–elimination reactions. This case may be viewed as a vinylogue of Case 1. Examples of Case 2 have rarely been observed to date, however extension to other systems would seem possible.

Case 3 involves firstly Michael addition of DMAP to a conjugate system to give intermediate **21**, which is an example of a DMAP-stabilized enolate anion. For example, DMAP has been more effective than Dabco® in the case of cyclohexenone (eq 14). One might consider the use of DMAP as a catalyst to extend, via DMAP-stabilized enolate anions, the scope of the Baylis–Hillman reaction to include new electrophiles. Currently, it is limited mainly to aldehydes and imines. This discussion of Cases 1, 2, and 3 is intended to suggest to the reader that DMAP is not just an acylation supercatalyst, but that it also has potential to facilitate many more reactions yet to be discovered in conjugated carbonyl and related systems.

It is worth noting that DMAP has also been utilized in areas outside organic synthesis. For example, DMAP has a stabilizing effect on nanoparticles through noncovalent interactions, thus making it possible to have high concentrations of metal nanoparticles in solution.[46] However, these applications fall outside the scope of this review.

9. References

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Ramiah Murugan was born in Madurai, India. He obtained his B.Sc. (Special) degree in chemistry from the American College and his M.Sc. degree in chemistry from Madurai University. He received his Ph.D. degree in chemistry from the University of Florida in 1987, working with Prof. Alan R. Katritzky. Following a couple of years of postdoctoral research in high-temperature aqueous organic chemistry in the laboratory of Professor Katritzky at the University of Florida, he joined Reilly Industries, Inc. His expertise is in heterocyclic chemistry. He has conducted research related to the synthesis of intermediates for pharmaceuticals, agrochemicals, and performance products; mechanistic studies; catalysis; polymer chemistry; and process development.

Eric F. V. Scriven was born in Pembrokeshire, Wales. He graduated from the University of Salford, U.K., obtained his M.Sc. degree from the University of Guelph, Canada, and received his Ph.D. from the University of East Anglia (with Prof. A. R. Katritzky) in 1969. After postdoctoral years at the University of Alabama and University College, London, he returned to the University of Salford in 1971, where he investigated the chemistry of aryl azides and nitrenes. While at Salford, he spent two semesters on secondment at the University of Benin, Nigeria. He joined Reilly Tar & Chemicals in 1979 and became director of R&D in 1991. He was editor of *Azides & Nitrenes* (1984) and a founding editor (with Prof. H. Suschitzky) of *Progress in Heterocyclic Chemistry* (1989). He also collaborated with A. R. Katritzky and C. W. Rees as editors in chief of *Comprehensive Heterocyclic Chemistry II* (1997). His current research interests are in heterocyclic chemistry, the applications of polymers in organic synthesis, ionic liquids, and in extensions of the Baylis–Hillman reaction.

DMAP and Other Heterocyclic Amines

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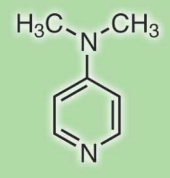

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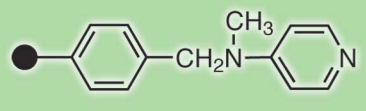

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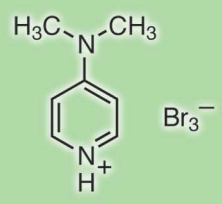

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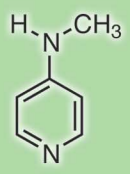

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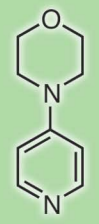

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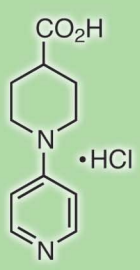

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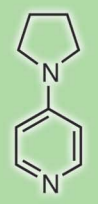

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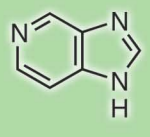

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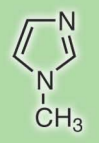

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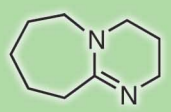

13,900-9

4-Aminopyridines

52,280-5 **4-(Dimethylamino)pyridine**, 99+%
10,770-0 **4-(Dimethylamino)pyridine**, 99%
52,282-1 **4-(Dimethylamino)pyridine**, prilled, 99%
35,988-2 **Dimethylaminopyridine, polymer-bound**, 5.5-6.0 mmol N/g
28,990-6 **4-(Dimethylamino)pyridinium tribromide**
19,551-0 **4-(Methylamino)pyridine**, 98%
48,065-7 **4-Morpholinopyridine**, 97%
57,243-8 **1-(4-Pyridinyl)-4-piperidinecarboxylic acid monohydrochloride**, 98%
21,337-3 **4-Pyrrolidinopyridine**, 98%

Other Heterocyclic Amines

56,183-5 **5-Azabenzimidazole**, 97%
33,609-2 **1-Methylimidazole**, redistilled, 99+%
M5,083-4 **1-Methylimidazole**, 99%
29,073-4 **Dabco® 33-LV** (1,4-diazabicyclo[2.2.2]octane)
D2,780-2 **1,4-Diazabicyclo[2.2.2]octane** (Dabco®), 98%
13,900-9 **1,8-Diazabicyclo[5.4.0]undec-7-ene**, 98%

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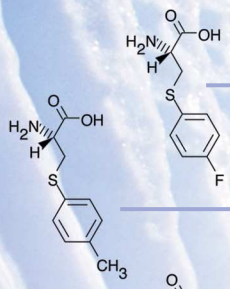
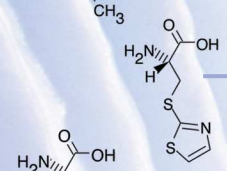
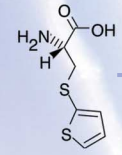


40209 ***S*-(4-Fluorophenyl)-L-cysteine**, (*R*)-2-amino-3-(4-fluorophenylthio)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_9H_{10}FNO_2S$ M_r 215.25 [331-90-8] 1g; 5g

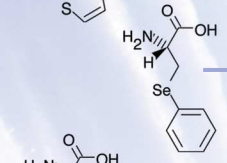
79256 ***S*-(*p*-Tolyl)-L-cysteine**, (*R*)-2-amino-3-(*p*-tolylthio)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_{10}H_{13}NO_2S$ M_r 211.28 – 1g; 5g



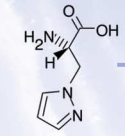
78904 ***S*-(2-Thiazolyl)-L-cysteine**, (*R*)-2-amino-3-(2-thiazolylthio)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_6H_8N_2O_2S_2$ M_r 204.27 [405150-20-1] 1g



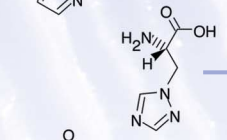
95631 ***S*-(2-Thienyl)-L-cysteine**, (*R*)-2-amino-3-(2-thienylthio)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_7H_9NO_2S_2$ M_r 203.3 – 1g



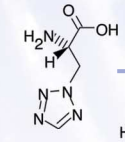
50827 ***Se*-Phenyl-L-selenocysteine**, (*R*)-2-amino-3-(phenylseleno)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_9H_{11}NO_2Se$ M_r 244.15 [71128-82-0] 1g



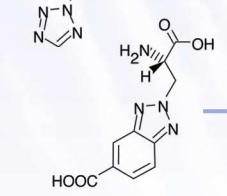
06993 **3-(1-Pyrazolyl)-L-alanine**, (*S*)-2-amino-3-(1-pyrazolyl)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_6H_9N_3O_2$ M_r 155.15 [2734-48-7] 1g



12227 **3-(1,2,4-Triazol-1-yl)-L-alanine**, (*S*)-2-amino-3-(1,2,4-triazol-1-yl)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_5H_8N_4O_2$ M_r 156.14 [4819-36-7] 1g



21682 **3-(2-Tetrazolyl)-L-alanine**, (*S*)-2-amino-3-(2-tetrazolyl)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_4H_7N_5O_2$ M_r 157.1 – 1g



48921 **3-(5-Carboxy-2*H*-benzotriazol-2-yl)-L-alanine**
(*S*)-2-amino-3-(5-carboxy-2*H*-benzotriazol-2-yl)propionic acid
purum, ≥95.0% (HPLC); **ee >99%** $C_{10}H_{10}N_4O_4$ M_r 250.21 [405150-18-7] 1g

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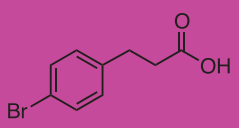
59,543-8
$C_9H_9BrO_2$



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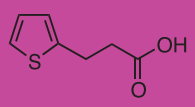

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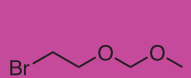

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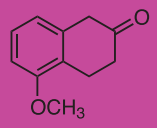

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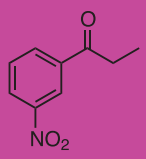
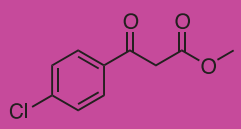
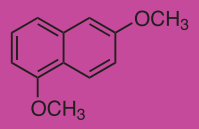
$C_9H_9NO_3$



59,044-4
$C_{10}H_9ClO_3$



57,925-4
$C_{12}H_{12}O_2$



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57,792-8
$C_6H_{18}LiNSi_2$

$LiN(SiMe_3)_2$

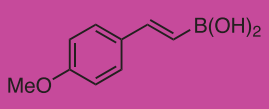
Lithium bis(trimethylsilyl)amide, 1.0*M* solution in toluene

57,701-4
$C_6H_{18}LiNSi_2$

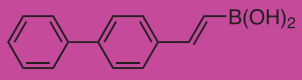
$LiN(SiMe_3)_2$

Lithium bis(trimethylsilyl)amide, 1.0*M* solution in *tert*-butyl methyl ether (TBME)

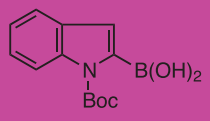
51,898-0
$C_9H_{11}BO_3$



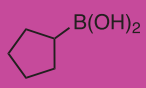
52,604-5
$C_{14}H_{13}BO_2$



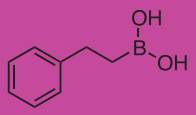
56,233-5
$C_{13}H_{16}BNO_4$



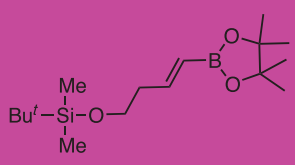
58,841-5
$C_5H_{11}BO_2$



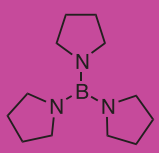
58,842-3
$C_8H_{11}BO_2$



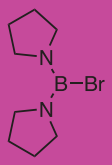
58,884-9
$C_{16}H_{33}BO_3Si$



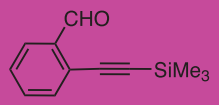
59,054-1
$C_{12}H_{24}BN_3$



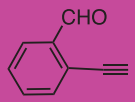
59,211-0
$C_8H_{16}BBrN_2$



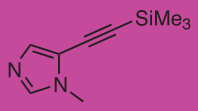
59,061-4
$C_{12}H_{14}OSi$



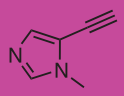
59,063-0
C_9H_6O



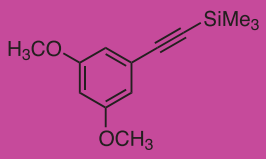
57,802-9
$C_9H_{14}N_2Si$



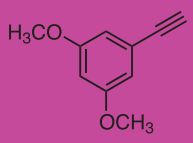
57,871-1
$C_6H_6N_2$



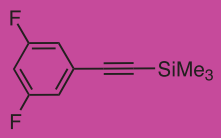
58,850-4
$C_{13}H_{18}O_2Si$



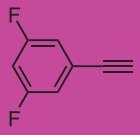
58,852-0
$C_{10}H_{10}O_2$



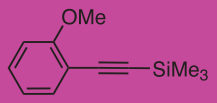
58,933-0
$C_{11}H_{12}F_2Si$



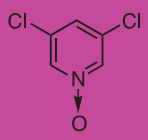
59,017-7
$C_8H_4F_2$



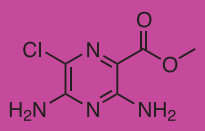
59,805-4
$C_{12}H_{16}OSi$



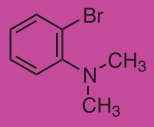
59,651-5
$C_5H_3Cl_2NO$



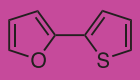
59,683-3
$C_6H_7ClN_4O_2$



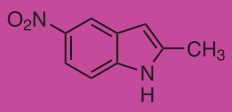
59,051-7
$C_8H_{10}BrN$



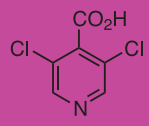
59,077-0
C_8H_6OS



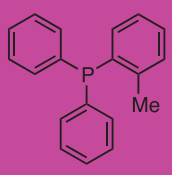
52,059-4
$C_9H_8N_2O_2$



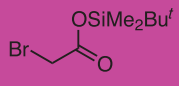
57,488-0
$C_6H_3Cl_2NO_2$



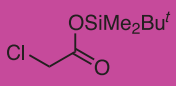
28,793-8
$C_{19}H_{17}P$



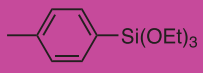
58,886-5
$C_8H_{17}BrO_2Si$



58,963-2
$C_8H_{17}ClO_2Si$



59,157-2
$C_{13}H_{22}O_3Si$



Aldrich Spectral Viewer™

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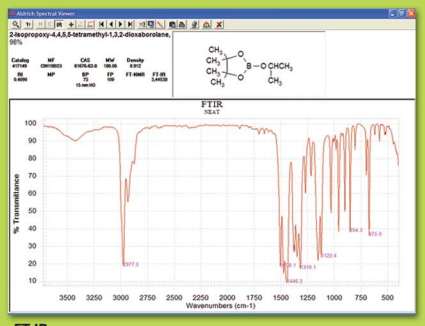
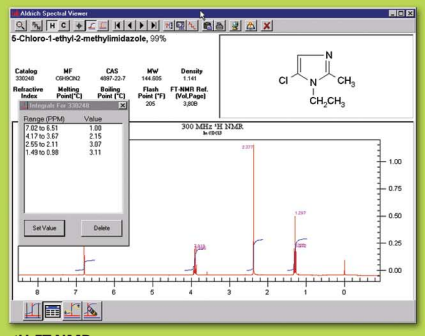
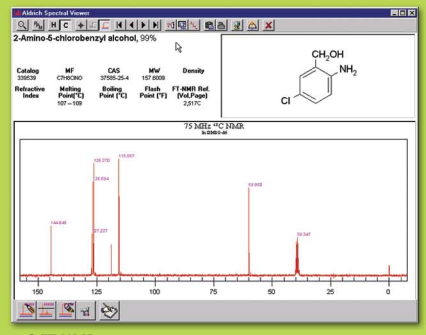


FT-IR



^{1}H FT-NMR



^{13}C FT-NMR

The Aldrich Spectral Viewer is an electronic reference book on CD-ROM that contains spectra from the Aldrich FT-IR and FT-NMR libraries. This easy-to-use software program is more powerful than a printed book, allowing text and data field searching, and the manipulation, printing, and exporting of spectra.

The libraries may be used individually or may be combined together. The full set of libraries includes FT-IR spectra for over 11,000 compounds and FT-NMR spectra (both 300 MHz ^{1}H and 75 MHz ^{13}C spectra) for over 15,000 compounds.

Features:

- **Displays FT-IR spectra or FT-NMR spectra** with chemical structure, and technical data.
- **Text searching** by Chemical Name, Aldrich Catalog Number, CAS Number, and Molecular Formula.
- **Advanced data field searching** on Chemical Category and physical properties such as Boiling Point, Melting Point, Density, Flash Point, Molecular Weight, and Refractive Index.
- **Spectra processing** using Zoom, Peak Integration (NMR only), and Peak Labeling.
- **Print** spectra, structure, technical data, integral table, and peak listings.
- **Export** spectra to a file (bitmap, metafile, or JPEG formats) or to the clipboard (bitmap or metafile formats).
- **Web link** button provides additional technical data from the Sigma-Aldrich website.
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	FT-IR 2002 library (11,000 compounds)	FT-NMR standard library (11,800 compounds)	FT-NMR 2001 supplemental library (3,500 compounds)
Version	Cat. No.	Cat. No.	Cat. No.
Single user, commercial	Z54,016-1	Z54,126-5	Z53,808-6
Single user, academic	Z54,028-5	Z54,138-9	Z53,818-3
Network	Z54,039-0	Z54,149-4	Z53,797-7
Demo program	Z54,159-1		

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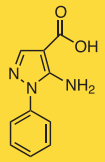
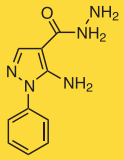
L25,198-4

$C_{10}H_9N_3O_2$
MW 203.20



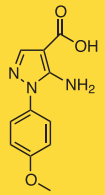
L25,153-4

$C_{10}H_{11}N_5O$
MW 217.23



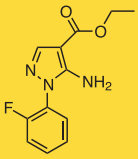
L25,202-6

$C_{11}H_{11}N_3O_3$
MW 233.23



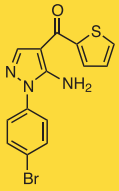
L25,152-6

$C_{12}H_{12}FN_3O_2$
MW 249.25



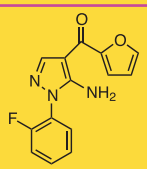
L25,226-3

$C_{14}H_{10}BrN_3OS$
MW 348.22



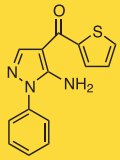
L25,221-2

$C_{14}H_{10}FN_3O_2$
MW 271.25



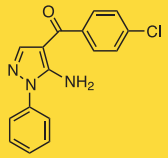
L25,209-3

$C_{14}H_{11}N_3OS$
MW 269.33



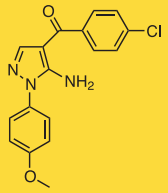
L25,167-4

$C_{16}H_{12}ClN_3O$
MW 297.75



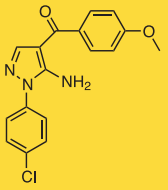
L25,174-7

$C_{17}H_{14}ClN_3O_2$
MW 327.77



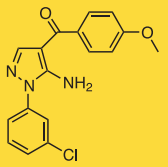
L25,179-8

$C_{17}H_{14}ClN_3O_2$
MW 327.77



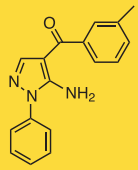
L25,191-7

$C_{17}H_{14}ClN_3O_2$
MW 327.77



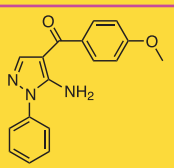
L25,170-4

$C_{17}H_{15}N_3O$
MW 277.33



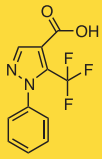
L25,166-6

$C_{17}H_{15}N_3O_2$
MW 293.33



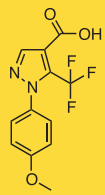
L25,136-4

$C_{11}H_7F_3N_2O_2$
MW 256.19



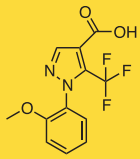
L25,139-9

$C_{12}H_9F_3N_2O_3$
MW 286.21



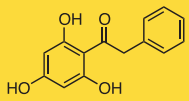
L25,143-7

$C_{12}H_9F_3N_2O_3$
MW 286.21



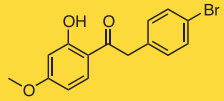
L25,120-8

$C_{14}H_{12}O_4$
MW 244.25



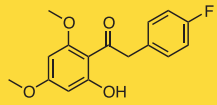
L25,118-6

$C_{15}H_{13}BrO_3$
MW 321.17



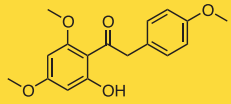
L25,128-3

$C_{16}H_{15}FO_4$
MW 290.29



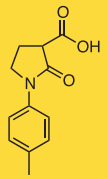
L25,127-5

$C_{17}H_{18}O_5$
MW 302.33



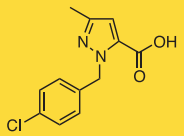
L18,293-1

$C_{12}H_{13}NO_3$
MW 219.24



L20,129-4

$C_{12}H_{11}ClN_2O_2$
MW 250.69



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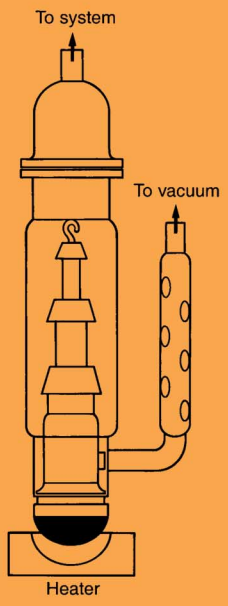

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- Pumping speed: 375 L/s
- Safely reduces sublimation and distillation temperatures
- All-glass construction with removable jet assembly for easy cleaning
- Chemically resistant to acidic solvents
- Includes step-by-step installation guide
- Overall dimensions (standard): 24 in. x 12 in.
- Overall dimensions (mini): 15 in. x 7 in.

Pump model	Max. vacuum (torr)	Cat. No.
Standard	10^{-9}	**Z54,478-7**
Mini	10^{-6}	**Z54,531-7**

Equipment Required for Diffusion Pump Operation

Description		Cat. No.
Mechanical vacuum pump, 160 Lpm minimum pumping speed		
Leybold TRIVAC® B, D8B, 197 Lpm	115V	**Z28,459-9**
	220V	**Z28,282-0**
Glas-Col® heating mantle, 500 mL	115V	**Z28,485-8**
	230V	**Z28,514-5**
Digitrol II heat controller (required for operation)		
	120V	**Z28,549-8**
	240V	**Z28,550-1**
Diffusion pump oil (250 mL required for operation)		
Dow Corning®, Type 704, 10^{-6} to 10^{-8} torr		**44,597-5**
Dow Corning®, Type 705, 10^{-9} to 10^{-10} torr		**44,598-3**
Vacuum tubing, latex rubber, 5/16 in. (i.d.)		**Z25,587-4**

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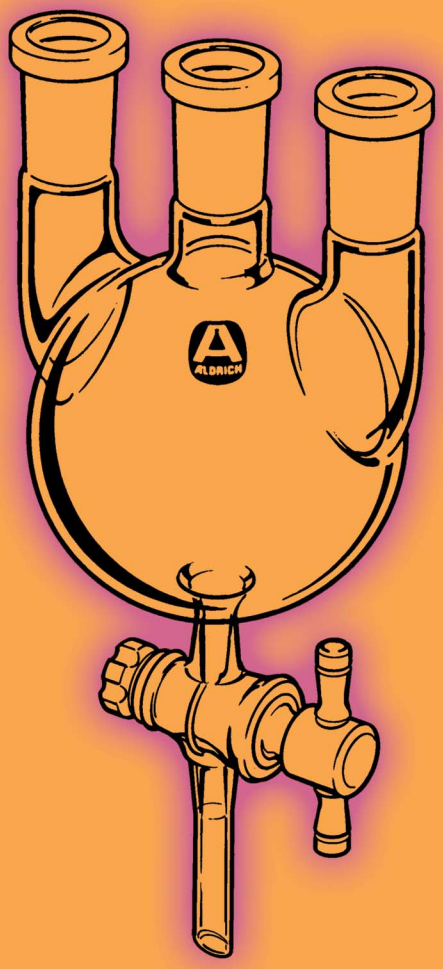

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Cap. (mL)	⅀ joints	Cat. No.
50	14/20	**Z53,294-0**
100	14/20	**Z53,295-9**
100	24/40	**Z53,296-7**
250	14/20	**Z53,297-5**
250	24/40	**Z53,298-3**
250	29/32	**Z53,299-1**
500	14/20	**Z53,300-9**
500	24/40	**Z53,301-7**
500	29/32	**Z53,302-5**
500	34/45 (24/40 side)	**Z53,303-3**
1000	24/40	**Z53,304-1**
1000	29/32	**Z53,306-8**
1000	34/45 (24/40 side)	**Z53,307-6**

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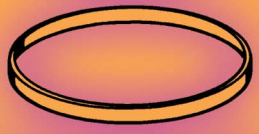
- Protection for air- and moisture-sensitive compounds
- Can be used for prolonged storage of volatile and sensitive chemicals
- Slide easily onto medium- and full-length joints
- Temp. range: up to 300 °C



PTFE Sealing Ring

For ⅀ joints	Cat. No.
10/30	**Z50,198-0**
14/10, 14/20, 14/35	**Z50,208-1**
19/22, 19/38	**Z50,220-0**
24/25, 24/40	**Z50,231-6**
29/26, 29/42	**Z50,241-3**
45/50	**Z50,252-9**

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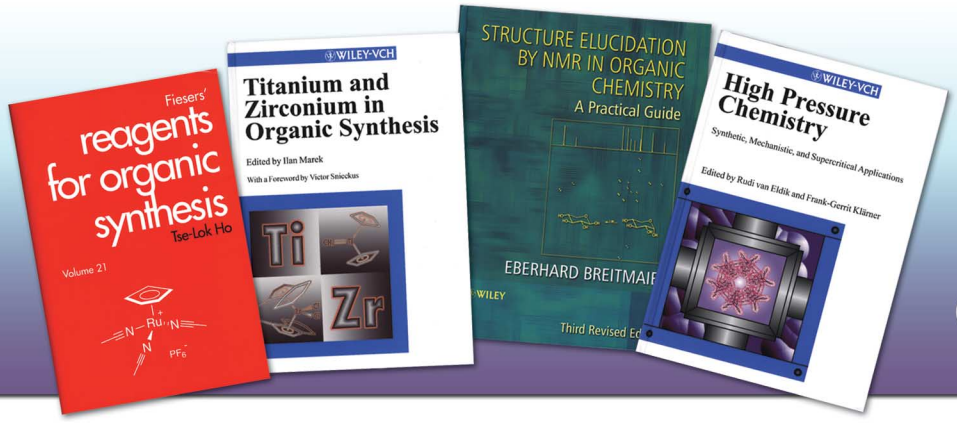

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5th ed., W.L.F. Armarego and C. Chai, Butterworth-Heinemann, Stoneham, MA, 2003, 608pp. Softcover. A classic reference that shows how to purify chemical reagents. Overviews physical techniques and chemical methods used for purification in modern laboratories. Includes general procedures for purifying certain classes of organic compounds and individual entries on substances with details on how they can be purified. Most entries also include literature references.

Z54,183-4

Microwaves in Organic Synthesis

A. Loupy, Ed., John Wiley & Sons, New York, NY, 2003, 524pp. Hardcover. Microwave technology is developing into a powerful alternative that can be applied to practically the whole spectrum of organic synthesis. This volume brings together the latest developments in this fascinating field, supplemented by numerous practical tips.

Z54,171-0

Structure Elucidation by NMR in Organic Chemistry: A Practical Guide

3rd ed., E. Breitmaier, John Wiley & Sons, New York, NY, 2003, 270pp. Hardcover. Provides a systematic guide to unraveling structural information from the NMR spectra of unknown synthetic and natural compounds. Offers an overview of basic principles and elementary instrumental methods of NMR spectroscopy with instructional strategy and tactical advice on how to translate spectra into meaningful structural information.

Z51,518-3

High Pressure Chemistry: Synthetic, Mechanistic, and Supercritical Applications

R. van Eldik and F.-G. Klärner, Eds., John Wiley & Sons, New York, NY, 2002, 474pp. Hardcover. This book is a compact source of technical data, references, and detailed synthetic procedures. Covers the most recent advances in apparatus, methods for monitoring high-pressure synthesis, mechanistic insights, fields of application, and more. Offers a clear, application-oriented approach.

Z54,127-3

Organic Synthesis on Solid Phase: Supports, Linkers, Reactions

2nd ed., F.Z. Dörwald, John Wiley & Sons, New York, NY, 2002, 554pp. Hardcover. Now in its second, expanded edition, this book offers a clear, comprehensive overview of supports, spacers, and linkers with 15% more material than the previous edition. Provides numerous experimental guidelines and literature references.

Z54,106-0

Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products

A. Padwa and W.H. Pearson, Eds., John Wiley & Sons, New York, NY, 2002, 952pp. Softcover. Provides a comprehensive, current reference for the synthesis of complex molecules based on cycloaddition reactions. Updating Padwa's popular 1984 volume, this new edition shifts the text's focus from theory, structure, reactivities, and selectivities to synthetic applications. Both carbonyl ylides and nitronates, important members of the 1,3-dipole family that were not reviewed previously, are now included.

Z54,117-6

Titanium and Zirconium in Organic Synthesis

I. Marek, Ed., John Wiley & Sons, New York, NY, 2002, 538pp. Hardcover. Summarizes the numerous applications and developments of these two group IV early-transition-metal complexes. Internationally renowned experts and leading scientists in this field cover all the significant aspects of this increasingly important part of organic chemistry. Includes typical experimental procedures.

Z54,084-6

Chemistry Connections: The Chemical Basis of Everyday Phenomena

K.K. Karukstis and G.R. Van Hecke, Academic Press, New York, NY, 2000, 226 pp. Hardcover. Provides a collection of contemporary real-world examples of chemistry in action, written in a question-and-answer format with presentations. Describes the chemical principles underlying numerous, familiar phenomena in both lay and technical terms.

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V.K. Ahluwalia and R.K. Parashar, CRC Press, Boca Raton, FL, 2002, 609pp. Hardcover. Covers all aspects of organic reaction mechanisms, named and unnamed, reviewing the chemical kinetics and mechanisms of the various types of molecular rearrangements. Provides extensive coverage of various organic reactions and rearrangements with emphasis on their applications in synthesis.

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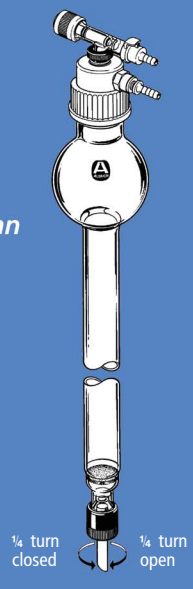
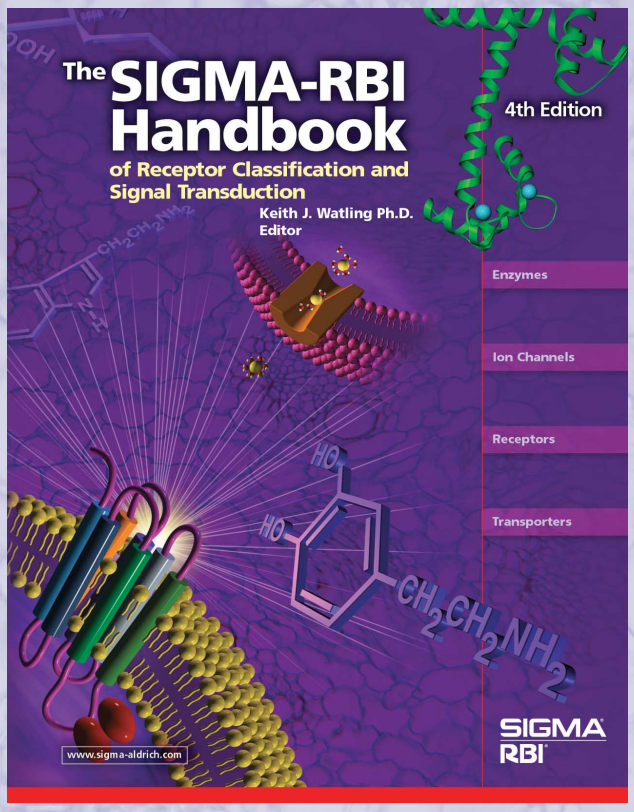
15 x 250	40	Z40,059-9	Z40,064-5
19 x 300	80	Z40,060-2	Z40,065-3
25 x 300	150	Z40,061-0	Z40,066-1
50 x 300	560	Z40,062-9	Z40,068-8





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SPECIAL FOCUS ON NONRACEMIC AZIRIDINES AND OXAZOLINES

Aldrichimica ACTA

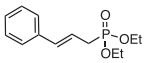
VOL. 36, NO. 2 • 2003

Aziridines and Oxazolines: Valuable Intermediates in the Synthesis of Unusual Amino Acids

Highlights of the Chemistry of Enantiomerically Pure Aziridine-2-carboxylates

New Products from Aldrich R&D

Diethyl *trans*-cinnamylphosphonate, 98%

59,438-5  5g, 25g

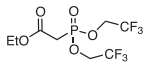
Diethyl (2-methylallyl)phosphonate, 97%

59,309-5  1g

These phosphonates were utilized in the Horner–Wadsworth–Emmons reaction to form conjugated carbon–carbon double bonds.[1] They were also employed as starting materials in an efficient and regiospecific synthesis of 4-oxo-2-alkenylphosphonates, which can serve as building blocks for the construction of polyethylenic chains.[2]

(1) Oestreich, M.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881. (2) Lee, B. S. et al. *J. Org. Chem.* **2000**, *65,* 4175.

Ethyl [Bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

59,557-8  5g, 10g

This compound was exploited in the Horner–Wadsworth–Emmons reaction to synthesize α,β-unsaturated esters derived from 6-methoxytetrahydropyran-3-one.

López Tudanca, P. L. et al. *J. Chem. Soc., Perkin Trans. 1* **1992**, 533.

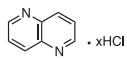
2,6-Dichloropyridine-1-oxide, 99%

59,405-9  1g, 5g

It oxidizes alkenes to epoxides[1] and alkanes to alcohols[2] in the presence of ruthenium catalysts.

(1) Zhang, J.-L.; Che, C.-M. *Org. Lett.* **2002**, *4*, 1911. (2) Yamaguchi, M. et al. *Chem. Lett.* **2002**, 434.

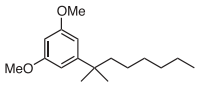
1,5-Naphthyridine hydrochloride

59,416-4  1g, 5g

Serves as a precursor of diaza-*cis*-decalins, a structurally novel class of diamine ligands.[1] Has also been used in the synthesis of one member of a series of antimicrobial parenteral 3′-quaternary ammonium cephalosporins.[2]

(1) Li, X. et al. *Org. Lett.* **2000**, *2*, 875. (2) Brown, R. F. et al. *J. Med. Chem.* **1990**, *33,* 2114.

1-(1,1-Dimethylheptyl)-3,5-dimethoxybenzene, 97%

59,522-5  1g, 5g

Employed as a starting material in the synthesis of a number of THC analogs that were evaluated for their binding affinity towards cannabinoid receptors.

Gareau, Y. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189.

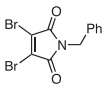
2,3-Dibromo-*N*-methylmaleimide

59,593-4  1g, 5g

2,3-Dibromomaleimide, 97%

55,360-3  1g, 5g

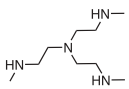
N-Benzyl-2,3-dibromomaleimide, 97%

55,778-1  1g, 5g

Dihalogenated maleimides can be used either as dienophiles or as electrophiles. 2,3-Dibromo-*N*-methylmaleimide is a key starting material in the synthesis of rebeccamycin[1] and 7-azarebeccamycin analogs.[2] These analogs were then evaluated for their antitumor activities.

Marminon, C. et al. *Bioorg. Med. Chem.* **2003**, *11*, 679. (2) Marminon, C. et al. *J. Med. Chem.* **2003**, *46*, 609.

Tris[(methylamino)ethyl]amine, 97%

46,353-1  5g, 10g, 25g

A tripodal metal chelating agent that has been employed in the preparation of *N*-methyl superbase (Aldrich Cat. No. **46,355-8**),[1] and its stilbene and bismuth azaatrane analogs:[2] *N,N′,N″*-trimethylazastibatrane and *N,N′,N″*-trimethylazabismatrane.

(1) Tang, J.-s.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903. (2) Shutov, P. L. et al. *Inorg. Chem.* **2002**, *41*, 6147.

N,N-Diethyl-1,1-dimethylsilylamine, 97%

58,624-2  1g, 5g

Complements $NaBH_3CN$, and has been used in the Lewis acid catalyzed reductive amination of carbonyl compounds.

Miura, K. et al. *Synlett* **2001**, 1617.

Please see pages 54–55 for additional new products.

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About Our Cover

The Railway (oil on canvas, 93.3 x 111.5 cm) was painted in 1873 by the French painter Edouard Manet. When it was exhibited in the following year, it was severely criticized by both the critics and the public, who were greatly puzzled by the subject of the picture, or rather by the fact that it seemed to have no real subject. In late 19th-century France, the most highly valued subjects in art were religious, mythological, historical, or literary. At the same time, a contrary naturalistic movement, paralleled in literature by the writings of reformist authors such as Émile Zola, favored subjects that portrayed the lower classes, like scenes of peasants working in the fields.

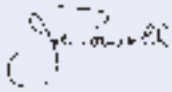
Photograph © Board of Trustees, National Gallery of Art, Washington.

Manet's picture, however, does not represent an imaginary literary subject or a glorious historical event, nor does it portray the travails of the poor or idealize the dignity of manual labor. It simply shows a young woman, who is neither rich nor poor, pausing to rest on a bench with a puppy in her lap, accompanied by a little girl with her back to us who grasps the bars of an iron fence. It does not even seem to show what is indicated by the title of the painting, and the only clue to this is the steam rising in the background.

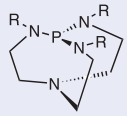
The clear outdoor light and bright color and the broad brushstrokes of his technique seem to link Manet with the impressionists, and indeed, a year after he painted *The Railway*, he was at Argenteuil painting in the open air alongside Renoir and Monet. Manet is not truly an impressionist painter, however. This is not a quickly executed representation of a chance moment, captured by the painter as a photographer makes a snapshot, but a carefully planned work. Manet sketched in the basic composition before carrying the canvas outdoors to work directly from the models. Such details as the placement of one figure facing out and the other into the picture, and the color scheme of the dresses, one white on blue and the other blue on white, show the calculation that underlies his representation of *The Railway*, a phenomenon common to modern life.

This painting is a gift of Horace Havemeyer to the National Gallery of Art, Washington, DC, in memory of his mother, Louisine W. Havemeyer.

"Please Bother Us."



Joe Porwoll, President



R = Me, *i*-Pr, *i*-Bu

Professor John G. Verkade of the Department of Chemistry at Iowa State University kindly suggested that we provide the following three proazaphosphatrane nonionic bases. This family of superbases has broad applications[1] including recently as ligands in the Pd-catalyzed amination of aryl bromides and iodides.[2]

(1) Wroblewski, A. E.; Bansal, V.; Kisanga, P.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 561. (2) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

46,355-8
2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

55,695-5
2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

56,588-1
2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

Naturally, we made these valuable superbases. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

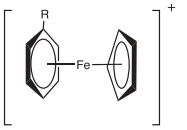
Use of the Microwave Oven for Sublimation: Flash Sublimation

Sublimation is a useful technique for the purification[1–3] or isolation[2–4] of some organic, inorganic, or organometallic compounds. Generally, if a compound can be sublimed, sublimation can be a good alternative to recrystallization or distillation. Sublimation has been known since alchemical times and, in the past, was carried out by simply heating the compound in a porcelain dish covered with a common filter paper.[5] Nowadays, a sublimation apparatus or, sometimes, a Kugelrohr oven[3,4] is used under ambient or reduced pressure.

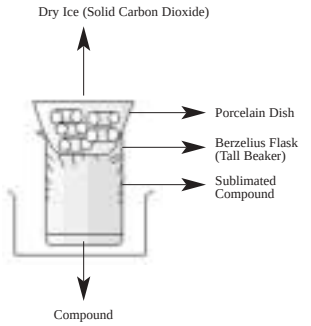
We have recently developed an improved method for the synthesis of arenocenium salts using a simple assembly for reactions under microwave conditions.[6a] It consists of a crystallizing dish and a 250-mL, tall beaker (Berzelius flask) that is covered with a porcelain dish containing dry ice. Dry ice does not absorb microwaves and, therefore, does not vaporize under microwave irradiation conditions.[6b] We found that this simple device may also be used for sublimations. Microwave sublimation has been utilized to manufacture and isolate carbon nanotubes[7] and essential powders from fresh animal, plant, or microbial matter.[8]

We have carried out the sublimation, under microwave heating, of some representative inorganic, organometallic, and organic compounds in the apparatus shown here. The sublimations were fast and easy to carry out. Collection of the sublimate with a spatula was also straightforward. The compounds tested and the "yields" of the corresponding sublimates are presented in **Table 1**. Even certain slightly air-sensitive compounds (Table 1, entries 7, 8, and 10), that are generally purified by sublimation under reduced pressure, may be purified by this method.

Acetyl ferrocene,[9] decadeuteroferrocene,[4] and (cyclopentadienyl)manganese tricarbonyl[3] were prepared by published procedures. Bromopentacarbonylmanganese was prepared by reaction of dimanganese decacarbonyl (Aldrich Cat. No. 24,526-7) and bromine. We tested all the recommended solvents for this reaction: CS_2,[10] dichloromethane,[10] carbon tetrachloride,[11] and hexane (used for the rhenium analog[12]), but found that benzene[13] was the best solvent. $Mn(CO)_5Br$ was obtained in 96% yield, in practically pure form, without formation of manganese(II) bromide as side product.[11] All other compounds in Table 1 were obtained from commercial sources.



(η^6-Arene)(η^5-cyclopentadienyl)iron(II) salts
(arenocenium salts)



References: (1) *Purification of Laboratory Chemicals*, 4th ed.; Perrin, D. D., Armarego, W. L., Eds.; Butterworth Publishers: New York, 1996. (2) Verberne, M. C.; Brouwer, N.; Delbianco, F.; Linthorst, H. J. M.; Bol, J. F.; Verpoorte, R. *Phytochem. Anal.* **2002**, *13*, 45. (3) Federman Neto, A.; Borges, A. D. L.; Miller, J.; Darin, V. A. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1299. (4) Federman Neto, A.; Borges, A. D. L.; de Arruda Campos, I. P.; Miller, J. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1543. (5) (a) Engel, R. *Traité Élémentaire de Chimie*; Librairie J.-B. Baillière et Fils (Publisher): Paris, France, 1896; p 13. (b) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, U.K., 1989; pp 153–155. (6) (a) Federman Neto, A. *An. Acad. Bras. Cienc.* **2003**, in press. (b) Dabirmanesh, Q.; Fernando, S. I. S.; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 743. (7) Mochizuki, T.; Yoshizawa, H. Jpn. Patent 2000 272,913, October 3, 2000; *Chem. Abstr.* **2000**, *133*, 254543z. (8) Maghami, P. Fr. Patent 2,618,450, January 27, 1989; *Chem. Abstr.* **1989**, *111*, 150119v. (9) Darin, V. A.; Federman Neto, A.; Miller, J.; de Freitas Afonso, M. M.; Fonsatti, H. C.; Borges, A. D. L. *J. Prakt. Chem.* **1999**, *341*, 588. (10) Quick, M. H.; Angelici, R. J. *Inorg. Synth.* **1979**, *19*, 160. (11) Abel, E. W.; Wilkinson, G. *J. Chem. Soc.* **1959**, 1501. (12) Schimidt, S. P.; Trogler, W. C.; Basolo, F.; Urbancic, M. A.; Shapley, J. R. *Inorg. Synth.* **1985**, *23*, 41. (13) Federman Neto, A.; Oliveira, W. J. S.; Borges, A. D. L. University of São Paulo, Ribeirão Preto, Brazil. Unpublished work, 2003.

Alberto Federman Neto (Ph.D.),* **Paloma Los Angeles Gazola Cordo**, **Wagner José Dos Santos Oliveira**, and **Aurea Donizete Lanchote Borges**
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Editor's Note: *Caution*. Sigma-Aldrich scientists have not tested this procedure in-house and do not have any experience with it. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich. The user should base his/her decision to use this technique solely on the claims made by the authors.

Microwave Synthesis: Chemistry at the Speed of Light by Dr. B. L. Hayes (Aldrich Cat. No. Z55,386-7). See pages 50 and 72 for more details.

Table 1. Sublimation Using a Microwave Oven[a]

Entry	Compound Sublimed: Formula or Name	Amount (g)	Microwave Setting (%)[b]	Heating Time (s)	"Yield" of Sublimate (%)
1	I_2	1.0	60	360	>99
2	$AlCl_3$	0.5	60	180	64
3	Hg_2Cl_2	0.5	60 and 80	360	–[c]
4	$(C_{10}H_{10})Fe$	0.5	30	60	92
5	$(C_{10}D_{10})Fe$	0.1	30	45	96
6	Acetyl ferrocene	0.5	60	60	15[d]
7	$Mn_2(CO)_{10}$	0.1	40	40	58
8	$Mn(CO)_5Br$	0.1	30	40	33[e]
9	$Mo(CO)_6$	0.3	30	60	81
10	$(C_5H_5)Mn(CO)_3$	0.1	30	30	72[e]
11	(–)-Menthol	0.5	30	180	98
12	(±)-Camphor	0.5	20	60	84
13	Vanillin	0.5	10	30	–[f]
14	Piperonal	0.5	80	20	66
15	Biphenyl	0.5	40	150	78
16	Naphthalene	0.5	40	120	96
17	Anthracene	0.5	40	360	89
18	Salicylic acid	0.5	40	120	97
19	Benzophenone	0.5	80	90	71
20	Benzoic acid	0.5	60	60	89

[a] Sharp microwave oven, model Carousel III; manufactured by SANYO®: Manaus, Amazonas State, AM, Brazil. Of all the conditions tested, the best ones are shown in this table. [b] Setting as a percent of maximum power of 800 W. [c] Hg_2Cl_2 appears to sublime only at higher temperatures. [d] With extensive decomposition. [e] With some decomposition. [f] The material sublimed easily, but the vapors were lost without good condensation, even when low power was used.

Aziridines and Oxazolines: Valuable Intermediates in the Synthesis of Unusual Amino Acids

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Dipartimento di Chimica "G. Ciamician"
Università di Bologna
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Email: cardillo@ciam.unibo.it

Outline

1. Introduction

Aziridines and oxazolines are interesting heterocycles that are present as structural motifs in a wide variety of strongly biologically active compounds. Examples of such compounds include azinomycins A and B,[1] which are potent antitumor and antibiotic agents that are isolated from the fermentation broth of *Streptomyces griseofuscus S42227*. The antineoplastic activity of mitomycins A, B, and C,[2a] produced by *Streptomyces caespitosus*, is associated with the high reactivity of the strained heterocycle. Furthermore, some synthetic aziridines show strong activity as enzyme inhibitors,[2b] or are versatile intermediates for enzyme inhibitors.[2c]

Moreover, a great number of oxazoline-containing biologically active compounds have been isolated from marine organisms, primarily sponges and ascidians. Ascidiacyclamide and lissoclinamide, for instance, are cyclic, oxazoline-containing antineoplastic peptides obtained from the tunicate *Lissoclinum patella*.[3] Their favorable cytotoxic and antineoplastic activities, as well as their role as chelating metabolites, have inspired synthetic and structural studies. As protected forms of hydroxyamino acids and amino alcohols, chiral oxazolines are also versatile building blocks for the synthesis of polyfunctionalized compounds, and are widely utilized as chiral ligands in asymmetric synthesis.

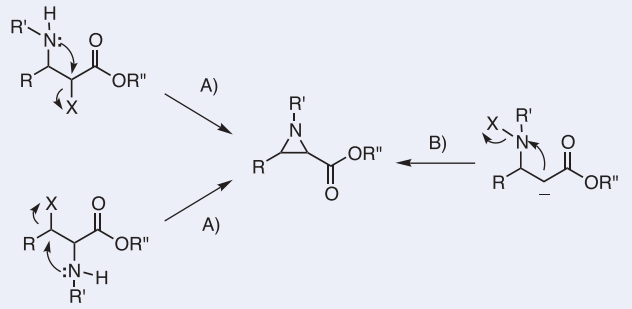
Since their discovery by Gabriel,[4] aziridines have attracted attention as starting materials for further transformations. The ring strain of aziridines, which amounts to 26–27 kcal/mol, renders these compounds susceptible to ring opening[5] and allows their use as precursors of a variety of nitrogen-containing compounds. The use of aziridine-2-carboxylates as intermediates in the synthesis of optically active amino acids, both natural and unnatural, is a subject of current interest.

While the reactivity of N-unsubstituted aziridines is relatively low, high reactivity is associated with aziridines incorporating an electron-withdrawing group on the nitrogen atom. For instance, the presence of an acyl group strongly activates the ring toward opening by a nucleophile. This reaction is generally favored by the presence of Lewis acids and proceeds with inversion of configuration at the stereogenic center of the aziridine. Another important reaction that is characteristic of *N*-acylaziridines is their isomerization to the corresponding oxazolines. This reaction generally occurs in the presence of a Lewis acid and leads to retention of configuration.

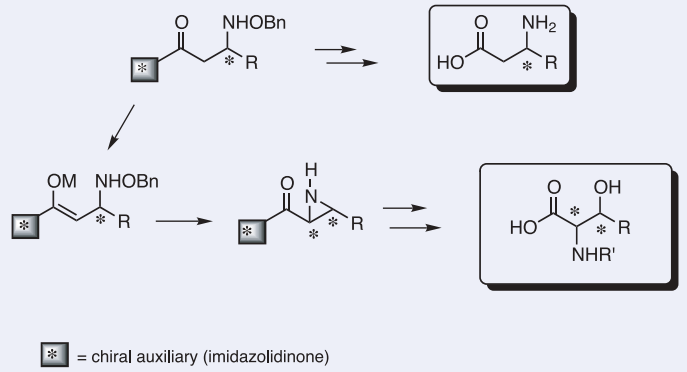
This short review covers primarily the literature of the past five years, and focuses on new syntheses of aziridines and oxazolines, which allow the preparation of a number of hydroxyamino acids in a stereoselective fashion.

2. Recent Advances in the Synthesis of Aziridinecarboxylates

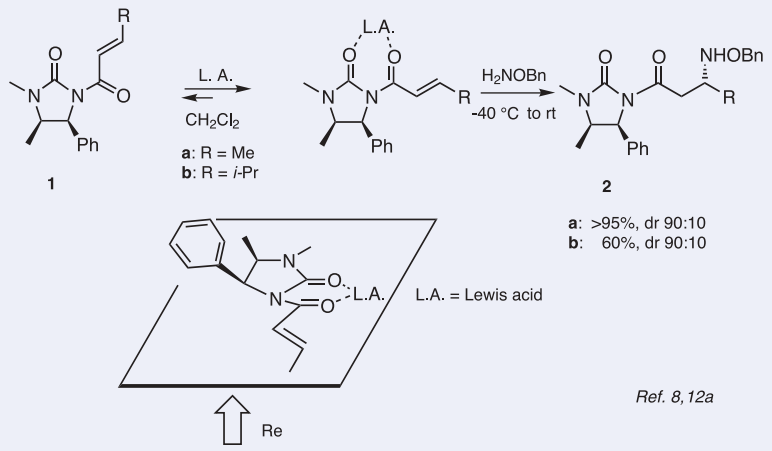
Excellent and exhaustive reviews[6] have surveyed the asymmetric syntheses of aziridines. Herein, we focus our attention on the more recent syntheses and transformations of aziridinecarboxylates, because of their structural similarities to α- or β-amino acids. Other aspects of the reactivity of aziridines are reported on in the review by Lee and Ha in this same issue. Two general approaches to the asymmetric synthesis of aziridines are illustrated in **Scheme 1**. In pathway A, a nucleophilic nitrogen atom affords the aziridine ring by attack on an adjacent carbon atom bearing a leaving group. The well-known Gabriel–Cromwell method,[7] modified with the use of chiral auxiliaries, and the cyclization of hydroxyamino acids are examples of this approach. In pathway B, the formation of a stabilized carbanion allows ring closure on an electrophilic nitrogen carrying a good leaving group.



Scheme 1. General Approaches to the Asymmetric Synthesis of Aziridines.



Scheme 2. Stereospecific Synthesis of Substituted Aziridinecarboxylates.



Scheme 3. Diastereoselectivity of the Nucleophilic Addition to α,β-Unsaturated Chiral Imides.

We have developed a new stereospecific method for preparing substituted aziridinecarboxylates for use as precursors of naturally occurring, nonproteinogenic β-hydroxy-α-amino acids. Our strategy mimics pathway B and starts with the diastereoselective β introduction of *O*-benzylhydroxylamine into α,β-unsaturated chiral imides in the presence of a Lewis acid.[8] This is followed by cyclization of the intermediate enolates to aziridines (**Scheme 2**).

The diastereoselectivity of the first step has been controlled by use of the chiral auxiliaries (+)- or (–)-1,5-dimethyl-4-phenylimidazolidin-2-one (**Scheme 3**),[9] both of which are commercially available in enantiomerically pure forms. MM^+ calculations performed on the ground state conformation of the starting unsaturated imide **1** reveal that the anti arrangement of the carbonyl groups is more stable than the syn conformation by ca. 5 kcal.[10] Nevertheless, the diastereofacial selectivity of the addition to the carbon–carbon double bond depends on the conformational changes induced by the presence of coordinating metals capable of binding both carbonyl groups. Spectroscopic evidence of the coordination of carbonyl groups with a metal atom has been reported in the literature.[8,11] Due to the presence of the substituents on the imidazolidin-2-one ring, preferential attack occurs on the less hindered face of the *s–cis* conformation. Among the variety of Lewis acids tested (Al, Ti, Zn, Mg, Yb, Sc salts, etc.), the best levels of diastereoselectivity have been obtained with BF_3•Et_2O (90:10 dr) and $Bu_2B(OTf)$ (>97:3 dr) in CH_2Cl_2.[12] This reaction allows the synthesis of β-amino acids, whose *S* or *R* configuration depends on the chiral imidazolidin-2-one used as auxiliary. An alternative, highly enantioselective route for the β introduction of a C–N bond involves the 1,4 addition of *O*-benzylhydroxylamine to pyrazole-derived crotonamides catalyzed by chiral $MgBr_2$ complexes.[13]

The 1,4 addition[14] is followed by cyclization of **2** to the corresponding aziridine[15] through the formation of a titanium[16] or aluminum enolate (**Scheme 4**). This reaction is highly diastereoselective affording exclusively the trans aziridine **3**. Since the configurations of the two new stereogenic centers depend on the initial 1,4-addition step, the chiral auxiliary and the Lewis acid selected determine the stereochemical outcome of the whole sequence. The nondestructive removal of the chiral auxiliary has been carried out by treatment with lithium hydroperoxide in tetrahydrofuran–water to afford the corresponding carboxylic acid, with methanol–toluene to afford the corresponding methyl ester, or with neat allylamine to give the corresponding amide.[17]

On the basis of the pathways shown in Schemes 3 and 4, we have developed a one-pot sequence for the preparation of *N*-Boc-3-*un*substituted aziridines (**Scheme 5**).[18] *N*-Boc-*O*-benzoylhydroxylamine, deprotonated with BuLi, reacts with acryloyl imide, and the intermediate enolate spontaneously cyclizes to aziridine **4** in 91% yield and 80:20 dr.

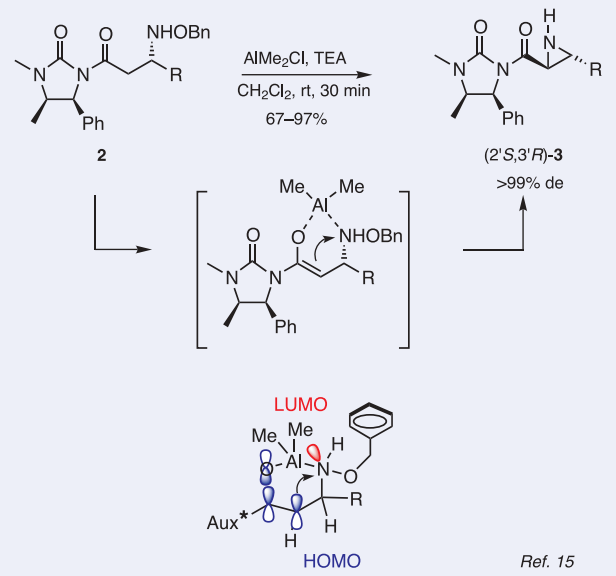
Enantiopure, cis aziridinecarboxylates have been synthesized by a recently disclosed methodology using the anion of optically pure chloroallyl phosphonamide with different oximes.[19] The reaction of the anion, generated using NaHMDS, with *tert*-butyl glyoxylate *O*-benzyl oxime led to the

corresponding cis aziridine in 78% yield as a single diastereoisomer (**Scheme 6**). Cleavage of the phosphonamide moiety by ozonolysis afforded enantiomerically pure cis aziridine **5**.

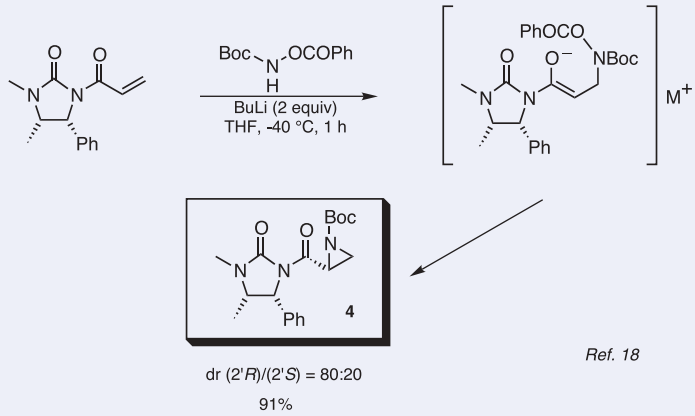
Synthetic 2,2-disubstituted aziridines show activity as protease inhibitors; for example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid[20] is a potent irreversible inhibitor of the bacterial enzyme diaminopimelic acid epimerase, while 2-(3-carboxypropyl)aziridine-2-carboxylic acid[21] is an irreversible inhibitor of glutamate racemase. Aziridine-2,3-dicarboxylates have been introduced in peptidomimetics as modified aspartic acid moieties for the purpose of preparing cysteine protease inhibitors.[22] Aiming to develop a similar application, racemic aziridine-2,2-dicarboxylates have been obtained through a Michael-type addition of *S,S*-diphenylsulfimide to arylidene malonates.[23]

We have recently turned our attention to the asymmetric synthesis of aziridine-2,2-dicarboxylates via a 1,4-addition reaction. A variety of methods exist for the synthesis of chiral, nonracemic aziridines through the metal-catalyzed aziridination[24] of olefins.[25] For example, the use of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) in the presence of bis(oxazoline)-copper complexes as chiral catalysts has resulted in the aziridination of styrene in 97% yield and 61% ee.[26] Our procedure[27] involved the conjugate addition of commercially available *N,O*-bis(trimethylsilyl)hydroxylamine to unsaturated malonates,[28] followed by cyclization under very mild basic conditions (**Scheme 7**). The hydroxylamine derivative reacted both as a nucleophile, during the addition step, and as an electrophile during the cyclization to aziridine **6** with the OTMS group behaving as a good leaving group. The presence of a chiral Lewis acid catalyst induced chirality during nucleophilic attack onto the alkylidenemalonates. $Cu(OTf)_2$ showed good catalytic activity, and the use of bis(benzyloxazoline) as ligand furnished the best results.

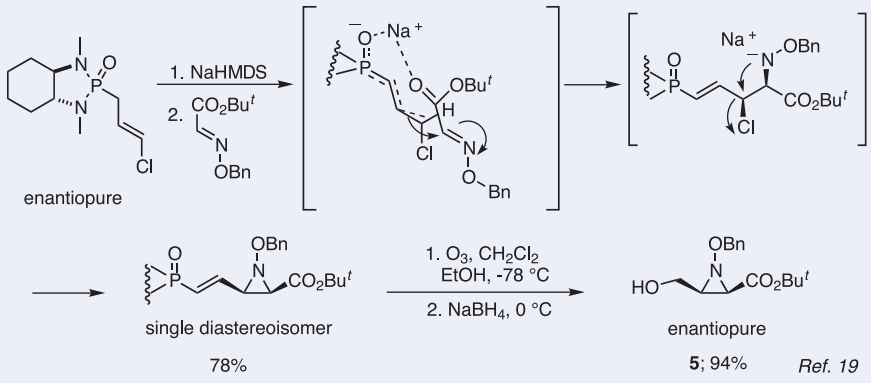
In an alternative strategy, racemic *N*-benzoylamidoaziridine diester **7** was regiospecifically hydrolyzed under mild basic conditions (**Scheme 8**). The resulting monoester, **8**, is a useful intermediate, which can be easily transformed into a mixture of diastereomeric derivatives, **9**, by use of (*S*)-α-methylbenzylamine. Upon slow crystallization from MeOH–H_2O, this mixture afforded a complete diastereomeric separation of **9a** and **9b**.[27d] Besides malonates, α-carbonyl enoates are also good substrates for aziridination. In fact, a simple



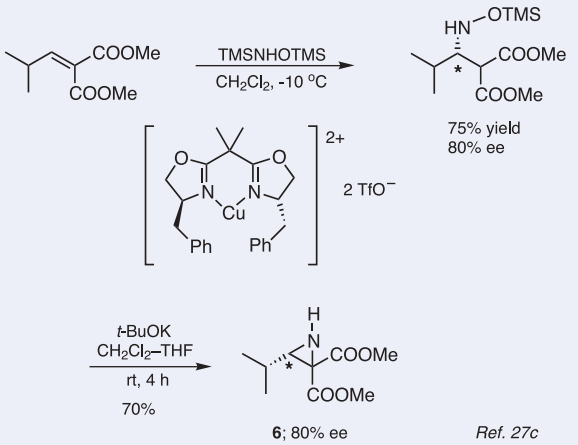
Scheme 4. Diastereoselective Aziridine Formation.



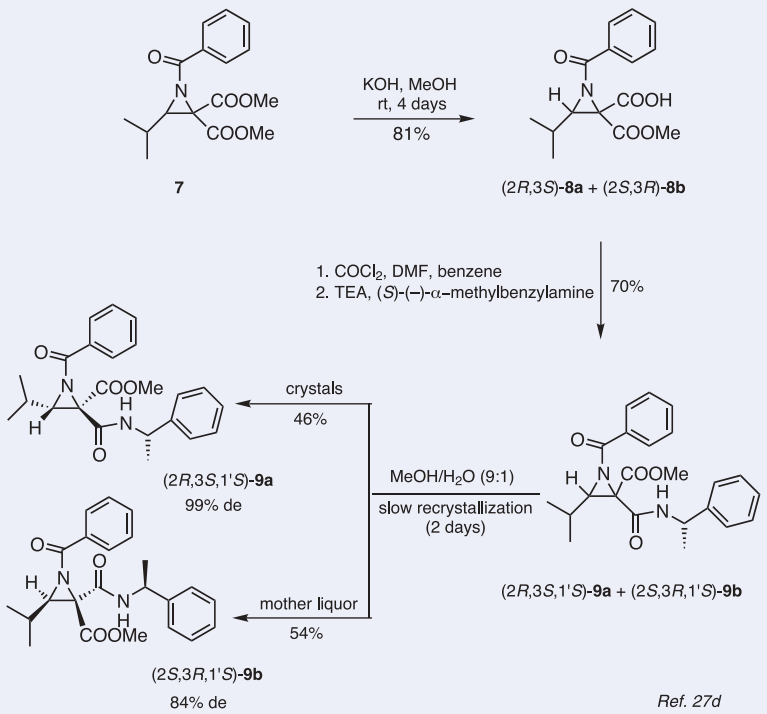
Scheme 5. Diastereoselective, One-Pot Aziridine Formation.



Scheme 6. Recent Method for Preparing Enantiomerically Pure Cis Aziridinecarboxylates.



Scheme 7. Synthesis of Aziridine-2,2-dicarboxylates by a 1,4-Addition Reaction.



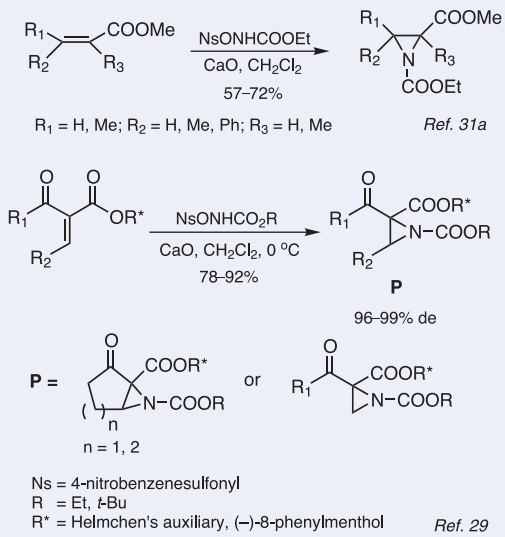
Scheme 8. Diastereomeric Resolution of Aziridine-2,2-dicarboxylates.

and efficient diastereoselective aziridination of chiral α-carbonyl enoates[29] has recently been reported using ethyl or *tert*-butyl nosyloxycarbamate.[30] In situ generated (ethoxycarbonyl)nitrene (NCO_2Et) reacts readily with electron-rich alkenes, but more slowly with electron-deficient ones. Inorganic bases, such as CaO, have been employed to facilitate nitrene formation, which allows the preparation of aziridines from α,β-unsaturated esters and ketones (**Scheme 9**).[31] The same reaction occurs with high diastereoselectivity (96–99% de) with chiral α-carbonyl enoates[29] derived from commercially available chiral alcohols such as Helmchen's auxiliary.[32]

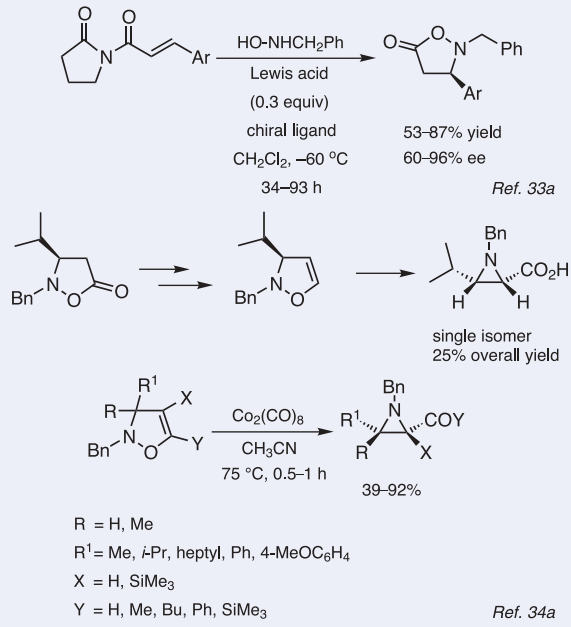
A ring contraction of 4-isoxazolines (2,3-dihydroisoxazoles) to aziridines is illustrated in **Scheme 10**. The conjugate addition of *N*-benzylhydroxylamine to achiral pyrrolidinones and oxazolidinones, in the presence of a chiral ligand, affords chiral 5-isoxazolidinones as precursors of 4-isoxazolines with moderate-to-good chemical yields.[33] 4-Isoxazolines have been utilized for the synthesis of acylaziridines through a $Co_2(CO)_8$ promoted rearrangement.[34]

The use of oxazolidinones as excellent achiral templates has been applied to a variety of enantioselective transformations.[35] For instance, the enantioselective aziridination of *N*-enoyloxazolidinones with *N*-aminophthalimide in the presence of lead tetraacetate and a chiral ligand, provides *N*-phthalimidoaziridines in 15 minutes at 0 °C in good-to-high enantiomeric excesses (**eq 1**).[36]

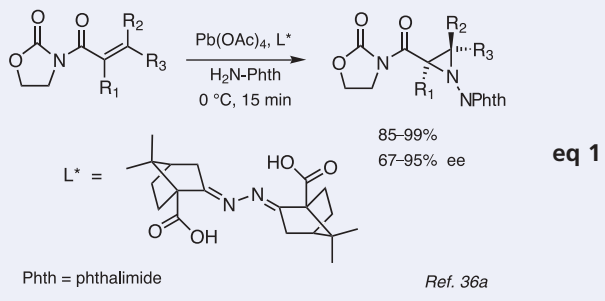
Finally, oxazolinylaziridines were synthesized in good yields and high diastereoselectivities by a Darzens-like reaction between 2-(1-chloroethyl)-2-oxazoline and Schiff bases (**eq 2**).[37]



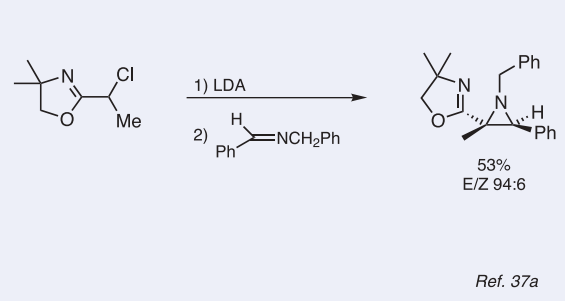
Scheme 9. Aziridination of α,β-Unsaturated Esters by Nosyloxycarbamate.



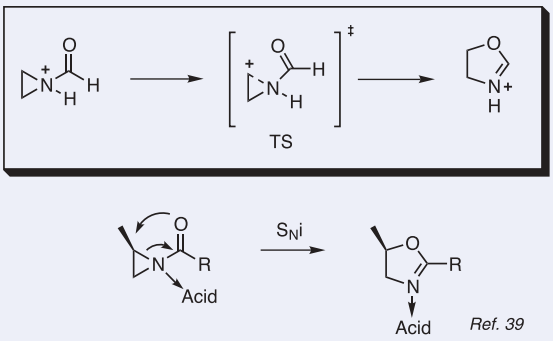
Scheme 10. Enantioselective Synthesis and Ring Contraction of 4-Isoxazolines.



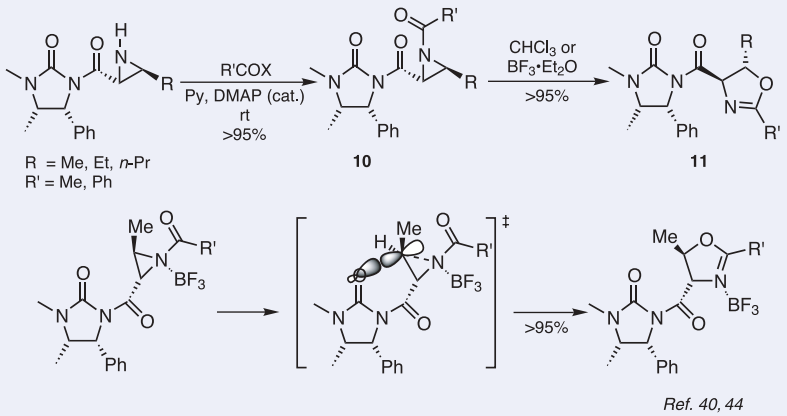
eq 1



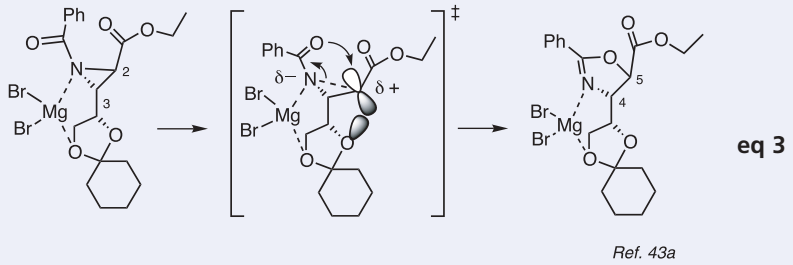
eq 2



Scheme 11. Retention of Configuration in the Ring Expansion of Aziridines to Oxazolines.



Scheme 12. Effect of the Imide Auxiliary on the Ring Expansion Rate and Regioselectivity.



3. Synthesis of Oxazolines

Oxazolines can be synthesized by several routes.[38] The most general methods are: (a) the ring-expansion reaction of acylaziridines; (b) the N-cyclofunctionalization of a double bond starting from a vicinal O-functionality, or the O-cyclofunctionalization of a double bond starting from an N-functionality; or (c) the formation of a C–C bond by an aldol condensation. Herein, we present some recent, original strategies that have been utilized in the synthesis of chiral oxazolines.

3.1. Ring-Expansion Reactions

The ring expansion of acylaziridines to oxazolines promoted by Lewis acids is a well-known reaction that has recently received renewed attention. Both chemical evidence and ab initio calculations have shown that this reaction occurs with retention of configuration of the stereogenic centers (**Scheme 11**).[39] We have confirmed these findings by following the spontaneous ring expansion of an *N*-acyl-3-ethylaziridine-2-imide by ^{1}H NMR spectroscopy.[40] The spectra showed a slow decrease of the intensity of the signals from the aziridine and a corresponding increase of the intensity of the signals from the trans oxazoline-4-imide ($J_{4,5}$ = 5.0 Hz).[41] No intermediate was observed in the reaction mixture. The ring expansion of 3-substituted aziridine-2-imides **10** is completely regioselective, affording oxazolines **11** as the only products (**Scheme 12**). It is generally assumed that the regioselectivity is driven by the stability of an incipient carbocation. Semiempirical calculations suggest that the imidazolidin-2-one chiral auxiliary could be responsible for the accelerated reaction rate and for the regiochemistry.[42] The aziridine presumably adopts a preferred conformation in which the endocyclic carbonyl oxygen is in proximity of the aziridine C3', thus stabilizing the incipient positive charge. This model is also in accord with our experimental observations that the ring expansion of aziridine-2-esters is slower than that of aziridine-2-imides, while the same reaction does not occur for aziridine-2-amides.

A similar neighboring-group-participation effect has recently been observed[43] in the ring expansion of a glyceraldehyde-derived aziridine-2-carboxylate. The oxygen of the cyclohexylidene protecting group appears to stabilize the incipient carbocation and to drive the regiochemistry of the ring expansion toward the formation of the oxazoline-5-carboxylate (**eq 3**).

N-Acyl-3-methylaziridine-2-imides underwent ring expansion to give the corresponding trans oxazoline-4-imides in good yields (see Scheme 12). The mild acid hydrolysis of the heterocycles, followed by the nondestructive removal of the chiral imidazolidinone auxiliary, furnished optically active threonines.[40] This reaction was also applied to a variety of *N*-acyl-3-alkylaziridine-2-imides to afford precursors of *threo*-β-hydroxy-α-amino acids.[44]

The removal of the chiral auxiliary in an earlier stage of the procedure, to transform the aziridine-2-imide into an aziridine-2-ester or an aziridine-2-amide, allowed us to perform the ring opening of the three-membered ring with acetic acid by following the published procedure.[45] This yielded the protected form of optically active *allo*-threonine, a nonproteinogenic amino acid present in many bioactive peptides and glycopeptides associated with biological recognition and selectivity.

Ring expansion and ring opening of aziridine derivatives are complementary: starting from trans acylaziridines, ring opening by an oxygen nucleophile affords

the anti amino acids, while ring expansion followed by hydrolysis leads to the syn isomers. Furthermore, depending on the chiral imidazolidin-2-one auxiliary used, *R* or *S* amino acids may be isolated.

3.2. C–O Bond Formation

We have recently developed a simple, direct, and general synthesis of nonracemic α-hydroxy-β-amino acids[46] through the intermediacy of chiral oxazoline-5-carboxylates **13** (**Scheme 13**).[47] This approach starts from chiral β-amido esters, and is based on the previously reported results by Seebach and Estermann[48] for the highly diastereoselective alkylation of *N*-acyl-β-amino esters. When these two workers quenched the lithium dianion of the amido ester with a range of alkylating agents, the anti α-alkylated products were obtained in high diastereomeric excesses. Our quenching of the dianion of *N*-benzoyl-β-amino esters with iodine at -60 °C afforded trans oxazolines **13** in 80–95% yields and 92–96% de's, after cyclization of the intermediate iodo derivatives. When the reaction was performed on (3*R*)-**12b**, acidic hydrolysis of the corresponding oxazoline, **13b**, afforded enantiopure (2*R*,3*S*)-*N*-benzoylphenylisoserine methyl ester (85% yield), a fragment of the anticancer Taxol® molecule,[49] without any racemization. Although considerable effort has been expended in the last few years toward the synthesis of this biologically important amino acid, our method compares favorably with the reported synthetic procedures in terms of its simplicity and the optical purities obtained.

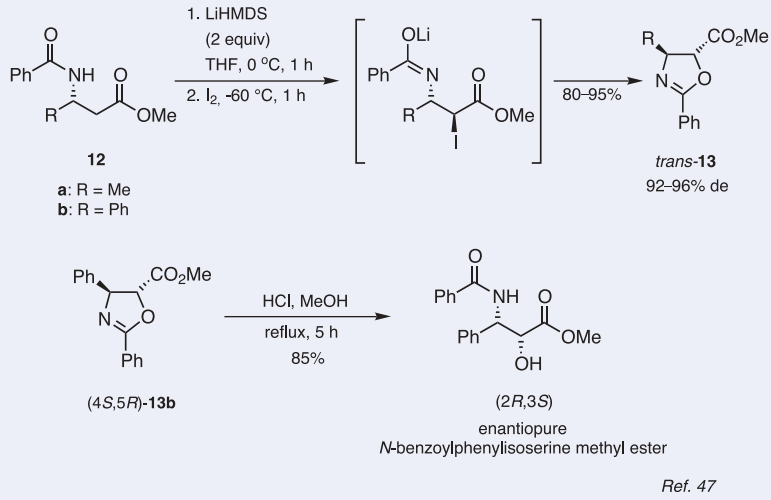
In a similar way, the synthesis of (2*S*,3*S*)-hydroxyaspartic acid,[50] an important component of the antibiotic lysobactin, was performed by deprotonation of *N*-benzoyl dimethyl aspartate at C-3, followed by quenching of the resulting dienolate with I_2 (**Scheme 14**). In this case, the reaction afforded the corresponding trans oxazoline, **14**, in 80% yield, together with the elimination product (20% yield). The hydrolysis with BF_3 in THF–H_2O allowed us to selectively obtain the O-protected amino ester, **16**, which undergoes an intramolecular O→N acyl shift,[51] leading to amido derivative **15**, upon adjusment of the pH of the reaction mixture to 9.5. On the other hand, mild acid hydrolysis of oxazoline **14** furnished amide **15**, while stronger acidic conditions led to the free amino acid.

3.3. C–C Bond Formation

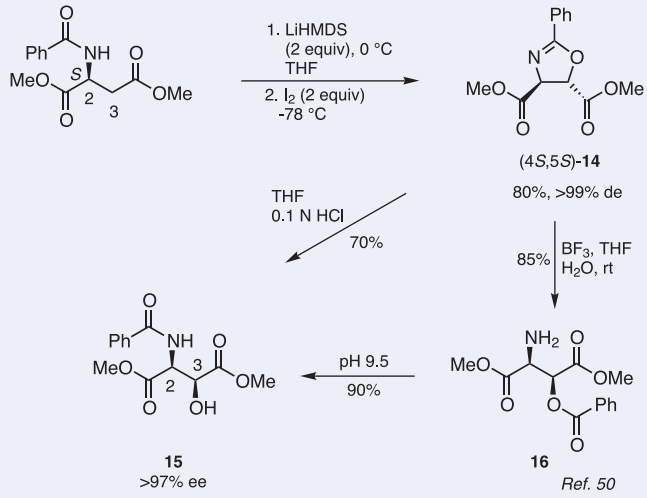
While the preceding method gave access to oxazoline-5-esters, precursors of α-hydroxy-β-amino esters, the regioisomeric (4*R*,5*S*)-*trans*-oxazoline-4-esters, **17**, precursors of phenylserine, have been obtained through an aldol-type reaction catalyzed by chiral Lewis acids. The aldol reaction between aldehydes and methyl isocyanoacetate afforded trans oxazolines through C–C bond formation. The introduction of an optically active ferrocenylphosphine ligand rendered this reaction highly enantio- and diastereoselective.[52] On the other hand, the enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates through a [3+2] cycloaddition of 2-aryl-5-methoxyoxazoles with aromatic aldehydes has been reported.[53] Recently, Evans et al.[54] performed the aldol-type reaction by utilizing chiral aluminum complexes of diaminobinaphthyl-derived ligands[55] and Na_2SO_4 as additive and drying agent (**Scheme 15**). This led to a strong improvement in enantiomeric excesses and yields (>90% yields, 99% ee's).

In addition, the resulting (4*S*,5*S*)-*cis*-oxazolines were easily epimerized to the more stable (4*R*,5*S*)-*trans* isomers, by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

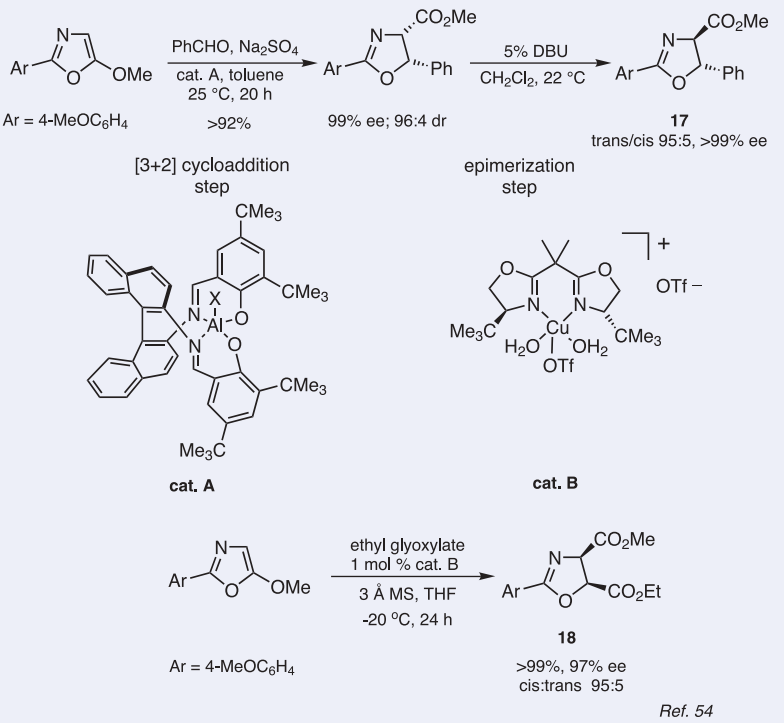
The reaction is not limited to the use of aluminum-derived Lewis acids. When Cu(II)–bisoxazoline complexes were employed in the reaction between ethyl glyoxylate and 5-methoxy-2-(4-methoxyphenyl)oxazole, (4*R*,5*S*)-*cis*-4,5-dialkoxycarbonyl-2-(4-methoxyphenyl)oxazoline (**18**) was obtained in quantitative yield and excellent stereoselectivity (95:5 dr, 97% ee).[54]



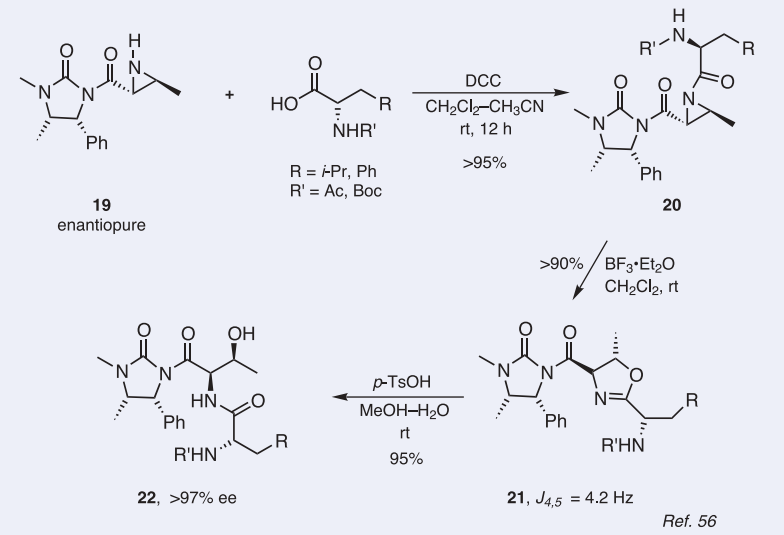
Scheme 13. General Synthesis of Nonracemic α-Hydroxy-β-amino Esters.



Scheme 14. Synthesis of (2*S*,3*S*)-Hydroxyaspartic Acid Derivatives.



Scheme 15. Synthesis of Phenylserine Precursors.



Scheme 16. New and Efficient Strategy for the Synthesis of Threonine-Containing Dipeptides.

4. Synthesis of Threonine-Containing Dipeptides

A new and efficient strategy for the synthesis of threonine-containing dipeptides relies on the ring expansion of enantiomerically pure aziridine-2-imides to oxazolines, which occurs in a regio- and stereocontrolled manner, according to the mechanism described in Section 3.1 (see Schemes 11 and 12, and eq 3).[56] Thus, enantiopure trans aziridine **19** was treated with an N-protected amino acid and DCC to give *N*-(α-aminoacyl)-3-methylaziridine **20** in excellent yield. Conversion of **20** into oxazoline-4-imide **21** and hydrolysis of the five-membered ring with TsOH gave the threonine-containing dipeptide **22** in excellent overall yield (**Scheme 16**). The trans geometry of the starting aziridine **19** was retained in the corresponding oxazoline **21**, as shown by ^{1}H NMR spectroscopy ($J_{4,5}$ = 4.2 Hz).[41]

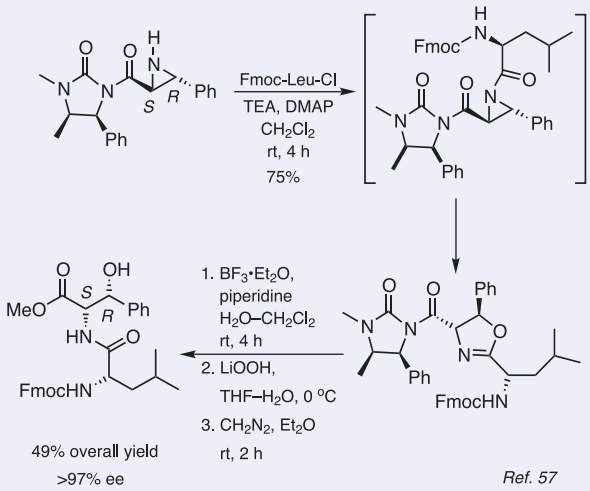
The activation of (2*S*,3*R*)-3-methylaziridine-2-imide with N-protected leucine and phenylalanine gave, after rearrangement, (4*S*,5*R*)-leucyloxazoline and (4*S*,5*R*)-phenylalanyloxazoline. These two fragments are found in the backbone of several cyclic polypeptide metabolites such as ascidiacyclamide and cyclodidemnamide, isolated from the marine organism *Lissoclinum patella*.[3]

The same protocol, shown in Scheme 16, was applied to the corresponding trans 3-phenylaziridine-2-imide, activated with *N*-Fmoc-leucine. Ring expansion, mild acidic hydrolysis, and removal of the chiral auxiliary afforded the dipeptide phenylserine-leucine, a structural fragment in the antibiotic lysobactin (**Scheme 17**).[57]

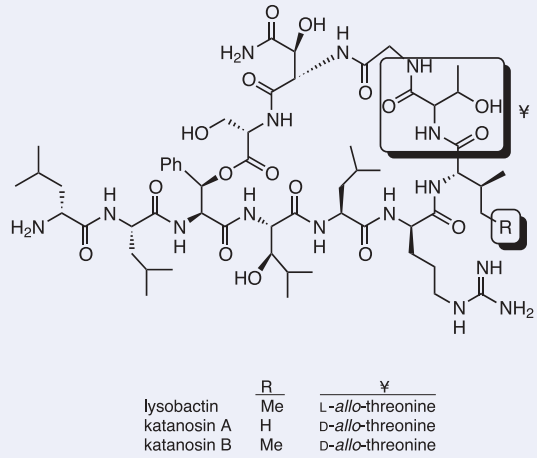
Lysobactin[58] (**Figure 1**) is a depsipeptide antibiotic that was isolated in 1988 from a species of *Lysobacter* (ATCC 53042). The backbone of this macrocycle contains eleven amino acids, five of which are syn or anti β-hydroxy-α-amino acids. Lysobactin is four times more potent than vancomycin,[59] but is slightly more toxic; however, it retains its activity even against vancomycin-resistant bacteria. Katanosins A and B[60] have the same peptide sequence as lysobactin but the opposite stereochemistry at the *allo*-threonine position. These two macrocycles show a high antibiotic activity that is strictly correlated to the inhibition of cell wall biosynthesis.

The methodologies that have been utilized in the synthesis of oligopeptides containing hydroxyamino acids have been easily applied to the preparation of other fragments present in lysobactin. Since activated aziridines give ring opening with inversion of configuration or ring expansion with retention of configuration, we have explored both of these approaches in the synthesis of a threonine or *allo*-threonine dipeptide sequence from a common starting aziridine.[61] For this purpose, a 2'*S*,3'*R* aziridine was acylated with *N*-Boc-isoleucine, and ring-expanded by treatment with BF_3•Et_2O to obtain the corresponding 4*S*,5*R* oxazoline in excellent yield. Hydrolysis of the oxazoline gave a 90% yield of the ester, which was transformed into the corresponding amide by a nucleophilic intramolecular displacement. This sequence led to the preparation of an Ile-Thr derivative.

To introduce *allo*-Thr into a peptide sequence, a different protocol, involving S_N2 aziridine ring opening, was required. In order to obtain the starting aziridine with the



Scheme 17. Preparation of Phenylserine-Leucine Dipeptide, a Structural Fragment in the Antibiotic Lysobactin.



	R	¥
lysobactin	Me	L-*allo*-threonine
katanosin A	H	D-*allo*-threonine
katanosin B	Me	D-*allo*-threonine

Figure 1. Macrocyclic Peptides Exhibiting High Antibiotic Activity.

proper configurations of the stereogenic centers, we performed the conjugate addition step using a (+)-imidazolidinone as chiral auxiliary in the presence of $AlMe_2Cl$. Cyclization of the adduct with $AlMe_2Cl$ led to the desired aziridine. Removal of the chiral imidazolidinone auxiliary by treatment with neat allylamine inhibited aziridine ring expansion and led to aziridine-2-allylamide **23** containing a masked glycine moiety (**Scheme 18**).[61] Coupling of **23** with *N*-Boc-isoleucine followed by ring opening with CH_3COOH gave the *allo*-threonine acetate derivative **25** in good overall yield. Tripeptide derivative Ile-*allo*-Thr-Gly, **26,** was obtained upon treatment of **25** with $KMnO_4/CH_3COOH$.[62]

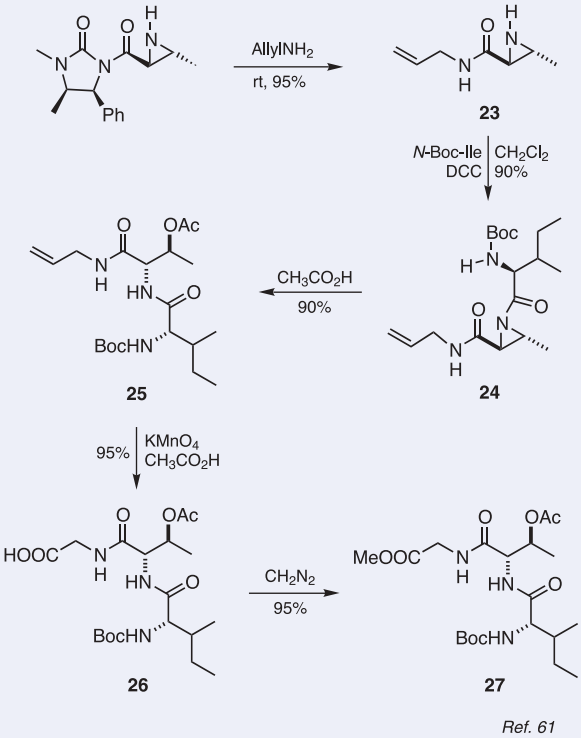
allo-Threonine-containing polypeptide sequences have been synthesized by Wipf and co-workers,[63] starting from the corresponding threonine-containing sequences. The key features of the synthesis include cyclization of the hydroxyamino acid with the Burgess reagent or under Mitsunobu conditions, followed by hydrolysis of the intermediate oxazoline heterocycle (**Scheme 19**).

5. Concluding Remarks

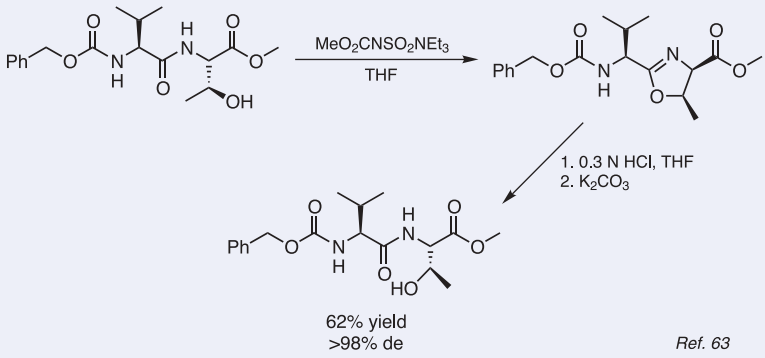
Over the past few decades, an increasing number of researchers have exploited aziridines and oxazolines as starting materials for the synthesis of nitrogen-containing compounds. The use of these heterocycles as intermediates in the synthesis of proteinogenic and nonproteinogenic, optically active amino acids is of current interest. Herein, we have highlighted some of the most recent methods for the asymmetric synthesis of aziridinecarboxylates and oxazolinecarboxylates. Furthermore, particular attention has been paid to the ring expansion of *N*-acylaziridines into oxazolines, which allows the synthesis of syn hydroxyamino acids and their direct insertion into peptide sequences.

6. Acknowledgements

We would like to thank all of the graduate students and postdoctoral fellows, who have developed the chemistry reported herein, and whose names are cited in the references. Furthermore, we gratefully acknowledge the financial support of the University of Bologna, MIUR, CSFM-CNR, ISOF-CNR, C.I.N.M.P.I.S., and NATO for our research, the results of which are presented in this review and in the cited publications.



Scheme 18. Synthesis of *allo*-Threonine Tripeptide Fragment of Lysobactin.



Scheme 19. Conversion of Threonine-Containing Dipeptides into *allo*-Threonine-Containing Dipeptides.

7. References and Notes

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About the Authors

Giuliana Cardillo has been a professor of organic chemistry at the University of Bologna since 1980. She studied chemistry at the University of Rome, where she received the "Laurea" in chemistry in 1960. She then moved to the Politecnico of Milan, where she accepted a C.N.R. (Consiglio Nazionale delle Ricerche) position and worked under the guidance of Professor A. Quilico on the identification and synthesis of naturally occurring chromenes, active flavons, and polyprenylphenols. The following two years, she worked at the University of Bari with Professor G. Cainelli on the chemistry of 3-methyl-2-butenoic acid dianion, as isoprene unit, and its application to the synthesis of terpenoids and Vitamin A. She was also interested in the preparation and use of supported polymeric reagents such as acetate, carbonate, and chromate ions. For her teaching and research work, she earned the "Habilitation" in natural product chemistry (1970). In 1972, she moved to the University of Bologna where, in 1980, she was promoted to the rank of professor and appointed to the chair of organic chemistry at the same university. From 1986 to 2001, she was director of the Centre for Macromolecular Physics and Chemistry Studies of the C.N.R. (Rome). She has been awarded the 2000 "A. Quilico Memorial Medal" from the Italian Chemical Society for her creative research in the field of natural products. Her current work focuses on the utilization of cyclofunctionalization reactions in the development of new synthetic methods for polyfunctionalized hydroxyl compounds as bioactive carbohydrates and amino acids. This includes new stereoselective syntheses of β-amino acids, peptide synthesis, and conformational analysis of modified, physiologically active peptides. The asymmetric conjugate addition of nitrogen nucleophiles, via chiral auxiliaries or chiral Lewis acids, has allowed Cardillo's group to develop new methods for the synthesis of aziridines and oxazolines, useful intermediates in the preparation of hydroxyamino acids.

Luca Gentilucci received his "Laurea" in chemistry in 1992 from the University of Bologna under the supervision of Professor C. Trombini, and his Ph.D. in 1996 under the direction of Professor G. Cardillo for research done on the conjugate addition in the synthesis of substituted amino acids. He spent a period of time in 1994 in Professor B. Zwanenburg's group at the Katholieke Universiteit Nijimegen (The Netherlands), working on the synthesis of aziridines and azirines. In 1996, he was a research assistant at the Interdepartmental Centre of Biotechnological Research of the University of Bologna. In 1997, he got a postdoctoral fellowship from the same university to develop research in the field of asymmetric synthesis of small heterocycles, and received the "Bracco Award for Young Researchers in Organic Chemistry" administered by Bracco S.p.A. Pharmaceuticals (Milan). Since 1998, he has been a research associate in Professor G. Cardillo's group working on the asymmetric synthesis of aziridines and other small heterocycles and the synthesis of opioid peptide analogues exhibiting analgesic activity.

Alessandra Tolomelli received her "Laurea" in chemistry from the University of Bologna in 1994 under the supervision of Professor G. Cardillo. In 1997, she spent a period of time in Professor J. Konopelski's laboratories at the University of California, Santa Cruz, working on the synthesis of pharmacologically active polypeptides. In 1999, she obtained her Ph.D. degree from the University of Bologna for research on the synthesis of polyfunctionalized biologically active compounds, which was carried out under the direction of Professor Cardillo. Currently, she works in the same group on the asymmetric synthesis of aziridines and oxazolines by the conjugate addition of nitrogen nucleophiles to unsaturated compounds.

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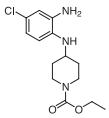
L15,785-6

$C_{14}H_{20}ClN_3O_2$
MW 297.79
250mg



L18,292-3

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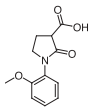
250mg



L18,295-8

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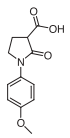

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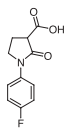

L18,297-4

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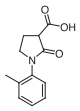

L18,298-2

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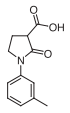

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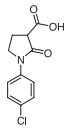

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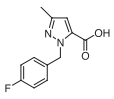

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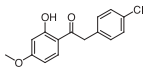

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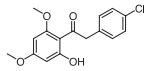

L25,129-1

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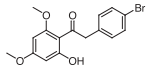
250mg



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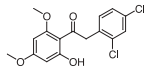

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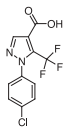
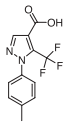


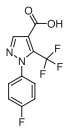
L25,138-0

$C_{12}H_9F_3N_2O_2$
MW 270.21
250mg



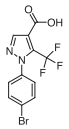
L25,140-2

$C_{11}H_6F_4N_2O_2$
MW 274.18
250mg



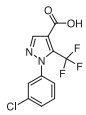
L25,141-0

$C_{11}H_6BrF_3N_2O_2$
MW 335.08
250mg



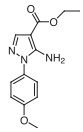
L25,142-9

$C_{11}H_6ClF_3N_2O_2$
MW 290.63
250mg



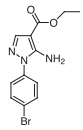
L25,146-1

$C_{13}H_{15}N_3O_3$
MW 261.28
250mg



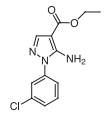
L25,149-6

$C_{12}H_{12}BrN_3O_2$
MW 310.15
250mg



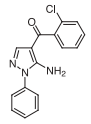
L25,151-8

$C_{12}H_{12}ClN_3O_2$
MW 265.70
250mg



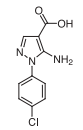
L25,168-2

$C_{16}H_{12}ClN_3O$
MW 297.75
250mg



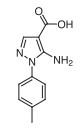
L25,199-2

$C_{10}H_8ClN_3O_2$
MW 237.65
250mg



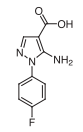
L25,201-8

$C_{11}H_{11}N_3O_2$
MW 217.23
250mg



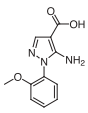
L25,203-4

$C_{10}H_8FN_3O_2$
MW 221.19
250mg



L25,207-7

$C_{11}H_{11}N_3O_3$
MW 233.23
250mg



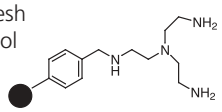
For more information on these products, or to view other similar products, please call us at 800-333-7306 (USA) or email us at bwandler@sial.com.

Scavenger Resins from Aldrich

Since their discovery,[1] scavenger resins have found increasing use not only in combinatorial chemistry, but in classical single-reaction chemistry as well. These resins mimic the limiting reagent(s) in the reaction mixture, and selectively react with excess reagents. The resins can then be simply removed by filtration, thus easing reaction workup. The choice of scavenger resin strongly depends on the type of reagent or byproduct that needs to be removed from the reaction mixture. Listed below are the scavenger resins available from Aldrich and the reagents they react with. If you have any questions on these resins, or have ideas for new resin products, please contact bseitz@sial.com.

Tris(2-aminoethyl)amine, polymer-bound[1a,1g]

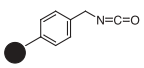
47,210-7 200–400 mesh, 4.5–5.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Isocyanate, polymer-bound[1a,1b]

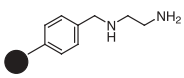
47,368-5 200–400 mesh, *ca.* 2.0 mmol — 1g, 5g, 25g



Reacts with:
RNH_2, R_2NH

Ethylenediamine, polymer-bound

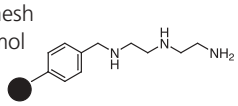
47,209-3 200–400 mesh, 2.5–3.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Diethylenetriamine, polymer-bound[1c,1d]

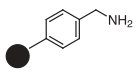
49,438-0 200–400 mesh, 4.0–5.0 mmol — 5g, 25g



Reacts with:
RCHO, RCO_2H, $RCOCl$, anhydrides

Poly(styrene-*co*-divinylbenzene), aminomethylated[1a,1e]

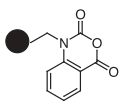
47,367-7 200–400 mesh, *ca.* 4.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Isatoic anhydride, polymer-bound[2]

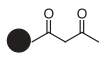
51,437-3 200–400 mesh, 2.0–2.5 mmol — 5g, 25g



Reacts with:
Amines

Activated ketone, polymer-bound[3,4]

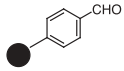
55,147-3 50–90 mesh, *ca.* 3.0 mmol — 5g, 25g, 100g



Reacts with:
Selectively binds primary amines in the presence of secondary amines

Formylpolystyrene, polymer-bound[1g]

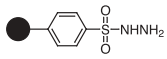
53,242-8 100–200 mesh, 2.0–3.0 mmol — 1g, 5g, 25g



Reacts with:
$RNHNH_2$, NH_2OR, RNH_2

p-Toluenesulfonyl hydrazide, polymer-bound[5]

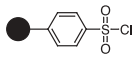
53,232-0 100–200 mesh, *ca.* 2.5 mmol — 1g, 5g, 25g



Reacts with:
Carbonyls

Sulfonyl chloride, polymer-bound[6]

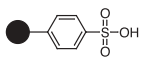
49,821-1 100–200 mesh, 1.0–3.0 mmol — 5g, 25g, 100g



Reacts with:
ROH, anilines

p-Toluenesulfonic acid, polymer-bound, macroporous[1d,1f,7]

53,231-2 30–60 mesh, 2.0–3.0 mmol — 5g, 25g, 100g



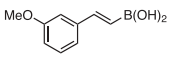
Reacts with:
Amines

References: (1) (a) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (b) Kaldor, S.W. et al. *Tetrahedron Lett.* **1996**, *37*, 7193. (c) Parlow, J. J. et al. *J. Org. Chem.* **1997**, *62*, 5908. (d) Flynn, D. L. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (e) Kaldor, S. W. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041. (f) Parlow, J. J.; Flynn, D. L. *Tetrahedron* **1998**, *54*, 4013. (g) Cresswell, M. W. et al. *ibid.* **1998**, *54*, 3983. (2) Coppola, G. M. *Tetrahedron Lett.* **1998**, *39*, 8233. (3) Yu, Z. et al. *ibid.* **2000**, *41*, 8963. (4) Yu, Z. et al. *J. Chem. Soc., Perkin I* **2001**, 1947. (5) Emerson, D. W. et al. *J. Org. Chem.* **1979**, *44*, 4634. (6) (a) Zhong, H. E. et al. *J. Org. Chem.* **1997**, *62*, 9326. (b) Rueter, J.K. et al. *Tetrahedron Lett.* **1998**, *39*, 975. (c) Baxter, E. W. et al. *ibid.* **1998**, *39*, 979. (d) Takahashi, T. et al. *ibid.* **1998**, *39*, 1369. (e) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998. (7) Shuker, A. J. et al. *Tetrahedron Lett.* **1997**, *38*, 6149.

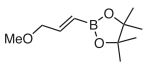
More New Products from Aldrich R&D

Boron Compounds

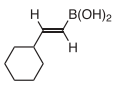
52,786-6
$C_9H_{11}BO_3$ — 1g, 10g



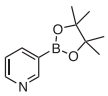
59,293-5
$C_{10}H_{19}BO_3$ — 1g, 10g



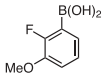
59,625-6
$C_8H_{15}BO_2$ — 1g, 10g



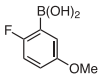
57,656-5
$C_{11}H_{16}BNO_2$ — 1g, 5g



59,425-3
$C_7H_8BFO_3$ — 1g, 5g



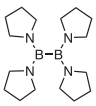
59,711-2
$C_7H_8BFO_3$ — 5g



59,306-0
$C_7H_7BF_2O_3$ — 1g, 5g

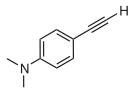
59,798-8
$C_3H_7BO_2$ — 1g, 5g

59,349-4
$C_{16}H_{32}B_2N_4$ — 1g, 5g

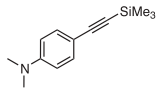


Arylacetylenes

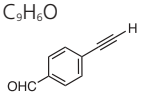
59,260-9
$C_{10}H_{11}N$ — 1g, 5g



59,283-8
$C_{13}H_{19}NSi$ — 1g, 5g



59,743-0
C_9H_6O — 1g, 5g

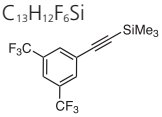


46,722-7
C_9H_8O — 1g, 5g

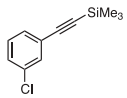
63,026-8
C_8H_5Cl — 1g, 5g

59,765-1
C_8H_7N — 1g, 5g

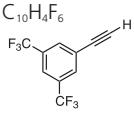
59,780-5
$C_{13}H_{12}F_6Si$ — 1g, 5g



59,770-8
$C_{11}H_{13}ClSi$ — 1g, 5g

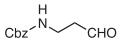


63,024-1
$C_{10}H_4F_6$ — 1g

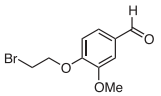


Organic Building Blocks

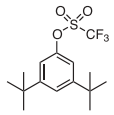
59,295-1
$C_{11}H_{13}NO_3$ — 1g



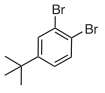
59,747-3
$C_{10}H_{11}BrO_3$ — 1g, 5g



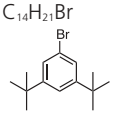
59,322-2
$C_{15}H_{21}F_3O_3S$ — 1g, 5g



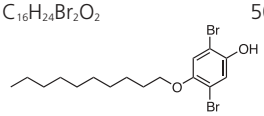
59,338-9
$C_{10}H_{12}Br_2$ — 1g, 5g



59,216-1
$C_{14}H_{21}Br$ — 1g, 5g

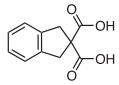


63,054-3
$C_{16}H_{24}Br_2O_2$ — 500mg, 1g

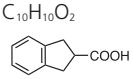


46,846-0
$C_{12}H_{12}O_2$ — 1g, 5g

59,545-4
$C_{11}H_{10}O_4$ — 1g

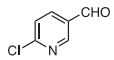


59,555-1
$C_{10}H_{10}O_2$ — 1g, 5g

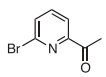


Organic Building Blocks (continued)

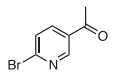
59,617-5
C_6H_4ClNO — 1g, 5g



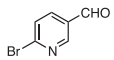
59,787-2
C_7H_6BrNO — 1g, 5g



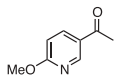
59,594-2
C_7H_6BrNO — 1g, 5g



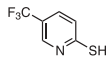
59,628-0
C_6H_4BrNO — 1g, 5g



59,776-7
$C_8H_9NO_2$ — 1g, 5g

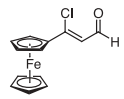


59,076-2
$C_6H_4F_3NS$ — 1g, 5g

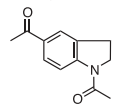


58,699-4
$C_5H_3ClO_2S$ — 1g, 5g

59,359-1
$C_{13}H_{11}ClFeO$ — 1g, 5g



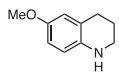
59,327-3
$C_{12}H_{13}NO_2$ — 1g, 5g



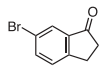
59,426-1
C_9H_6BrN — 1g, 5g

59,726-0
$C_8H_7FO_2$ — 1g, 5g

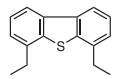
59,614-0
$C_{10}H_{13}NO$ — 1g



59,714-7
C_9H_7BrO — 1g, 5g



59,799-6
$C_{16}H_{16}S$ — 1g

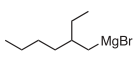


Miscellaneous Products

59,437-7
$C_6H_{15}B$ — 100mL

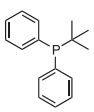
Triethylborane, 2.0M solution in diethyl ether

63,055-1
$C_8H_{17}BrMg$ — 100mL, 800mL



(2-Ethylhexyl)magnesium bromide, 1M solution in diethyl ether

59,168-8
$C_{16}H_{19}P$ — 1g, 5g



59,655-8
$C_{10}H_{15}P$ — 1g, 5g

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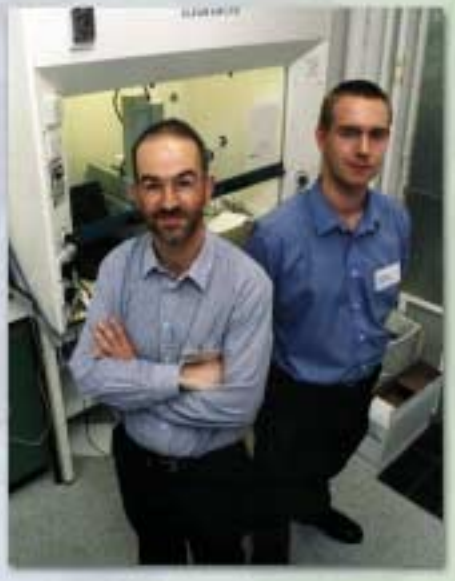
For competitive quotes on larger quantities contact **www.sigma-aldrich.com/safc**.

Kirk Malone—Winner of Sigma-Aldrich Award



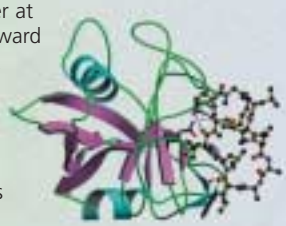
Nick Turner (left) and Kirk Malone in their laboratory at the Edinburgh Protein Interaction Centre. Photo © Jonathan Littlejohn.

Kirk Malone, a Ph.D. student in the laboratory of Professor Nick Turner at the University of Edinburgh, is the winner of a three-year research award from Sigma-Aldrich Company Ltd., U.K. Kirk's winning research project focuses on the "*Design and Synthesis of High-Affinity Ligands for Human Immunophilins*".

The aim of the project is to develop new classes of nonpeptidic inhibitors for the human immunophilins cyclophilin A (CypA) and FK binding protein (FKBP). Such inhibitors could be further developed as drugs for the treatment of HIV and parasitic infections. In collaboration with Professor Malcolm Walkinshaw at Edinburgh, Turner and Malone have used in silico screening to identify a novel class of ligand for CypA and FKBP. One round of chemical synthesis has led them to a family of compounds with a 20,000-fold increase in binding. The next step in the project is to apply combinatorial chemistry methodology to synthesize a library of potential ligands to further explore the ligand–protein interactions and thereby develop more potent inhibitors.

This leading-edge research is being carried out within the Wellcome Trust funded Edinburgh Protein Interaction Centre (EPIC; www.epic.ed.ac.uk), which is located in the School of Chemistry at the University of Edinburgh. The Centre fosters multidisciplinary research and is equipped with state-of-the-art facilities for the characterization of proteins, along with combinatorial and parallel synthesis equipment for high-throughput chemistry.

For further information, please contact Nick Turner (n.j.turner@ed.ac.uk).



CypA

FKBP

Congratulations to Kirk and Best Wishes for a Successful, World-Class Research Project!

Highlights of the Chemistry of Enantiomerically Pure Aziridine-2-carboxylates†

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Outline

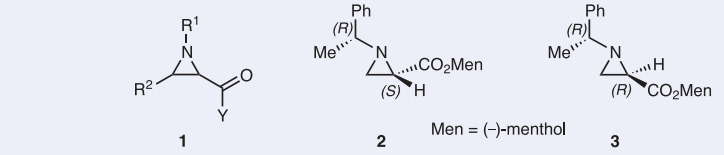
1. Introduction

The chemistry of enantiomerically pure substituted aziridines has been the subject of extensive research, because of their versatility in the synthesis of various nitrogen-containing molecules. Owing to the ring strain in aziridines, regio- and stereoselective ring-opening reactions with various nucleophiles, including carbon and heteroatoms, proceed smoothly and allow access to various nitrogen-containing compounds with predictable stereochemistry. In particular, the ring-opening reactions of enantiomerically pure aziridine-2-carboxylates provide either α- or β-amino esters and their derivatives. Many of these are biologically active and can serve as precursors for the synthesis of other biologically important compounds. Most such ring-opening reactions have focused on N-activated aziridines possessing a functional group that conjugatively stabilizes the lone-pair electrons on the nitrogen. There have been few reports on the ring-opening reactions of *N*-alkylaziridines.

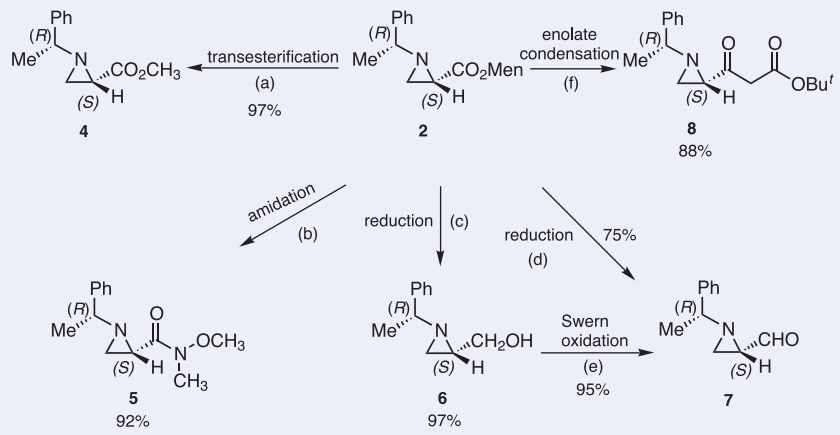
A number of surveys of the chemistry of chiral aziridines have been published.[1] Aziridines **1** in which R^2 is an alkyl or aryl group can be easily prepared, mainly as the trans isomers, from the corresponding imines and olefins. This is not the case for simple aziridine-2-carboxylates in which R^2 = H. The conformational stability and reactivity of the aziridine ring toward nucleophiles are dependent on the nature of R^1.[1e] When R^1 is an electron-withdrawing group such as carboxamide or sulfonamide, the aziridine becomes quite reactive, which is consistent with conformational destabilization of the aziridine ring. However, if R^1 is an electron-donating group, especially alkyl, the opposite is observed: the aziridine ring conformation is more stable and less reactive toward nucleophiles. This review focuses on the preparation and utilization of *N*-(*R*)-α-methylbenzylaziridine-2-carboxylates **2** and **3** and their derivatives.

2. Preparation of Enantiomerically Pure Aziridine-2-carboxylates

Enantiomerically pure aziridine-2-carboxylates can be prepared from suitably protected chiral serine.[2] Asymmetric synthesis can be achieved by either the

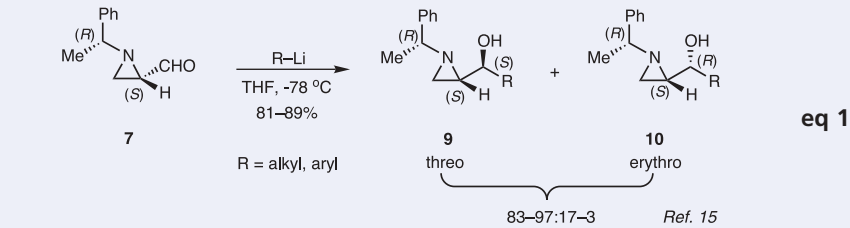


1 2 3

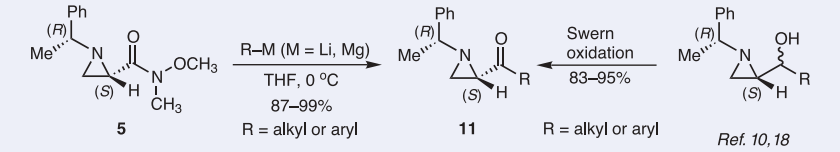


Representative reaction conditions: (a) Mg, CH_3OH, reflux, 2 h; (b) *N,O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, CH_2Cl_2, -10 °C, 2 h; (c) $LiAlH_4$, Et_2O, 0 °C, 1 h; (d) DIBAL-H, toluene, -78 °C, 2 h; (e) DMSO, oxalyl chloride, CH_2Cl_2, NEt_3, -78 °C, 1.5 h; (f) LiHMDS, $CH_3CO_2Bu^t$, THF, -78 °C, 30 min.

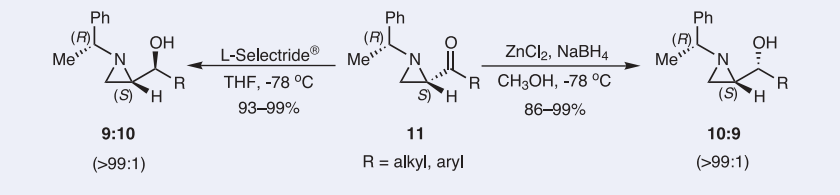
Scheme 1. Elaboration of the C-2 Carboxylate Group.



eq 1



Scheme 2. Syntheses of Enantiomerically Pure α-Amino Ketone **11**.



Scheme 3. Improved Diastereoselectivities in the Preparation of α-Amino Alcohols **9** and **10**.

Gabriel–Cromwell reaction of camphorsultam[3] or imidazolidin-2-one[4], or by nitrene addition to α,β-unsaturated acid derivatives bearing a chiral auxiliary.[5] The aza-Darzens reaction of *N*-bromoacetylcamphorsultam has also been used and gives high stereoselectivities.[6] A chiral phase-transfer catalyst mediated the reaction between *N*-arylhydroxamic acids and *tert*-butyl acrylates to give *N*-arylaziridine-2-carboxylates in 16–61% ee's.[7] Chromatographic separation or fast ester cleavage with a strong base[8] can be used to resolve a diastereomeric mixture of aziridine-2-carboxylates bearing a chiral group on the nitrogen. Lipase-mediated stereoselective transesterification[9] or ammonolysis[10] of aziridine-2-carboxylates have also been developed. However, none of the preceding methods is suitable for the multikilogram-scale preparation of aziridine-2-carboxylates, since most are not stereoselective and/or require a chiral auxiliary or chromatographic separation. Recently, we have achieved the selective crystallization and isolation of each diastereomer of 1-(1'-α-methylbenzyl)-aziridine-2-carboxylic acid menthol esters.[11] The *N*-α-methylbenzyl group differentiates the stereoisomers at the C-2 position of the aziridine and controls the reactivity in ring-opening reactions. Furthermore, it serves as a good nitrogen protecting group, which tolerates various chemical transformations and is easy to remove either by hydrogenolysis, metal–ammonia reduction, or treatment at the carbamate stage with methanesulfonic acid and anisole.

3. Elaboration of the C-2 Carboxylate Group

The C-2 menthol ester group of chiral aziridine **2** can be transesterified into the methyl, **4**, or ethyl ester upon treatment with 1.0 equivalent of Mg in methanol or ethanol (**Scheme 1**). The reaction of **2** with Weinreb's amine hydrochloride and $AlMe_3$ in CH_2Cl_2 provides the corresponding Weinreb amide **5** in high yield.[12] We have obtained the primary alcohol **6** in almost quantitative yield by reduction of **2** with $LiAlH_4$ or $NaBH_4$. We have also prepared the α-amino aldehyde **7** in high yield by careful reduction of **2** with DIBAL-H at -78 °C or by Swern oxidation of primary alcohol **6**. α-Amino aldehydes usually have a low configurational stability; however, the presence of the three-membered ring at the α position of **7** makes the C-2 proton nonenolizable and allows the purification of **7** using silica gel chromatography. We have found that enantiomerically pure aziridine-2-carbox-

aldehyde **7** can be stored in the refrigerator for months without losing its stereochemical integrity. We believe that **7** is the most configurationally stable α-amino aldehyde reported to date. The reaction of aziridine-2-carboxylate **2** with enolates provides β-keto esters **8** in high yields.[13]

Vicinal amino alcohol units are found in many important natural products and biologically active compounds including ephedra alkaloids and sphingolipids bearing a distinctive sphingoid backbone.[14] The reaction of amino aldehyde **7** with various organometallic reagents is expected to yield a diastereomeric mixture of two aziridine-2-methanols, **9** and **10** (**eq 1**). Alkyl- or aryllithium reagents provide better stereoselectivity in the addition reactions than Grignard reagents, and increasing the steric requirement around the nucleophilic center results in better stereoselectivity.[15] The diastereoselectivity of the addition reaction of organolithium reagents to enantiomerically pure **7** varies from 1:1 to 32:1 in favor of **9**, depending on the reaction conditions (source of the organometallic reagent, solvent, and the presence of additional lithium salt).

We found, however, a better way to increase the diastereomeric ratio of the secondary alcohols by stereoselectively reducing the corresponding α-amino ketones, **11**, with a suitable hydride reducing agent. In this regard, enantiomerically pure **11** can be precursors for various 1,2-amino alcohols. Ketones **11** are easily prepared by addition of organometallics[12,16] to Weinreb amide **5**,[10] or by oxidation[17] of secondary alcohols of type **9** or **10** (**Scheme 2**).[18]

The reduction of ketones **11** with L-Selectride® in THF provides predominantly the threo isomers **9** through a "Felkin-Anh" transition state. Most of the substrates exhibit high stereoselectivities, except for the 1-hexynyl ketone, which does not have adequate steric requirements due to the geometry of the triple bond at the α position of the ketone.[18] We have recently found that the chelation-controlled reduction of (2*S*)-2-acylaziridines **11** in the presence of the bidentate Lewis acid $ZnCl_2$ and $NaBH_4$ predominantly gives the erythro isomers **10** in high chemical yields (**Scheme 3**).[19]

The excellent stereochemical control of the reaction using $ZnCl_2$ and $NaBH_4$ can be explained by hydride delivery to the chelated intermediate (**Figure 1**). Ab initio calculations showed this intermediate to be the most stable form, lying at least 30 kcal/mol below the other local minimum structures. This chelated structure appears to be stabilized by strong interactions of the empty *d* orbitals of Zn^{2+} with the lone pairs of the nitrogen and oxygen atoms as well as with the aromatic π electrons in the benzene ring.[19]

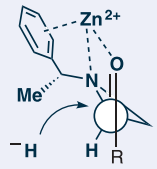
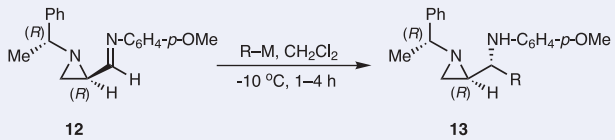
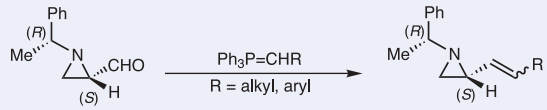


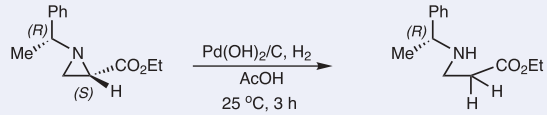
Figure 1. Most Stable Structure of the Chelated Intermediate in the $ZnCl_2$–$NaBH_4$ Reduction of **11**.



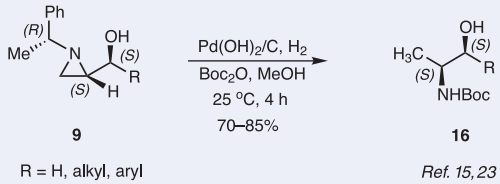
eq 2



eq 3



eq 4



eq 5

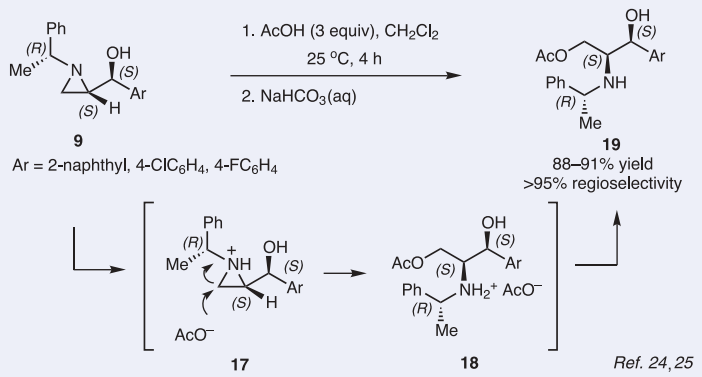
Aziridinylaldimine **12**, formed by the condensation of aldehyde (*R*,*R*)-**7** and *p*-anisidine, readily reacts with organometallics to give the corresponding amines in high yields. In most cases, addition of alkyl or aryl Grignards in the presence of BF_3•OEt_2 yields the chelation-controlled products, **13**, as the major isomers with >95% de's (**eq 2**).[20,21]

The aldehyde group of aziridine-2-carboxaldehyde **7** can be transformed into an olefin by Wittig reaction with suitable ylides (**eq 3**). This reaction efficiently provides various chain-extended 2-vinylaziridines, **14**. The reaction usually gives a mixture of trans and cis olefins, but the Horner–Emmons–Wadsworth conditions lead exclusively to the trans olefin.[22]

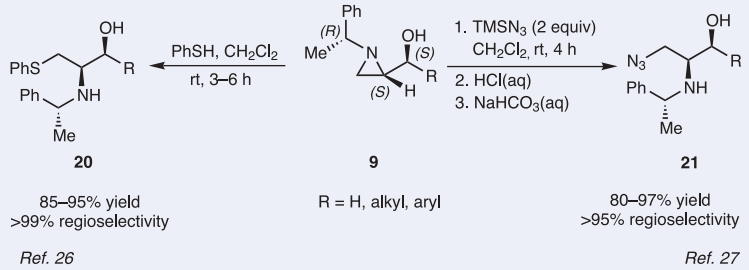
4. Aziridine Ring Opening

4.1. Regioselective Reductive Ring Opening

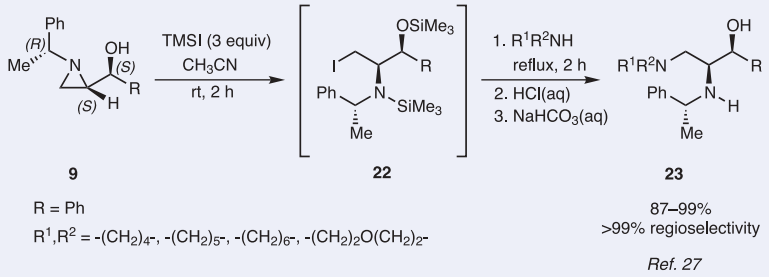
We have found that the regioselectivity of the catalytic hydrogenation of 2-substituted aziridines is controlled by the electronic character of the substituent. With an electron-withdrawing substituent at C-2, the ring-opening reduction takes place at the C(2)–N bond, with a resulting loss of the stereochemistry at C-2, and leads to the β-amino carbonyl derivative **15** highly regioselectively (**eq 4**).[23] However, when the



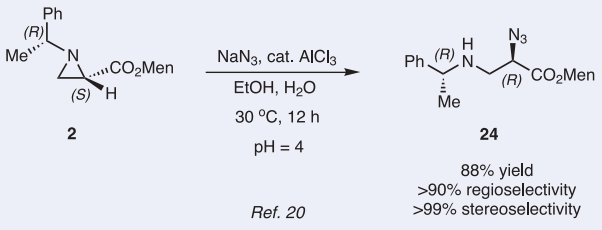
Scheme 4. Regioselective Ring Opening of Nonactivated Aziridines **9**.



Scheme 5. Regioselective Ring Opening with Nitrogen and Sulfur Nucleophiles.



Scheme 6. Regioselective Ring Opening with Iodide.



eq 6

carbonyl group is first reduced to the corresponding alcohol, thus removing the electron-withdrawing character at C-2, ring-opening reduction occurs at the C(3)–N bond and yields β-amino alcohol **16** (**eq 5**).[15,23] The presence of Boc_2O in the reaction medium facilitates cleavage of the α-methylbenzyl group from the nitrogen after ring reduction.[23] Since we can stereoselectively prepare the secondary alcohols **9** and **10** by reduction of ketones **11** (see Scheme 3), both (*S*,*S*)- and (*R*,*S*)-β-amino alcohols (**16** and their diastereomers) can readily be obtained from **11** via aziridinols **9** and **10**.

4.2. Regioselective Ring Opening with Heteroatom Nucleophiles

The regioselective introduction of a heteroatom nucleophile into enantiomerically pure 2-substituted aziridines makes it possible to synthesize polyfunctionalized chiral compounds. The ring strain present in aziridines is responsible for the facile ring-opening reactions of N-activated aziridines that have been cited in the literature.[1] To our knowledge, there has been less extensive reporting on the reactions of nonactivated aziridines. 2-Alkyl-*N*-(α-methylbenzyl)aziridines have an electron-rich nitrogen, and their reactions with strong organometallic nucleophiles do not provide any ring-opened product. However, the addition of Brønsted or Lewis acids facilitates their ring-opening reactions, an example of which is the efficient, room-temperature conversion of *N*-(*R*)-(α-methylbenzyl-2-methanol derivatives **9** into (1*S*,2*S*)-2-amino-1,3-propanediols **19** (**Scheme 4**). The ring-opening reaction is accelerated by protonation of the nitrogen atom with AcOH to form aziridinium salts **17**. The nucleophile, AcO^-, then attacks the aziridine ring at the less sterically hindered C-3 position to form ammonium salts **18**. Subsequent treatment with saturated aqueous $NaHCO_3$ solution affords the ring-opened products **19** in high yields and excellent regioselectivities.[24,25]

Sulfur[26] and azide nucleophiles[27] react similarly (**Scheme 5**). The aziridine ring-opening reaction with thiols usually requires Lewis acid activation even for activated aziridines. However, the nitrogen of nonactivated aziridine **9** is basic enough to pick up a proton from thiols. This proton transfer produces an aziridinium intermediate, which is attacked by the thiolate ion at the less sterically hindered C-3 position to provide the ring-opened product **20** exclusively and in high yield. We hypothesized that the rate-determining step of the ring-opening reaction was proton transfer from the thiol to the ring nitrogen to form the aziridinium intermediate, and that the reaction rate could be influenced by the acidity of the thiol. A kinetic study of the ring-opening reaction showed a good correlation between the acidity of thiols and the reaction rate.[26]

Sodium azide has traditionally been used as a nitrogen nucleophile in most of the ring-opening reactions of activated aziridines. However, the presence of the *N*-(α-methylbenzyl substituent in the nonactivated aziridine **9** requires activation of the basic

nitrogen prior to ring opening. Azidotrimethylsilane serves a dual function: it activates the basic ring nitrogen of **9** and provides a source of N_3^-, which attacks the less substituted position, C-3. The ring-opened product, **21**, was obtained in high yield, and was further elaborated into the corresponding diamino alcohol by $LiAlH_4$ reduction of the azido group. Similarly, iodotrimethylsilane reacts with **9** and leads to an alkyl iodide intermediate, **22**, which produces 3-hydroxy-1,2-diamines, **23**, in high yields upon reaction with secondary heterocyclic amines (**Scheme 6**).[27]

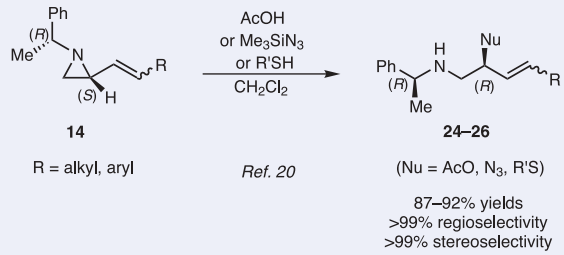
In contrast to the preceding results, a different regioselectivity is observed in the reaction of enantiomerically pure aziridine-2-carboxylate **2** with NaN_3 in aqueous ethanol and in the presence of a catalytic amount of $AlCl_3$ (pH 4). In this reaction, the nucleophile, N_3^-, selectively attacks the more electron-deficient carbon, C-2, to give 2-azido-3-aminopropanoate **24** in high yield and regioselectivity (**eq 6**).[20]

Another example of nucleophilic attack at the more sterically hindered C-2 is provided by the ring-opening reactions of 2-vinylaziridines with heteroatom nucleophiles. Upon allylic activation, the C(2)–N bond is regio- and stereospecifically cleaved by treating 2-vinylaziridines **14** with 2.5 equiv of AcOH, RSH, or $TMSN_3$ in CH_2Cl_2 to provide the ring-opened products **24–26** (**eq 7**).[20]

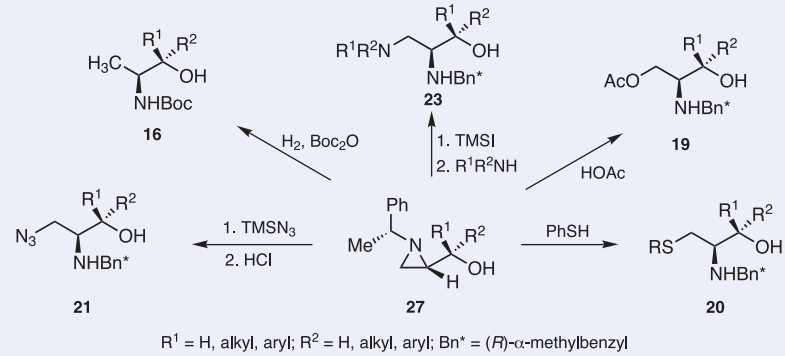
The regioselective ring-opening reactions of enantiomerically pure aziridine-2-methanols with heteroatom nucleophiles are summarized in **Scheme 7**.

5. Ring Expansions Leading to Oxazolidinones[28]

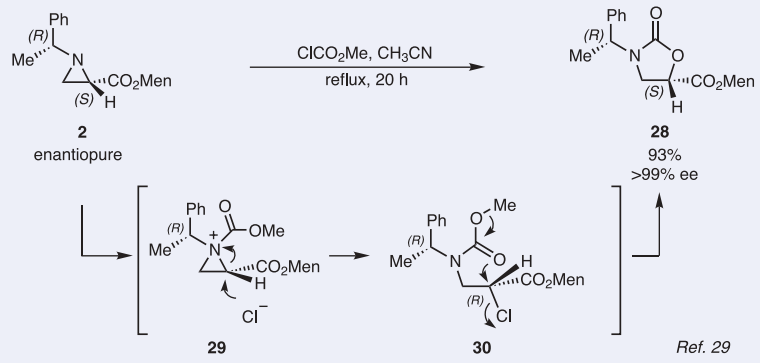
Since the aziridine nitrogen is basic and nucleophilic, we envisaged a regioselective aziridine ring-opening reaction initiated by acylation of the aziridine nitrogen to produce an activated aziridinium species. Reaction of enantiomerically pure aziridine-2-carboxylic acid menthol ester **2** with 1.5 equiv of methyl or allyl chloroformate in refluxing CH_3CN proceeded smoothly to give oxazolidin-2-one-5-carboxylic acid menthol ester **28** in 93% yield (**Scheme 8**).[29] The crystal structure of **28** enabled us to determine the stereochemical course of the reaction, which occurred with retention of configuration at C-2 of the aziridine. A plausible mechanism involves the formation of α-chlorocarboxylate **30**, which was isolated and characterized from its spectral data including HRMS. Intermediate **30** is formed by S_N2 attack of Cl^- at C-2 of the activated aziridine



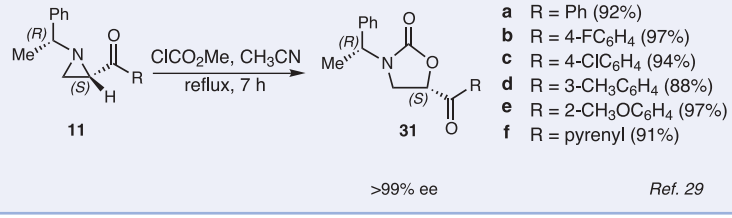
eq 7



Scheme 7. Conversion of Aziridine-2-methanols, **27**, into More Functionalized Amino Alcohols.



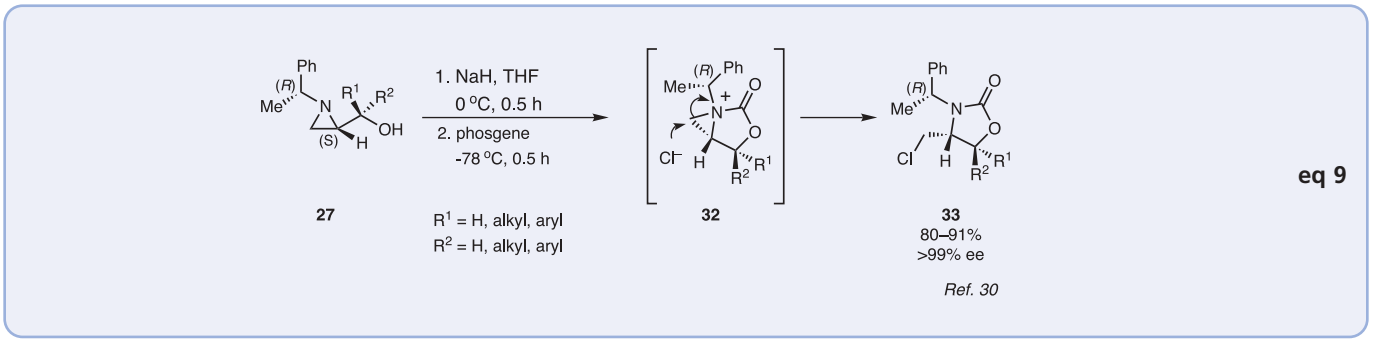
Scheme 8. Ring Expansion of Aziridine-2-carboxylate **2** into the Corresponding Oxazolidinone.



eq 8

29 and concomitant regioselective cleavage of the C(2)–N bond. Subsequent intramolecular cyclization by the carbamate oxygen of **30** provides oxazolidinone **28** with an overall retention of configuration. We have also confirmed that the same reaction with enantiopure **3** provides the corresponding oxazolidin-2-one in excellent yield and enantioselectivity.[29]

The preceding results show that



eq 9

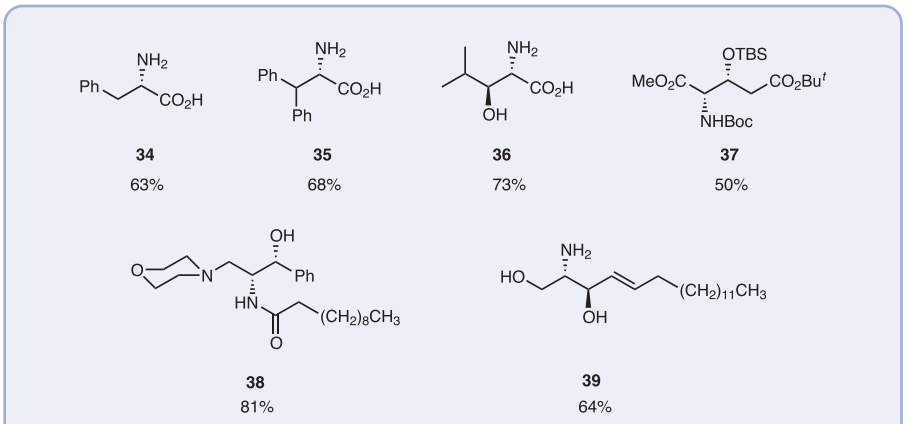


Figure 2. Amine-Containing, Biologically Active Compounds Readily Available from Aziridine-2-carboxylates.

5-functionalized enantiomerically pure oxazolidin-2-ones can be obtained very efficiently with retention of configuration from the corresponding aziridines bearing an electron-withdrawing group at C-2. We have extended the scope of this reaction by employing various C(2)-substituted aziridines to obtain 5-functionalized chiral oxazolidin-2-ones, **31**, in excellent yields and stereoselectivities (**eq 8**).[29]

We have also successfully carried out the ring opening of aziridine-2-methanols with concomitant ring expansion leading to enantiomerically pure 4-functionalized oxazolidin-2-ones.[30] Thus aziridine-2-methanols **27** led, upon treatment with NaH in THF and then phosgene, to (4*R*)-4-chloromethyl-5-substituted oxazolidin-2-ones **33** in good yields and stereoselectivities (**eq 9**). Oxazolidinones **33** presumably arise from chloride attack at the sterically less hindered C-3 of the activated aziridinium intermediates **32**. We were able to establish the absolute configuration at C-4 of **33** indirectly by measuring the coupling constants of the two vicinal protons at C-4 and C-5 in cases where R^1 or R^2 = H.[31]

The preceding results provide a novel route toward functionalized 2-oxazolidinones, which can be utilized as chiral synthons or chiral auxiliaries in a variety of asymmetric transformations.

6. Asymmetric Synthesis of Amino Acids and Alcohols

The versatility of aziridine-2-carboxylates in stereoselective transformations has led to a wide variety of optically pure, amine-containing molecules including natural and unnatural amino acids and their biologically active derivatives. Examples include phenylalanine (**34**),[32] homophenylalanine,[30] diphenylalanine (**35**),[33] 3-hydroxyleucine (**36**), and *threo*-β-hydroxy-L-glutamic acid (**37**).[13] The methodology that leads to 2,3-diamino alcohols (see Scheme 6) provides a way for the efficient synthesis of the glycosylceramide synthase inhibitor D-*threo*-PDMP (**38**)[27] and sphingosine (**39**)[20] from chiral aziridine-2-carboxylates.

7. Conclusion

Both (2*R*)- and (2*S*)-aziridine-2-carboxylates and some of their derivatives are now commercially available in bulk quantities in optically pure forms.[34] Stereo- and regioselective transformations including aziridine ring-opening reactions permit the preparation of a variety of nitrogen-containing molecules. Some of them are useful in practical syntheses of commercially valuable compounds and as starting molecules to generate diverse compound libraries. We hope that the material presented in this review will catch the attention of readers, who are actively engaged in synthesis and other aspects of research and development in many different disciplines.

8. Acknowledgement

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9. References and Notes

(†) WKL dedicates this review to Professor Manfred T. Reetz on the occasion of his 60th birthday.

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About the Authors

Won Koo Lee was born in 1962 in Seoul, Korea. He received a B.S. degree in 1984 and an M.S. degree in 1986 from Sogang University, Seoul, Korea. He obtained his Ph.D. degree in 1991 from the University of Illinois at Urbana-Champaign (with Professor Peter Beak). After two years of postdoctoral work with the late Professor Henry Rapoport at the University of California, Berkeley, he returned to Korea in 1993 as an assistant professor at Sogang University. He was promoted to full professor in 2002. In 2000, he received an Alexander von Humboldt research fellowship and was a visiting professor in Professor Manfred T. Reetz's research group at the Max Planck Institute for Coal Research in Muelheim/Ruhr, Germany. He is a cofounder of ChemBioNex Co., Ltd., and a member of the board of scientists of ImaGene. He is a member of the Korean and American Chemical Societies. His research interests include developing new synthetic methodologies, the synthesis of biologically active molecules, and the elaboration of chiral aziridines.

Hyun-Joon Ha was born in 1959 in Jinju, Korea. He obtained his B.S. degree in chemistry in 1982 from Seoul National University, and his Ph.D. degree in 1987 from Brown University, Providence, RI (with Professor David E. Cane). After a one-year postdoctoral fellowship with Professor Michael C. Pirrung at Stanford University, he returned to Korea in 1988, and accepted the position of senior research scientist at the Korea Institute of Science and Technology (KIST). In 1991, he joined the faculty of the chemistry department at Hankuk University of Foreign Studies, and is now a full professor and chairman of the department. In 1993, he carried out research at Cambridge University, U.K., as a short-term visiting scholar. He is a cofounder of ChemBioNex Co., Ltd., and a member of the board of scientists of ImaGene. His research interests include the exploitation of new methods in organic synthesis, imines and iminium ions, asymmetric synthesis of biologically active molecules, and lipase-mediated chiral resolutions. He has recently become interested in medicinal chemistry for drug discovery, process development for pharmaceuticals, and the design and synthesis of radiopharmaceuticals. He is a member of the Korean and American Chemical Societies and is on the editorial board of the electronic journal *Arkivoc*. He has coauthored over 60 papers and three reviews.

Enantiomerically Pure Aziridines and Oxazolidinones

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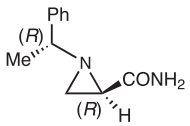
(2*R*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxamide

57,055-9 — 1g, 5g



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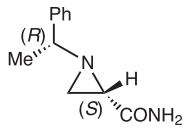

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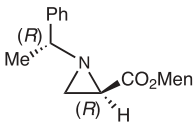
57,054-0 — 5g, 25g



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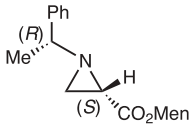
57,051-6 — 5g, 25g



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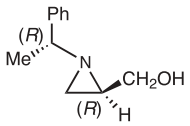
57,056-7 — 1g, 5g



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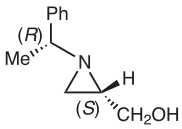
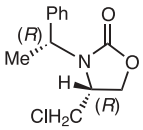


(4*R*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

57,061-3 — 1g, 5g



(4*S*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

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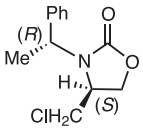

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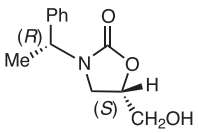

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55mmID x 30mmH	12.5g	6qty/pk	52591-U
70mmID x 40mmH	25g	6qty/pk	52592-U
90mmID x 48mmH	50g	6qty/pk	52593-U
110mmID x 66mmH	100g	3qty/pk	52594-U
Merck-Si			
55mmID x 30mmH	12.5g	6qty/pk	2026-U
70mmID x 40mmH	25g	6qty/pk	2027-U
90mmID x 48mmH	50g	6qty/pk	2028-U
110mmID x 66mmH	100g	3qty/pk	2029-U
Charcoal			
55mmID x 30mmH	12.5g	6qty/pk	2031-U
70mmID x 40mmH	25g	6qty/pk	2032-U
90mmID x 48mmH	50g	6qty/pk	2033-U
110mmID x 66mmH	100g	3qty/pk	2034-U
Magnesium Sulfate			
55mmID x 30mmH	12.5g	6qty/pk	2037-U
70mmID x 40mmH	25g	6qty/pk	2041-U
90mmID x 48mmH	50g	6qty/pk	2043-U
110mmID x 66mmH	100g	3qty/pk	2044-U
Celite®			
55mmID x 30mmH	12.5g	6qty/pk	2047-U
70mmID x 40mmH	25g	6qty/pk	2048-U
90mmID x 48mmH	50g	6qty/pk	2049-U
110mmID x 66mmH	100g	3qty/pk	2064-U

Bed Description	Wt.	Qty.	Cat. No.
Florisil®			
55mmID x 30mmH	12.5g	6qty/pk	2074-U
70mmID x 40mmH	25g	6qty/pk	2076-U
90mmID x 48mmH	50g	6qty/pk	2077-U
110mmID x 66mmH	100g	3qty/pk	2078-U
Alumina-A			
55mmID x 30mmH	12.5g	6qty/pk	2084-U
70mmID x 40mmH	25g	6qty/pk	2087-U
90mmID x 48mmH	50g	6qty/pk	2088-U
110mmID x 66mmH	100g	3qty/pk	2089-U
Alumina-N			
55mmID x 30mmH	12.5g	6qty/pk	2091-U
70mmID x 40mmH	25g	6qty/pk	2092-U
90mmID x 48mmH	50g	6qty/pk	2093-U
110mmID x 66mmH	100g	3qty/pk	2094-U
Alumina-B			
55mmID x 30mmH	12.5g	6qty/pk	2096-U
70mmID x 40mmH	25g	6qty/pk	2097-U
90mmID x 48mmH	50g	6qty/pk	2098-U
110mmID x 66mmH	100g	3qty/pk	2099-U
DPA-6S			
55mmID x 30mmH	6g	6qty/pk	2079-U
70mmID x 40mmH	12.5g	6qty/pk	2081-U
90mmID x 48mmH	25g	6qty/pk	2082-U
110mmID x 66mmH	50g	6qty/pk	2083-U

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56,542-3	Acetonitrile with 0.035% TFA	4x4L 18L
57,472-4	Acetonitrile with 0.05% TFA	4x4L 18L
57,473-2	Acetonitrile with 0.10% TFA	4x4L 18L
57,694-8	Acetonitrile with 0.035% formic acid	4L 18L
57,854-1	Acetonitrile with 0.05% formic acid	4L 18L
57,695-6	Acetonitrile with 0.10% formic acid	4x4L 18L
59,750-3	Acetonitrile with 0.035% acetic acid	4x4L 18L
59,739-2	Acetonitrile with 0.05% acetic acid	4x4L 18L
59,075-4	Acetonitrile with 0.10% acetic acid	4x4L 18L
57,789-8	Methyl alcohol with 0.10% TFA	4x4L 18L
63,254-6	Methyl alcohol with 0.10% formic acid	4x4L 18L
59,014-2	Water with 0.05% TFA	4x4L 18L

Catalog No.	Product Name	Unit
59,015-0	Water with 0.06% TFA	4x4L 18L
57,690-5	Water with 0.10% TFA	4x4L 18L
57,691-3	Water with 0.10% formic acid	4x4L 18L
59,772-4	Water with 0.035% acetic acid	4x4L 18L
59,761-9	Water with 0.05% acetic acid	4x4L 18L
59,116-5	Water with 0.10% acetic acid	4x4L 18L
57,696-4	Acetonitrile with 0.10% formic acid, 0.01% TFA	4L 18L
57,692-1	Water with 0.10% formic acid, 0.01% TFA	4L 18L
63,233-3	Acetonitrile with 10% water, 0.10% TFA	4x4L 18L
63,232-5	Water with 10% acetonitrile, 0.10% TFA	4x4L 18L
63,245-7	Methyl alcohol with 10% water, 0.10% TFA	4x4L 18L
63,244-9	Water with 10% methyl alcohol, 0.10% TFA	4x4L 18L

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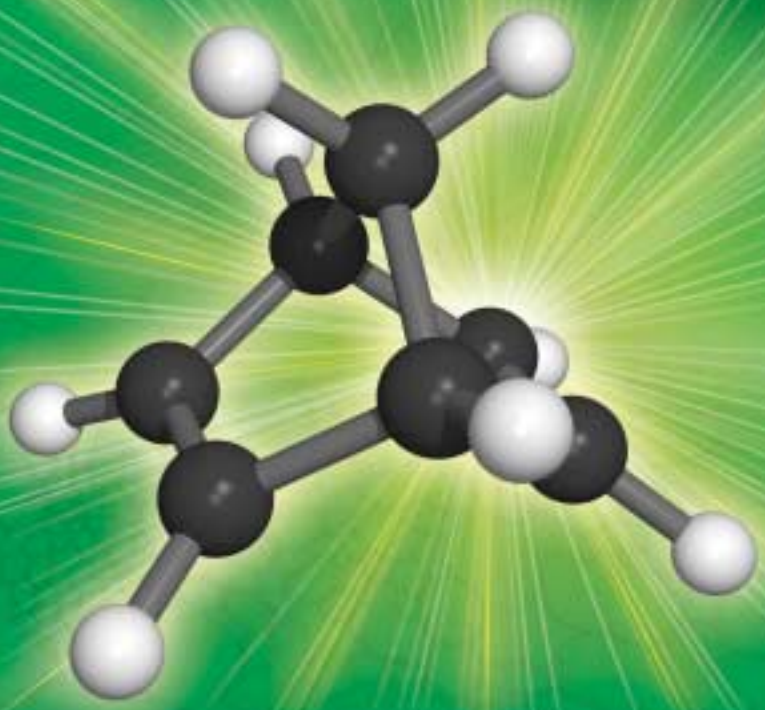
(Bicyclo[2.2.1]hepta-2,5-diene
Product No. B3,380-3, CAS No. 121-46-0)



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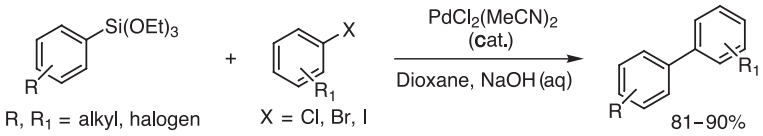
New Alkoxysilanes

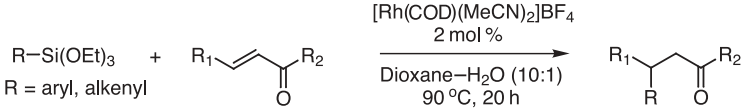
The use of silicon compounds as transmetalation reagents has attracted much attention as a viable alternative to the popular Stille and Suzuki coupling reactions, mainly due to the formation of nontoxic byproducts and the stability of the reagents to many reaction conditions.[1] Silicon-based coupling reactions can be carried out using aryl, heteroaryl, or alkenyl halides and alkoxysilanes in the presence of palladium or rhodium catalysts. Among the various types of silicon compounds available, alkoxysilanes are most effective in the coupling reactions.[2]



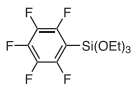
R, R_1 = alkyl, halogen

X = Cl, Br, I

Recently, considerable attention has been paid to the rhodium-catalyzed addition of aryl(trialkoxy)silanes to carbonyl compounds, such as aldehydes, α,β-unsaturated ketones and esters.[3]



59,275-7

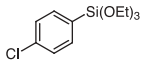


5g
10g
25g

17,556-0

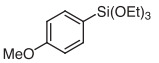
100mL
500mL

59,791-0



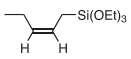
1g
10g

59,701-5



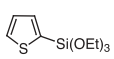
5g
20g

59,264-1



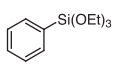
1g
5g

59,700-7



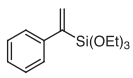
1g
10g

17,560-9



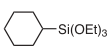
5g
250g
1kg

59,635-3



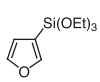
1g
10g

59,242-0



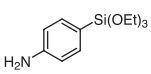
1g
5g

59,231-5



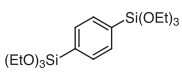
5g

59,647-7



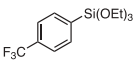
1g
10g

59,803-8



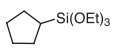
5g
20g

63,043-8



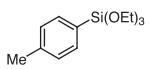
1g
5g

59,604-3



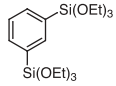
5g

59,157-2



1g
5g

59,813-5



1g
10g

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References: (1) (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (b) Chuit, C. et al. *Chem. Rev.* **1993**, *93*, 1371. (c) Horn, K. A. *ibid.* **1995**, *95*, 1317. (d) Hiyama, T.; Shirakawa, E. In *Topics of Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Heidelberg, 2002; Vol. 219, p 61. (2) (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Tamao, K. et al. *Tetrahedron Lett.* **1989**, *30*, 6051. (c) Shibata, K. et al. *Chem. Commun.* **1997**, 1309. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (e) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2140. (f) Lee, H. M.; Nolan, S. P. *ibid.* **2000**, *2*, 2053. (g) Murata, M. et al. *Synthesis* **2001**, 2231. (3) Oi, S. et al. *Org. Lett.* **2002**, *4*, 667.

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Coiled Reflux Condenser

Coolant circulates through the coil. The jacket provides additional cooling capacity by allowing vapors to condense on the inner wall of the jacket. Ʇ24/40 joints.

Overall L (mm)	Cat. No.
200	Z55,360-3
300	Z55,361-1
400	Z55,363-8

Modified Friedrichs Condenser

Molded spiral condensing coolant tube fits closely within jacket to force vapors along the spiral path. The modified feed tube reduces the chance of breakage. Ʇ24/40 joints.

Jacket o.d. (mm)	Overall L (mm)	Cat. No.
37	270	Z55,358-1
37	370	Z55,364-6
54	300	Z55,365-4

Liebig Condenser

Ʇ24/40 outer-top joint with lower, inner, drip-tip joint.

Overall L (mm)	Cat. No.
200	Z55,366-2
300	Z55,367-0
400	Z55,368-9

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ALDRICH®

Dry Ice Condenser Trap

4mm PTFE stopcock. Use with or without dry ice to condense and collect material in trap.

Reservoir cap. (mL)	Overall L (mm)	Cat. No.
250	450	Z55,355-7
500	470	Z55,356-5
1,000	490	Z55,357-3

Safety Bubbler

Built-in flash arrester bulb prevents backflow. Capacity: 15mL fill mark.

Z55,387-5

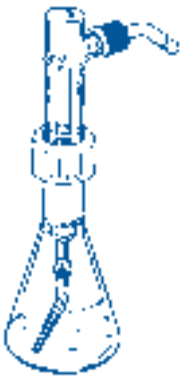
Chromatography Sprayer

Provides a fine, uniform spray that is optimized for the development of TLC plates. Also suited for use in electrophoresis.

- Adjustable spray pattern using thumb on vent hole
- Greaseless, screw-threaded T joint will not seize; a simple turn of the threaded cap pulls joint apart safely
- Uses low-pressure gas or air (<5 psi)

Flask size (mL)	Cat. No.
10	Z52,971-0
50	Z52,972-9
125	Z52,973-7
250	Z52,974-5

Replacement SafetyBarbs™	
Consists of PBT cap, PP barbed connector, and silicone rubber seal. Choice of straight or angled barb.	
Straight barb	Z54,778-6
Angled barb	Z54,788-3



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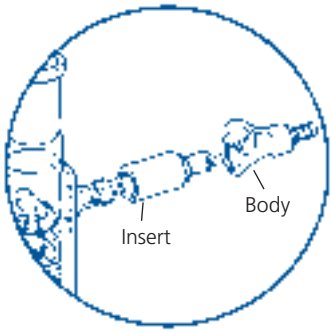
Coupling insert, GL 14 inner thread Z55,337-9
Coupling body, ¼ in. i.d. tubing connection Z55,338-7



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Z55,382-4

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K. Tanaka, John Wiley & Sons, New York, NY, 2003, 433pp. Hardcover.

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Z55,370-0

The Laboratory Quality Assurance System: A Manual of Quality Procedures and Forms (with CD-ROM)

3rd ed., Thomas A. Ratliff, John Wiley & Sons, New York, 2003, 236pp. Softcover.

Incorporates changes to ANSI/ISO/ASQ 9001-2000 pertaining to laboratories and provides information on the inter-relationship of ANSI/ISO 17025:1999 and ANSI/ISO/ASQ. Also provides blank forms used in preparing a quality manual.

Z55,340-9

Wiley Guide to Chemical Incompatibilities

R. P. Pohanish and S.A. Greene, John Wiley & Sons, New York, NY, 2003, 1408pp. Hardcover.

Compiles hard-to-find data on over 11,000 chemical compounds, describing a wide range of chemical reactions that produce undesirable results in uncontrolled situations.

Z55,348-4

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F. X. McConville, FXM Engineering and Design, Worchester, MA, 2002, 312pp. Softcover.

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Z55,385-9

Candid Science: Conversations with Famous Chemists

I. Hargittai, Imperial College Press, London, UK, 2000, 516pp. Softcover.

36 chemists discuss their lives in science, how they began, their aspirations, and their hardships and triumphs.

Z55,383-2

Candid Science II: Conversations with Famous Biomedical Scientists

I. Hargittai, Imperial College Press, London, UK, 2002, 604pp. Softcover.

Contains 36 interviews that present a cross-section of biomedical science, important research areas, and discoveries.

Z55,384-0

Purification of Laboratory Chemicals

5th ed., W. L. F. Armarego and C. Chai, Elsevier-Science, 2003, 624pp. Softcover.

Updated to include more detailed descriptions of commonly used techniques. New procedures, ionization constants, and more detail about trivial compound names are included.

Z54,183-4

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B. L. Hayes, CEM Publishing, Matthews, NC, 2003, 289 pp. Hardcover.

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Z55,386-7

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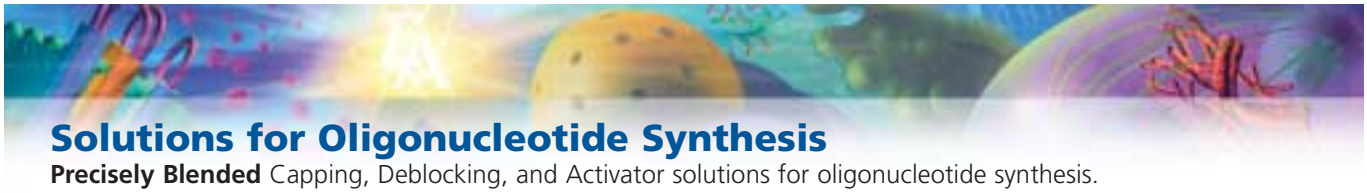

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55,531-2	**Cap Mix A, with 2,6-lutidine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% 2,6-lutidine)	1L 2L
55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L

Catalog No.	Product Name	Unit
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L
56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L
55,404-9	**Activator** (1-*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L

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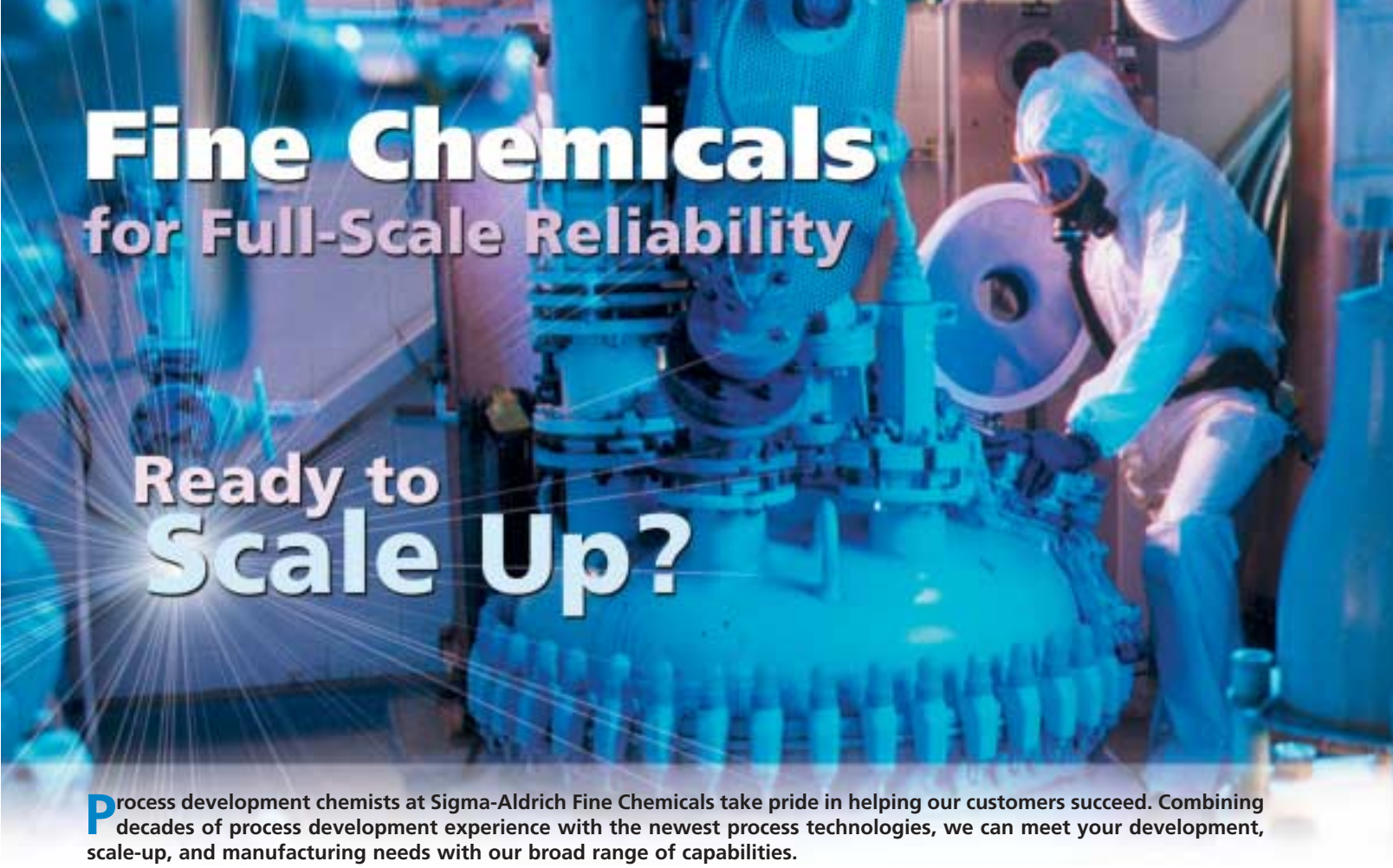

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(Last issue in 2003)

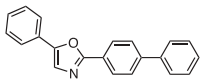
Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

Cross Metathesis of Nitrogen-Containing Systems

New Products from Aldrich R&D

2-(4-Biphenylyl)-5-phenyloxazole, 98%

21,698-4 — 1g, 5g

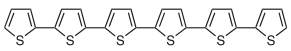


Widely used as an activator in C_6F_6-based scintillators for the study of α-particles,[1] γ-rays,[2] and solar neutrinos from β-decay.[3]

(1) Britvich, G.I. et al. *Nucl. Instrum. Methods Phys. Res., Sect. A* **1993**, *A326*, 483; *Chem. Abstr.* **1993**, *118*, 200826r. (2) Barabanov, I.R. et al. *Prib. Tekh. Eksp.* **1995**, 75; *Chem. Abstr.* **1995**, *123*, 125307v. (3) Barabanov, I.R. et al. *ibid.* **1996**, 41; *Chem. Abstr.* **1996**, *125*, 98054t.

α-Sexithiophene

59,468-7 — 1g

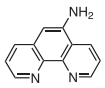


This thiophene oligomer is known for its semiconducting, electrochemical, and photoelectric properties.

Bungs, M.; Tributsch, H. *J. Appl. Electrochem.* **2002**, *32*, 91.

1,10-Phenanthrolin-5-ylamine, 97%

63,150-7 — 5g

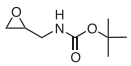


Employed in the formation of luminophores and metal–ligand complexes for the detection of chemical and biochemical materials.[1,2]

(1) Lecomte, J.-P. et al. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3261. (2) Meggers, E. et al. *Helv. Chim. Acta* **1997**, *80*, 640.

tert-Butyl *N*-(2-oxiranylmethyl)carbamate

63,066-7 — 1g

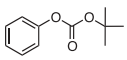


This functionalized epoxide can undergo hydrolytic kinetic resolution.[1] It has also been used as a building block for the construction of HIV proteinase inhibitors.[2,3]

(1) Schaus, S.E. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (2) Rocheblave, L. et al. *J. Med. Chem.* **2002**, *45*, 3321. (3) Kitchin, J. et al. *J. Med. Chem.* **1994**, *37*, 3707.

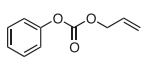
tert-Butyl phenyl carbonate, 98%

12,430-3 — 25g, 100g



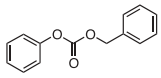
Allyl phenyl carbonate, 97%

63,065-9 — 1g, 5g



Benzyl phenyl carbonate, 97%

63,064-0 — 5g



These carbonates provide a practical and versatile method for selective Boc, Alloc, and Cbz protection of primary amines in simple symmetrical aliphatic diamines, and can selectively protect primary amines in the presence of secondary amines.

Pittelkow, M. et al. *Synthesis* **2002**, 2195.

2,4,6-Trichloropyridine, 97%

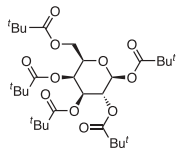
63,353-4 — 1g, 5g

Building block for a variety of biologically active compounds such as some cephalosporins,[1] anticancer agents,[2] and herbicides.[3]

(1) D'Andrea, S.V. et al. *Tetrahedron* **2000**, *56*, 5687. (2) Kyoji, T. et al. Int. Patent Appl. WO 9534,559, Dec 21, 1995; *Chem. Abstr.* **1996**, *124*, 289559a. (3) Hisashi, K. et al. Eur. Patent Appl. EP 693,490, Jan 24, 1996; *Chem. Abstr.* **1996**, *124*, 289242s.

β-D-Galactose pentapivalate, 98%

63,247-3 — 1g, 5g



This fully protected carbohydrate is a convenient precursor for 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine, a useful chiral auxiliary for chiral α-amino nitrile preparation via the Strecker synthesis.

Kunz, H. et al. *Tetrahedron Lett.* **1988**, *29*, 4397.

6-Chloropyran-2-one, 97%

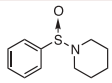
63,299-6 — 1g, 5g

Has been used as a starting material for alkynylpyranones,[1] and for a wide spectrum of biologically active substrates including pretetramides.[2]

(1) Biagetti, M. et al. *Tetrahedron Lett.* **2003**, *44*, 607. (2) Gilbreath, G. S. et al. *J. Am. Chem. Soc.* **1988**, *110*, 6172.

1-Benzenesulfinylpiperidine, 97%

63,023-3 — 1g, 5g

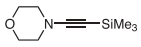


Novel reagent for the synthesis of glycosides from thioglycoside donors in high yields and excellent stereoselectivities.

Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640.

4-(Trimethylsilylethynyl)morpholine, 97%

63,277-5 — 1g, 10g

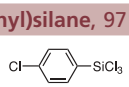


Employed in the Lewis acid mediated ring opening of terminal epoxides leading to the corresponding γ-butanolides.

Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456.

Trichloro(4-chlorophenyl)silane, 97%

63,045-4 — 1g, 5g



Employed as a starting material in the synthesis of tripod-shaped oligophenylenes designed for thin-film applications.

Deng, X.; Cai, C. *Tetrahedron Lett.* **2003**, *44*, 815.

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About Our Cover

Photograph © Board of Trustees, National Gallery of Art, Washington.

Autumn—On the Hudson River (oil on canvas, 151.8 x 274.9 cm) was signed and dated by the American painter Jasper Francis Cropsey in 1860. This enormous painting represents a panoramic view of the Hudson River valley about 60 miles north of New York City near West Point and Storm King Mountain.

At first glance, this landscape, painted in brilliant autumnal colors under a magnificent sunlit sky, may appear to show nature in a completely wild state. Mankind is not entirely absent, however. In the foreground and left of center, three hunters and their dogs have stopped to rest; a log cabin sits among the trees in the middle distance on the right; a town can be seen along the bank of the river; and a number of boats, including a steamer, are on the river itself. The setting is neither completely untouched by man nor overly domesticated. Man may at first seem dwarfed by nature, but is shown here to take his place harmoniously in the natural world.

More than simply a visual record of a certain time and place, however, this painting embodies certain ideas that were current in nineteenth-century America. The natural world was thought to be the most profound manifestation of the Divine order. Moreover, the magnificence of the American landscape came to signify the expansionist ideal and the opportunities and potential greatness of this new country. The critics praised the picture extravagantly when it was exhibited in London, where it was painted from memory and from sketches brought from America during the second of two study trips the artist made to Europe. Viewers, however, questioned the brilliant colors of the foliage represented in the painting, which were more intense than anything they had ever seen. Cropsey, however, had thought to bring from America samples of brightly colored autumn leaves pasted on cardboard to demonstrate that his painting was not an exaggeration, but was quite true to nature, at least in America.

This painting is a gift of the Avalon Foundation to the National Gallery of Art, Washington, DC.

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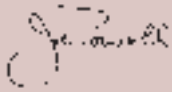
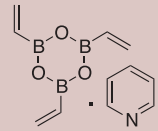


Joe Porwoll, President



Professor Donal F. O'Shea of the Department of Chemistry at University College Dublin kindly suggested that we offer 2,4,6-trivinylcyclotriboroxane-pyridine complex. This stable vinylboronic acid equivalent undergoes facile Suzuki cross-coupling with aryl halides to provide valuable functionalized styrene derivatives.

Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968.

63,799-8
Vinyl boronic anhydride-pyridine complex

56,814-7
Vinylboronic acid dibutyl ester, 97%

63,334-8
Vinylboronic acid pinacol ester, 95%

Naturally, we made not only this reagent but also two other stable vinylboronic acid esters—vinylboronic acid dibutyl ester and vinylboronic acid pinacol ester—which are useful for the Suzuki coupling, Heck coupling, and Grubb's olefin cross-metathesis reactions. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

A Funnel Assembly for the Safe Disposal of Nitrogen Discharged from an NMR Magnet during Cryogen Refilling

In NMR laboratories, where large volumes of cryogens are routinely dispensed, a condition of displacement or deprivation of atmospheric oxygen may occur if the released gases are not efficiently removed. There is at least one reported case of displacement of oxygen by nitrogen during the installation of a magnetic resonance imaging system causing the death of a worker by asphyxiation.[1] In addition, similar incidents of asphyxiation resulting from unsafe handling of liquid nitrogen have been reported in other laboratory settings.[2,3] In setting up a Bruker 400 MHz NMR instrument in our laboratory, we were constrained to install the magnet as well as the ancillary LC-NMR components in a 6 ½ '-deep well and the computers at the main level of the room. The well and the main level of the room were equipped with ZoneGuard sensors (Biosystems Inc., Middletown, CT) for a constant monitoring of the well and room oxygen levels. The monitoring systems were set to activate an audible alarm if the oxygen level dropped to 19.5% from the normal reading of 20.9%. During refilling of the magnet with liquid nitrogen, the oxygen level in the well dropped below the danger level of 18.0% and the alarm rang continuously.[4] To minimize the risk of oxygen displacement, we explored the possibility of diverting the flow of cold nitrogen gas exiting the magnet into an area outside the NMR room. To accomplish this goal, we have fabricated a funnel assembly (**Figure 1**) for efficiently capturing and disposing of nitrogen gas and for maintaining safe oxygen levels in the room.

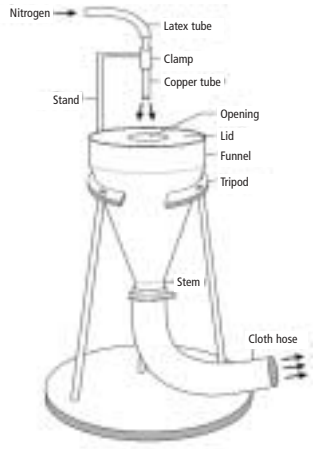


Figure 1. Schematic Diagram of the Funnel Assembly.

The assembly consists of a funnel mounted on a tripod, a clamp supported by the funnel, and a flexible hose attached to the stem of the funnel—as shown in the figure.[5] The mouth of the funnel is sealed with a lid that has a circular opening (3" diam) at its center, and through which the nitrogen stream enters the funnel's chamber. The internal diameter of the funnel at the lid is 9" and that of the stem 2¾" and, at 2" into its depth, the funnel's body gradually begins to narrow along the 8"-long curvature. The length of the funnel, including the two-inch-long stem, is 12" and its capacity is adequate to capture the nitrogen gas emitted from the NMR magnet during refilling. The clamp (4" long x ¼" thick) is supported by a stand (7" high x ¼" thick) welded to the rim of the funnel. A copper tube (7" long x ⅜" i.d.) is clamped in an upright position to deliver the nitrogen gas at the center of the funnel. The tip of the copper tube is positioned approximately 3" above the opening in the funnel lid, and its top end is attached to a latex tube (5' long x ⅜" i.d.) that receives nitrogen gas from the magnet. The supporting tripod consists of a partial O-ring (7" i.d.) mounted on top of 3 legs (16" high), which are fastened to a heavy circular base (14" diam). The O-ring has a 3½"-wide slit through which the funnel along with its attached stand can be readily dismounted from the tripod whenever needed. The material used for the fabrication of the funnel is nonmagnetic stainless steel, whereas that of the tripod is aluminum. The stem of the funnel is connected to a cloth hose (14' long x 3" i.d.) for carrying nitrogen gas into an exhaust line. The figure shows a segment of the latex tubing carrying nitrogen into the funnel and of the cloth hose discharging the gas.

Before liquid-nitrogen refilling, the funnel assembly is placed near the magnet and the funnel's latex tubing is connected to the left-hand-side turret. During refilling of the magnet, the funnel collects the gas discharge with no significant diffusion into the air. As it is denser than air, cold nitrogen gas settles well in the funnel and flows through the hose without applying suction. It also appears that the force of nitrogen streaming through the circular opening prevents back diffusion and exerts pressure sufficient to cause expulsion of the gas from the funnel through the hose. The gas is discharged near an exhaust line located in the well. When the magnet is full, liquid nitrogen spraying into the funnel is clearly visible from several feet away. There is practically no drop in the oxygen level in the well or in the rest of the room during the refilling procedure, suggesting efficient trapping and disposal of nitrogen by this device. Occasionally, water condenses in the first two-foot segment (from the stem of the funnel) of the exterior of the cloth hose carrying the cold gas; placing an absorbent pad underneath the hose takes care of this problem.

The funnel assembly helps in maintaining the room oxygen level during refilling of the NMR magnet with liquid nitrogen, especially if the room is not spacious or not adequately ventilated. In addition, it minimizes the chances of spillage of the cryogen and thus accidental freezing of the O-rings in the base plate and top flange of the magnet cryostat. (If freezing occurs, the sealing O-rings will be hardened leading to loss of vacuum between the casings of the magnet cryostat.) Certain modifications of the funnel assembly may be needed depending on the room's configuration or on whether added efficiency in the removal of nitrogen gas is warranted. For instance, if an exhaust line is not accessible, the delivery end of the hose may be placed outside the room for safe disposal of the gas. If improved gas flow is needed, a suction fan may be attached at the delivery end of the hose.

References and Notes: (1) Gill, J.R.; Ely, S.F.; Hua, Z. Environmental gas displacement: three accidental deaths in the workplace. *Am. J. Forensic Med. Pathol*. **2002**, *23*, 26; abstract available at the National Library of Medicine website at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi (accessed March 2003). (2) Kernbach-Wighton, G.; Kijewski, H.; Schwanke, P.; Saur, P.; Sprung, R. Clinical and morphological aspects of death due to liquid nitrogen. *Int. J. Legal Med.* **1998**, *111*, 191. (3) Tabata, N.; Funayama, M.; Ikeda, T.; Azumi, J.-i.; Morita, M. On an accident by liquid nitrogen—histological changes of skin in cold. *Forensic Sci. Int.* **1995**, *76*, 61. (4) Aside from recommending the installation of oxygen sensors, the manufacturer does not provide any device or recommend any procedure for handling the nitrogen discharged from the magnet during cryogen refilling. (5) The funnel, stand, and clamp were fabricated by Atlantic Sheet Metal Manufacturing (Essex, MD). The tripod was fabricated at the Division of Engineering Services, National Institutes of Health (Bethesda, MD). The entire assembly can be readily fabricated in any workshop using nonmagnetic metal sheets and rods (e.g., aluminum, copper, or nonmagnetic stainless steel) and cloth hose.

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Editor's Note: *Caution*. The potential user of this note should carefully evaluate its suitability for a particular application, as well as familiarize himself/herself with any potential hazards associated with the construction and use of this assembly. The procedure described in this note has not been tested by Sigma-Aldrich scientists. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich.

Organosilicon Reagents: Synthesis and Application to Palladium-Catalyzed Cross-Coupling Reactions

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Outline

Professor Scott E. Denmark (left) receiving the *2003 ACS Award for Creative Work in Synthetic Organic Chemistry* from Dr. Chris D. Hewitt, Aldrich Vice President of Marketing and R&D. Photo © James Tkatch.

Michael H. Ober

1. Introduction

Transition-metal-catalyzed cross-coupling of organometallic reagents with organic halides has become a powerful method for carbon–carbon-bond formation. Organotin,[1] organoboron,[2] and organozinc[3] reagents are well established as competent precursors for palladium-catalyzed cross-coupling reactions, and have found wide application in synthetic organic chemistry. But, due to a number of drawbacks inherent to these substrates, organosilicon reagents have emerged as competitive alternatives. The lack of toxicity, high chemical stability, and low molecular weight of organosilanes make them ideal for use as nucleophilic partners in cross-coupling with organic halides and pseudohalides. Silicon-based reagents were originally considered to be insufficiently active toward palladium-catalyzed cross-coupling, but early work by Hiyama et al. showed that organosilanes could be activated by a nucleophilic promoter.[4] Following this discovery, a multitude of organosilanes bearing a wide variety of substituents about the silicon center as well as an assortment of transferable groups have been identified.[5] This review will concentrate on recent advances in the use of organosilanes in palladium-catalyzed cross-coupling reactions, with an emphasis on the preparative

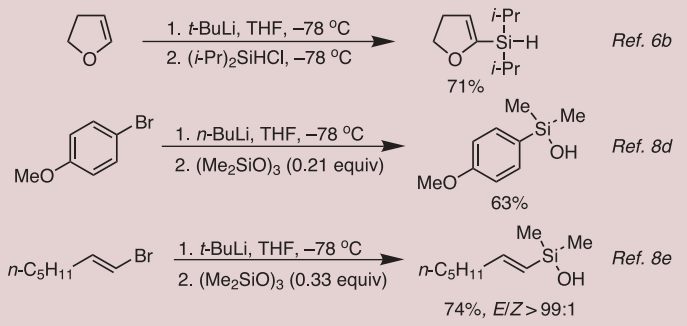


Figure 1. Preparation of Organosilanes by Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes.

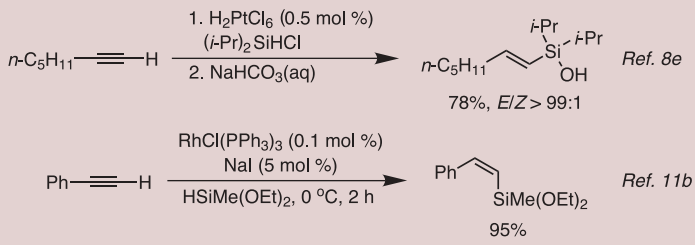


Figure 2. Preparation of Organosilanes by Hydrosilylation of Alkynes.

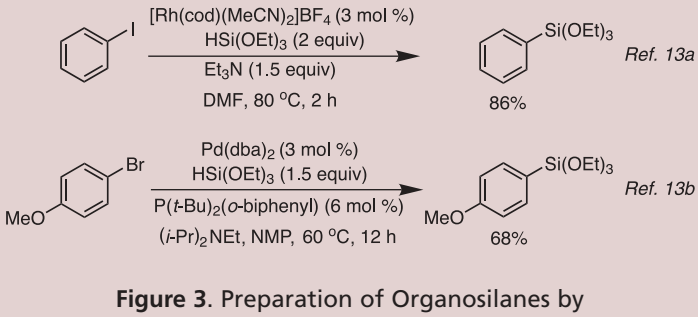


Figure 3. Preparation of Organosilanes by Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides.

aspects of this chemistry and on the synthesis and applications of these substrates.

2. Synthesis of Organosilicon Reagents

In response to the growing interest in the palladium-catalyzed cross-coupling of organosilicon compounds, a number of methods to prepare a wide range of coupling precursors are now available. The preparations of these compounds are diverse, and are based on the type of organic moiety being employed as well as the substituents about the silicon atom. Of the methods described, most can be preformed on a large scale to provide useful quantities of material thanks, in large measure, to the relatively low cost and availability of the silicon-containing starting materials. Once synthesized, organosilanes are stable compounds that can be purified by chromatography or distillation and can be easily handled in most cases.

2.1. Reaction of Organometallic Reagents with Halosilanes or Cyclosiloxanes

The use of organolithium and organomagnesium reagents for the nucleophilic displacement of a leaving group at the silicon center is one of the simplest methods to introduce silicon into an organic molecule (**Figure 1**). The reaction of phenyllithium or vinylmagnesium bromide with a dialkylchlorosilane[6] readily provides the corresponding aryl- or vinylsilyl hydride. The newly formed silyl hydride can then be subjected to further manipulations to gain access to silyl ethers, silyl halides, and silanols.[6,7] Direct formation of organosilanols can be similarly accomplished by addition of the organometallic reagent to a number of readily available and inexpensive *cyclo*-siloxanes.[8] Aqueous hydrolysis of the substituted polysiloxane formed in situ provides the organosilanol, which can then be easily purified by column chromatography or distillation. Although this method of synthesis is both straightforward and efficient, it is limited by substrate compatibility with the organometallic agent employed. This problem can be avoided by protection of the sensitive functional group or, better still, by use of one of the alternative methods described below.

2.2. Hydrosilylation of Alkynes and Alkenes

The metal-catalyzed hydrosilylation of alkynes and alkenes to provide substituted alkenylsilanes and alkylsilanes avoids the use of highly reactive organometallic reagents and the limitations associated with them.[9] The insertion of a platinum,[8e,10] rhodium,[11] or ruthenium[12] catalyst into an Si–H bond, provides an active metal hydride that undergoes addition across an unsaturated organic precursor generating an organosilyl halide or organosilyl ether (**Figure 2**). As with the previous method, the organosilicon compounds thus generated can be further manipulated to obtain organosilanols or other silicon species. The stereo- and regioselectivity of the hydrosilylation are dependent on the catalyst employed and the silicon precursor involved in the reaction, but a judicious choice of the two agents can lead to high levels of control in most cases.[9] Obviously, this method is well suited for the preparation of alkenylsilanes and alkylsilanes. Other methods are needed to install the silicon functionality into aryl or heteroaryl subunits.

2.3. Transition-Metal-Catalyzed Coupling of Aryl Halides with Silyl Hydrides

Recently, investigations into the transition-metal-catalyzed coupling of organic halides with silyl hydrides have provided a powerful method for the synthesis of organosilanes. Base-activated insertion of a transition-metal complex into an Si–H bond

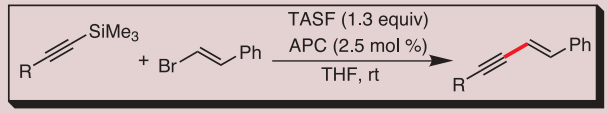
followed by transfer of the silyl group to an aryl or vinyl halide successfully provide the desired organosilane (**Figure 3**).[13] This reaction is limited to the coupling of alkoxysilanes, alkylsilanes, and halosilanes with electron-rich aryl iodides and bromides. The process is catalyzed by $Pd(dba)_2$[13b,c] or $[Rh(cod)(MeCN)_2]BF_4$[13a] in the presence of a stoichiometric amount of base, and is thought to proceed through Si–H/C–I bond exchange by oxidative addition of the hydrosilane followed by σ-bond metathesis of the Si–Pd/C–I bonds.[13c]

3. Palladium-Catalyzed Cross-Coupling

The coupling of organosilicon reagents with organic halides and pseudohalides has evolved to be comparable in scope to other palladium-catalyzed coupling methods.[4,5] Generally, the conditions for the palladium-catalyzed cross-coupling are mild, but do require a promoter [tetrabutylammonium fluoride (TBAF), tetramethylammonium fluoride (TMAF), tris(diethylamino)sulfonium trimethyldifluorosilicate (TASF), potassium trimethylsilanolate (TMSOK), Ag_2O, Cs_2CO_3, etc.] to provide high yields of the desired cross-coupling products. The byproducts of the cross-coupling reaction are polysiloxanes, which can be removed by conventional methods such as chromatography (silica gel or reverse-phase) or distillation. Many types of organosilanes are competent coupling partners for the palladium-catalyzed reaction. The following survey of silicon-containing cross-coupling components is organized around three principal rubrics: (1) the type of transferable group on the organosilane, (2) the method of organosilane activation, and (3) the nontransferable substituents about the silicon center.

3.1. Alkynylsilanes

The palladium-catalyzed coupling reaction of terminal alkynes developed by Sonogashira and co-workers has been widely applied in many synthetic endeavors.[14] Nevertheless, new general methods that employ mild conditions are still of great interest for the synthesis of substituted alkynes. Alkynyl(trialkyl)silanes and alkynylsilanols, which are easily synthesized by addition of alkynyllithium reagents to chlorosilanes, are competent reagents for the palladium-catalyzed cross-coupling reaction.[15] The successful coupling of substituted trimethylsilylethynes with aryl or vinyl iodides or with vinyl bromides requires the use of 1.3 equiv of TASF and 2.5 mol % of



eq 1

APC = allylpalladium chloride dimer, $[\pi\text{-allylPdCl}_2]_2$
TASF = tris(diethylamino)sulfonium trimethyldifluorosilicate

Ref. 15a

R	Yield
Ph	83%
$n\text{-}C_5H_{11}$	86%
CH_2OH	84%

$[\pi\text{-allylPdCl}_2]_2$ (APC) in THF at ambient temperature, to provide substituted alkynes in good yields (**eq 1**).[15a] Catalytic amounts of CuCl or CuCl–$Pd(PPh_3)_4$ can also be used at elevated temperatures in DMF to effect the coupling of alkynyl(trialkyl)silanes with aryl chlorides or triflates.[15b] Alternatively, dimethyl(phenylethynyl)silanol undergoes facile coupling with aryl iodides in THF at 60 ˚C in the presence of a stoichiometric amount of TBAF or Ag_2O and 5 mol % of $Pd(PPh_3)_4$.[15c]

3.2. Alkenylsilanes

The palladium-catalyzed cross-coupling of alkenylsilanes with organic halides and pseudohalides has gained much attention because of the mild reaction conditions required and broad scope of olefinic products that can be obtained.[4,5] In general, the cross-coupling reactions of alkenylsilanes are highly efficient, but several side processes can intervene under the reaction conditions. Of these undesirable processes, the most notable are the unproductive removal of the silicon moiety (protodesilylation) and the formation of undesired regioisomers. In most cases, manipulation of the reaction conditions (choice of promoter, palladium catalyst, and ligands) can avoid many of these pitfalls to provide high-yielding and selective reactions.

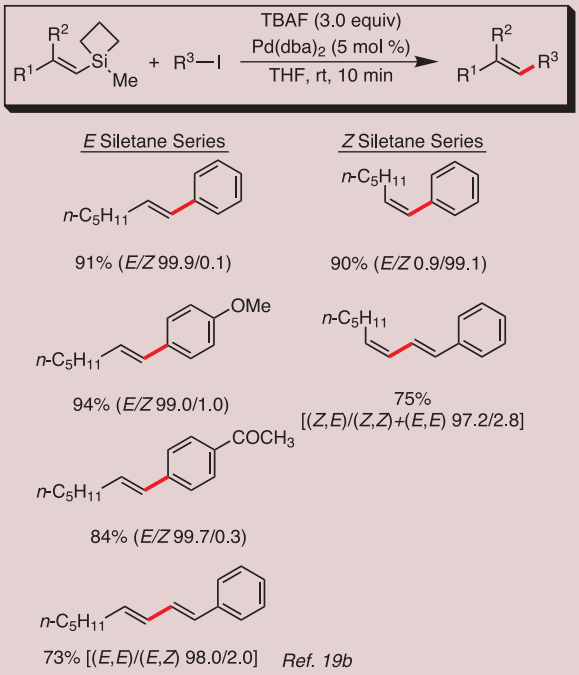
3.2.1. Fluoride Activation

Because of the high affinity of fluoride for silicon (BDE Si–F = 135 kcal/mol),[16] the use of a fluoride ion source (in the form of TBAF, TMAF, TASF, KF, or CsF) together with tetracoordinate silanes is believed to provide pentacoordinate fluorosiliconate intermediates, which are considered to be the "active" species in the palladium-catalyzed cross-coupling reactions.[4] Silicon-29 NMR spectroscopic studies on the use of TBAF as a promoter for the palladium-catalyzed cross-coupling of several types of alkenylsilanes (alkenylsiletanes, alkenylsilyl halides, alkenylalkoxysilanes, alkenyldisiloxanes, and alkenylsilanols) provide that all of these precursors react via a common intermediate, hypothesized to be a hydrogen-bonded silanol–fluoride adduct.[17] Because of this mechanistic commonality, a wide range of organosilanes, that display a similar reactivity yet provide a variety of precursor options, are competent reagents for the fluoride-activated cross-coupling reaction.

Three classes of alkenylsilanes undergo facile fluoride-promoted cross-coupling: (1) alkenylsilanes bearing alkyl groups on the silicon, (2) alkenylsilanes bearing fluoride-cleavable organic groups (alkenylsilanol surrogates), and (3) heteroatom-substituted alkenylsilanes. In general, alkyl-substituted alkenylsilanes are extremely stable to chemical manipulations prior to fluoride activation, but do not readily undergo productive cross-coupling. Alkenylsilanol surrogates are also stable under conditions for many reactions. However, these silanes contain a cleavable group that, in the presence of a fluoride activator, produces a heteroatom-substituted alkenylsilane in situ, which provides a compromise of stability and reactivity. Heteroatom-substituted alkenylsilanes are, of all the types identified here, the most reactive toward palladium-catalyzed cross-coupling due to the ease with which they can access an "active" species under fluoride promotion. Unfortunately, these silanes are also the most labile toward unproductive reactions including hydrolysis, protodesilylation, and dimerization and, therefore, must be promptly subjected to palladium-catalyzed cross-coupling without prior chemical manipulations. Thoughtful selection of the alkenylsilanes and the reactions in which they can be employed leads to a balanced combination of precursor and conditions, allowing for a wide range of olefinic cross-coupling products.

3.2.1.1. Alkenyl(trialkyl)silanes

The combination of readily available trimethyl(vinyl)silane and an aryl iodide, under somewhat modified conditions to those developed for alkynyl(trialkyl)silanes mentioned previously (2.4 equiv of TASF and 5 mol % of $Pd(PPh_3)_4$ in THF at 50 ˚C),



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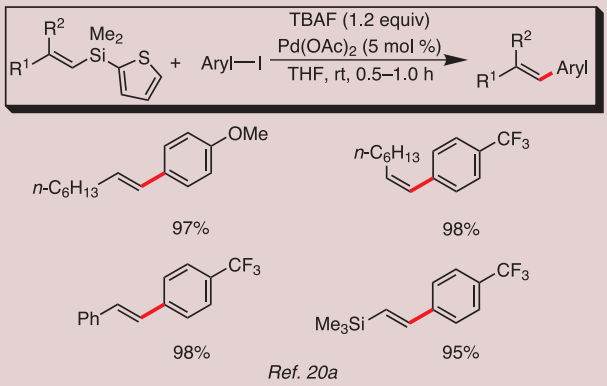

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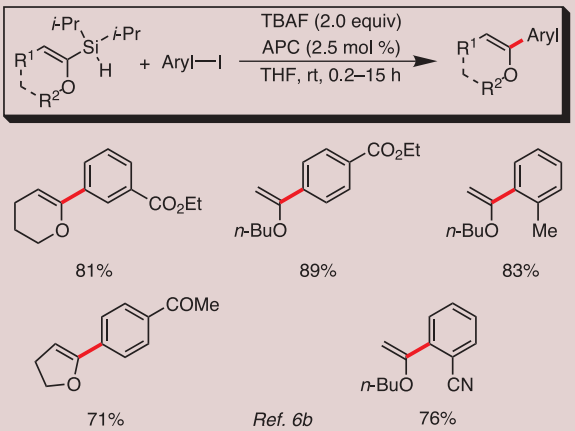


eq 4

is effective for the production of vinylated products. The reaction is tolerant of diverse functionality on the aryl iodide, but substitution on the trimethyl(vinyl)silane inhibits productive cross-coupling. The failure to engage substituted alkenyl(trialkyl)silanes in this process is believed to arise from their inability to form the required pentacoordinate fluorosiliconate species.[18]

3.2.1.2. Alkenylsilanol Surrogates

3.2.1.2.1. Alkenylsiletanes

Alkenylsilacyclobutanes represent a special class of alkenyl(trialkyl)silanes that can undergo facile palladium-catalyzed cross-coupling with aryl and vinyl iodides. These reactions proceed rapidly in the presence of 3 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at ambient temperature (**eq 2**).[19] Alkenylsiletanes, which can be readily prepared from organometallic addition to 1-chloro-1-methylsilacylobutane,[19b] originally were thought to undergo cross-coupling this rapidly due to the enhanced Lewis acidity of the silicon center from strain release during the formation of the pentacoordinate fluorosiliconate.[19c] However, under the reaction conditions, the siletanes are observed to undergo a fast initial ring opening to form alkenyl(propyl)(methyl)silanols, which are most likely the active species for the cross-coupling reaction.[17] Direct comparisons to alkenylsilanols, alkenylsilyl halides, and alkenylsilyl ethers reveal a similar reactivity, and corroborate the observation that these alkenylsilanes react via the same intermediate.[17]

3.2.1.2.2. Alkenyl(thienyl)- and Alkenyl(pyridyl)silanes

The observation that 2-thienyl and 2-pyridyl groups on silicon are not transferred to organic halides under standard palladium-catalyzed cross-coupling conditions, combined with the fact that at least one activating group or heteroatom is required on the silicon center to provide the coupling product, prompted the investigation of alkenyldimethyl(2-thienyl)silanes and alkenyldimethyl(2-pyridyl)silanes. These compounds are considered excellent cross-coupling substrates due to the enhanced stability provided by the heterocyclic groups toward moisture, acid, and base as compared to the corresponding halosilanes or other heteroatom-substituted silanes.[20a] This allows for the alkenylsilane coupling precursors to resist some chemical manipulations prior to palladium-catalyzed cross-coupling. Alkenyldimethyl(2-thienyl)silanes undergo cross-

coupling with a number of aryl iodides and bromides in the presence of 1.2 equiv of TBAF and 5 mol % of $Pd(OAc)_2$ in THF at ambient temperature (**eq 3**).[20a] Similarly, alkenyldimethyl(2-pyridyl)silanes afford cross-coupling products from aryl and vinyl iodides at slightly elevated temperatures.[20b,c]

3.2.1.2.3. Alkenyl(benzyl)silanes

Benzyldimethylsilyl-substituted alkenes are similar to the aforementioned 2-thienyl- and 2-pyridylsilanes in that the benzyl group is also considered non-transferable. In addition, it is stable to acid, buffered fluoride medium, and strong base. However, the benzyl substituent does suffer rapid cleavage with 2.2 equiv of TBAF in THF at 0 °C to provide the corresponding silanol. Accordingly, benzyldimethylsilanes are expected to possess enhanced chemical stability compared to heteroaryl-containing silanes and yet still be activated with TBAF for cross-coupling.[21]

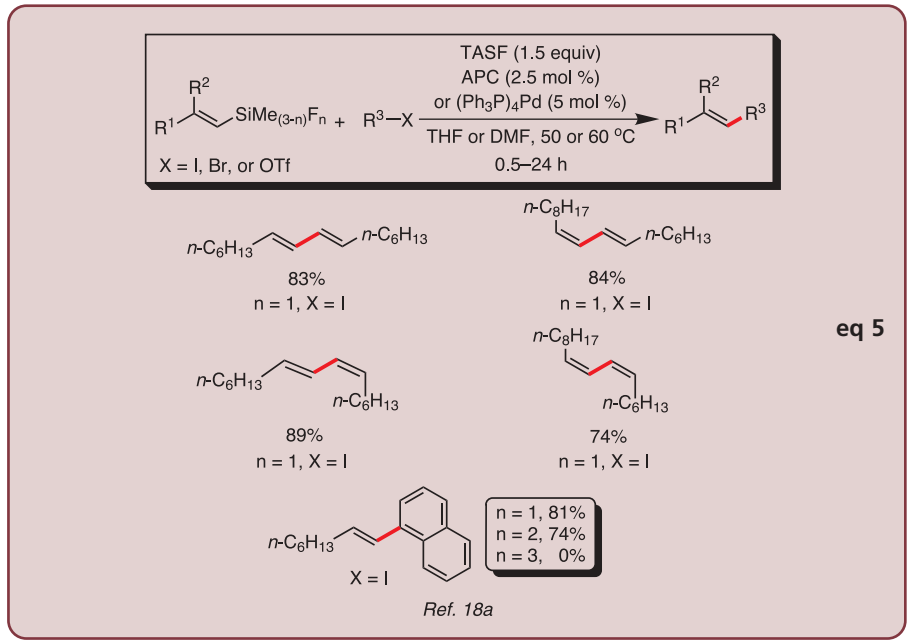
3.2.1.2.4. Alkenylsilyl Hydrides

Silyl hydrides, which are easily synthesized through organometallic addition to dialkylchlorosilanes, are more stable to hydrolysis than are the heteroaryl-substituted organosilanes. In addition, they have lower molecular weights compared to other non-heteroaryl-substituted organosilanes and are thus ideal for use with sensitive or precious substrates. These characteristics are illustrated in the palladium-catalyzed cross-coupling of 2-(4,5-dihydrofuranyl)-diisopropylsilane and 2-(5,6-dihydro-4*H*-pyranyl)diisopropylsilane These alkenylsilyl hydrides undergo oxidative hydrolysis when combined with TBAF•$3H_2O$, producing the alkenylsilanols in situ.[22] Indeed, the corresponding silanols give similar results under identical conditions. A number of (α-alkoxyvinyl)silyl hydrides are effective cross-coupling agents when combined with aryl iodides in the presence of 2 equiv of TBAF and 2.5 mol % of APC in THF at room temperature (**eq 4**).[6b] The reaction is compatible with a broad range of functional groups, and manipulation of the intermediate alkoxy vinyl ethers with 1 N HCl provides the corresponding ketones directly.[6b]

3.2.1.3. Heteroatom-Substituted Alkenylsilanes

3.2.1.3.1. Alkenylsilyl Halides

Alkenylsilyl chlorides and fluorides were among the first alkenylsilanes to act as effective and general substrates in the palladium-catalyzed cross-coupling reaction.[4] The combination of halo(alkyl)silanes or dihalo(alkyl)silanes with organic halides in the presence of 1.5 equiv of TASF and 2.5 mol % of APC in THF at 50 °C or, alternatively, with 5 mol % of $(Ph_3P)_4Pd$ in DMF at 60 °C provides the desired cross-coupling products in good yields (**eq 5**).[18a] Many organic halides and pseudohalides are suitable as coupling partners, and the reaction is highly stereo- and regioselective in the case of (*E*)- and (*Z*)-fluoro(dimethyl)silyl-1-alkenes. Interestingly, trihalosilanes are ineffective in the cross-coupling reaction of 1-iodonaphthalene, but do function in the coupling with an alkenyl triflate.[18b]



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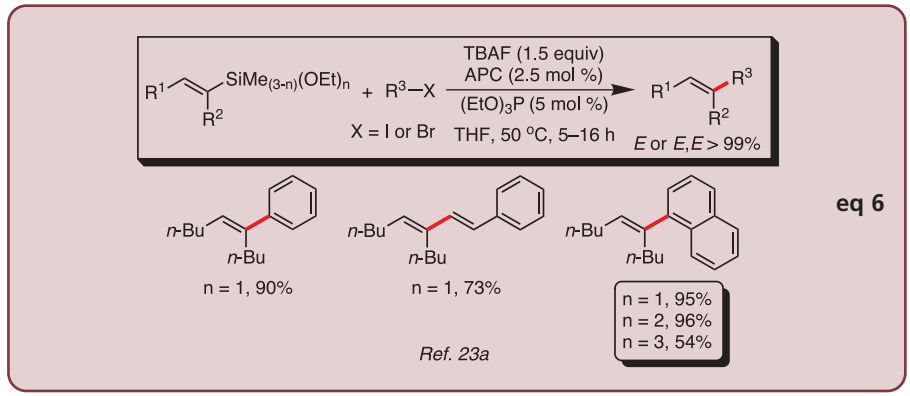


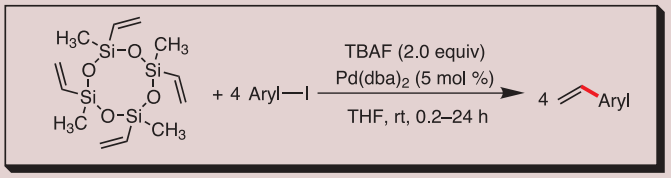
eq 6

3.2.1.3.2. Alkenyl(alkoxy)silanes

Alkenyl(alkoxy)silanes (silyl ethers) react at rates comparable to those of alkenylsilanols and alkenylsilyl halides with similar numbers of heteroatoms about the silicon center, but are less prone to hydrolysis or oligomerization. Alkenylmono-, di-, and trialkoxysilanes—in the presence of 1.5 equiv of TBAF, 2.5 mol % of APC, and 5 mol % of $(EtO)_3P$ in THF at 50 °C—undergo cross-coupling with a number of organic halides (**eq 6**).[23a] Vinyltrimethylsiloxane has also proved useful as a vinyl transfer agent for aryl iodides.[23b]

3.2.1.3.3. Alkenyldisiloxanes and Poly(alkenylsiloxanes)

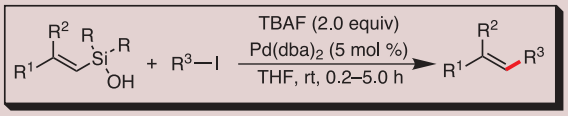
Alkenyldisiloxanes are readily formed by dehydrative dimerization of their parent alkenylsilanols with a catalytic amount of base.[17] The disiloxane moiety is thermodynamically stable, making alkenyldisiloxanes one of the more easily handled types of organosilicon compound. Because they converge to the same intermediate in the presence of TBAF as the corresponding alkenylsilanols, alkenyldisiloxanes undergo cross-coupling with the same outcome.[17] Similarly, the readily available siloxane oligomers also provide productive cross-coupling with

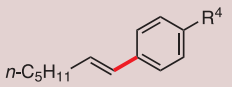


Aryl:	2-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	3-NO$_2$C$_6$H$_4$	4-CH$_3$COC$_6$H$_4$	4-EtO$_2$CC$_6$H$_4$
Yield:	72%	63%	87%	88%	85%

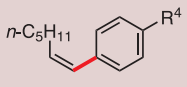
Ref. 24b

eq 7

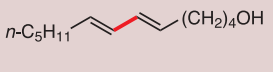




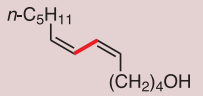
R = Me, R^4 = MeO: 95% (*E*/*Z* 97.2/2.8)
R = *i*-Pr, R^4 = Ac: 80% (*E*/*Z* 99.5/0.5)



R = Me, R^4 = MeO: 94% (*E*/*Z* 2.6/97.4)
R = *i*-Pr, R^4 = Ac: 86% (*E*/*Z* 1.0/99.0)



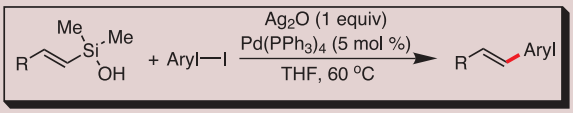
R = Me: 91% [(*E*,*E*)/(*E*,*Z*) 95.8/4.2]
R = *i*-Pr: 87% [(*E*,*E*)/α-isomer 97.8/2.2]
α-isomer = cine-rearranged product

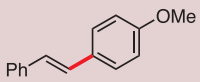


R = Me: 64% [(*Z*,*Z*)/AOI 87.8/12.2]
R = *i*-Pr: 68% [(*Z*,*Z*)/AOI 92.4/7.6]
AOI = all other isomers

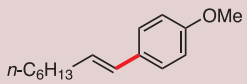
Ref. 8e

eq 8





67%, 3 h



95%, 4 h

Ref. 26a

eq 9

TBAF activation. Poly(alkenylsiloxanes) are easily synthesized by hydrosilylation of terminal alkynes with poly(methylhydrosiloxane) (PMHS) and a catalytic amount of $(Bu_4N)_2PtCl_6$. Cross-coupling of poly(alkenylsiloxanes) with a number of aryl iodides proceeds smoothly with 5 equiv of the polysiloxane, 1.2 equiv of TBAF, and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ in THF at 60 °C.[24a] Several commercially available cyclooligodisiloxanes, orthosiliconates, and disiloxanes are extremely efficient vinyl transfer agents for a broad range of aryl iodides with 2–3 equiv of TBAF and 1–5 mol % of $Pd(dba)_2$ in THF at ambient temperature.[24b] 1,3,5,7-Tetravinyl-1,3,5,7-tetramethylcyclotetrasiloxane is the most competent of the vinyl transfer agents under these conditions, allowing all of the possible vinyl groups to transfer during the cross-coupling reaction (**eq 7**). This reaction is general and, due to the inexpensive and nontoxic nature of the starting materials, amenable to large-scale preparations.[24b]

3.2.1.3.4. Alkenylsilanols

Alkenylsilanols are excellent substrates for the palladium-catalyzed cross-coupling reaction when activated by TBAF. Alkenyl(dimethyl)silanols and alkenyl(diisopropyl)silanols couple rapidly with a large number of aryl and vinyl iodides in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at ambient temperature (**eq 8**).[8e] Highly substituted and functionalized (*E*)- and (*Z*)-alkenyl(dialkyl)silanols also undergo facile coupling, with good efficiency and high stereospecificity.[25a] The palladium-catalyzed cross-coupling of alkenyl(dimethyl)silanols with aryl and vinyl triflates and nonaflates can also be accomplished at ambient temperature by the use of a hydrated TBAF (TBAF•3–10H_2O) in 1,4-dioxane solution in the presence of 5 mol % of $PdBr_2$ and 10 mol % of 2-[di(*tert*-butyl)phosphino]-1,1'-biphenyl. Under these conditions, the undesired cleavage of the pseudohalide to the corresponding phenol or ketone is minimized by the increased hydration level of the TBAF solution.[25b]

3.2.2. Fluoride-Free Activation of Alkenylsilanols, Diols, and Triols

Tetrabutylammonium fluoride (TBAF) and other fluoride-containing reagents are highly effective for promoting the palladium-catalyzed cross-coupling of a range of organosilanes. However, the widespread use of silicon protecting groups in complex-molecule synthesis precludes the application of a fluoride-activated coupling that may jeopardize the integrity of the silicon protecting groups. Thus, a non-fluoride promoter that would facilitate the silicon-based couplings with equal efficiency and selectivity is highly desirable. The first such promoter that has been identified is silver oxide (Ag_2O), which can activate alkenylsilanols, diols, and triols in the presence of a palladium catalyst in THF at 60 °C (**eq 9**).[26a,b] Silver oxide is thought to act as a nucleophilic activator for the silanol to form a pentacoordinate silicate species, and to assist in halide abstraction from the palladium center thus facilitating transmetalation.[26a]

Alternatively, the inexpensive salt, potassium trimethylsilanolate (TMSOK), can also be employed for the activation of alkenyl(dimethyl)silanols.[26c,d] For example, the cross-coupling of (*E*)- and (*Z*)-1-heptenyl(dimethyl)silanols with a variety of aryl and vinyl iodides is efficiently promoted by 2 equiv of TMSOK and 5 mol % $Pd(dba)_2$ in DME at ambient temperature (**eq 10**).[26c] When activated by TMSOK, silanols are as reactive as when activated by TBAF and give rise to cross-coupling products in high yields and with excellent regio- and stereoselectivities. Direct comparison of the palladium-catalyzed cross-coupling of alkenyl(dialkyl)silanols under activation by TBAF or TMSOK reveals a striking difference in the sensitivity of the coupling rate to steric effects at the silicon center.[26d] For example, whereas under TBAF activation both alkenyldimethyl- and alkenyldiisopropylsilanols couple at the same rate, under TMSOK activation the

dimethylsilanols react nearly 20 times faster! This and other observations suggest that a different mechanism may be operating under the fluoride-free conditions. It is possible to employ other bases (e.g., KH, NaH, KO*t*-Bu, NaO*t*-Bu, or NaOH) for the palladium-catalyzed cross-coupling of alkenyl(dialkyl)-silanols, but they are not as effective nor as well studied as those already mentioned.[26b-d]

3.3. Arylsilanes

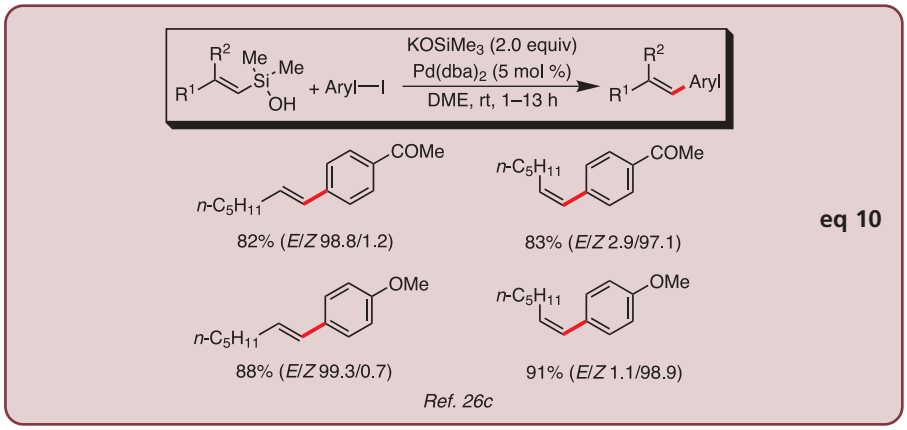
Compared to alkenylsilanes, arylsilanes have similar physical and chemical properties and may be prepared through similar synthetic routes. Unlike their alkenyl counterparts, however, arylsilanes require more forcing conditions to undergo palladium-catalyzed cross-coupling with aryl and vinyl halides. These harsher conditions often lead to undesirable side reactions such as protodesilylation and homocoupling of the organic halide.[4,5] A number of protocols have been developed to suppress or minimize the unproductive pathways and maximize the formation of the desired cross-coupling products.

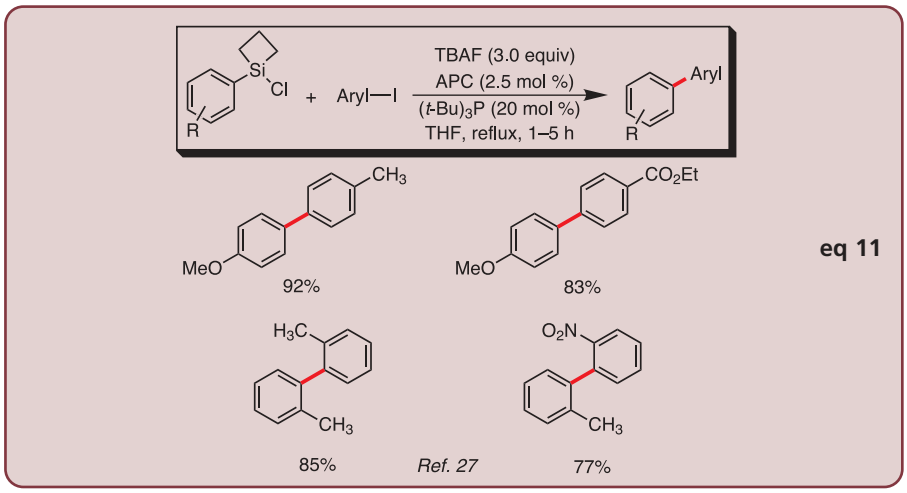
3.3.1. Arylsiletanes

Unlike alkenylsilacyclobutanes, the palladium-catalyzed cross-coupling of methyl(phenyl)silacyclobutane with aryl iodides in the presence of 3 equiv of TBAF and 5 mol % of APC in refluxing THF provides no desired cross-coupling products. However, activation of the siletane by substituting a chloride or fluoride for the methyl group on the silicon allows these halo(aryl)silacyclobutanes to couple readily with aryl iodides under somewhat modified conditions (**eq 11**).[27] These conditions also provide a moderate amount of undesired homocoupling product, which can be minimized by the addition of 20 mol % of (*t*-Bu)$_3$P to the reaction mixture. The addition of the phosphine ligand to the reaction retards both the homocoupling and cross-coupling pathways, but overall provides a more favorable ratio of the two observed products. Under these conditions, both aryl(chloro)silacyclobutanes and aryl(fluoro)silacyclobutanes are competent coupling precursors, with aryl(chloro)-silacyclobutanes providing biaryl cross-coupling products with slightly extended reaction times.[27]

3.3.2. Arylsilyl Halides

Palladium-catalyzed phenyl transfer to aryl iodides, bromides, and triflates can be performed with tetrabutylammonium triphenyldifluorosilicate (TBAT), an active difluorosiliconate, in the presence of 10 mol % of Pd(dba)$_2$ in DMF at 95 °C to afford unsymmetrical biaryls in good yields.[28a] The cross-coupling of substituted aryl(alkyl)-difluorosilanes with aryl iodides, bromides, and triflates takes place smoothly to provide a number of biaryls in high yields.[18b,28b,c] Aryl(alkyl)dichlorosilanes can also be employed as cross-coupling partners with aryl halides under activation with fluoride [KF, APC (5 mol %), DMF, 120 °C],[28c] or with sodium hydroxide [Pd(OAc)$_2$, Ph$_3$P, THF, 60 °C].[28d] Application to solid-phase synthesis can also be accomplished using iodobenzoic acid tethered to Wang resin.[28e]



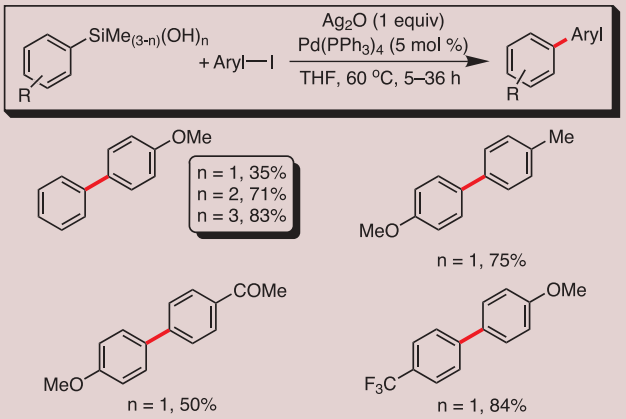


3.3.3. Aryl(alkoxy)silanes

Compared to the corresponding halides, aryl(alkoxy)silanes are more stable and, in some cases, readily available. Phenyltrimethoxysilane undergoes facile palladium-catalyzed cross-coupling with aryl iodides and bromides. In the presence of 2 equiv of TBAF and 10 mol % of Pd(dba)$_2$ in DMF at 95 °C, the desired substituted benzene products are formed with little or no homocoupling byproduct observed.[23b] The cross-coupling of phenyltrimethoxysilane with aryl chlorides can also be accomplished with the addition of phosphine[29a] or N-heterocyclic carbene[29b] ligands to the reaction mixture. *Alkyl* halides can also be subjected to the palladium-catalyzed cross-coupling with substituted aryltrimethoxysilanes in the presence of 2.4 equiv of TBAF, 4 mol % of PdBr$_2$, and 10 mol % of (*t*-Bu)$_2$MeP in THF. Both alkyl iodides and bromides are competent coupling partners, and the reaction is preformed at ambient temperature to provide alkyl-substituted arenes in good yields.[29c]

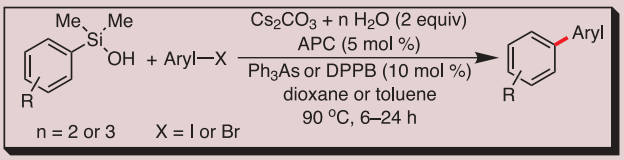
3.3.4. Arylsilanols, Diols, and Triols

The preparation of arylsilanols is discussed in Section 2.1. Arylsilanediols and triols can easily be synthesized by addition of aryllithium reagents to chlorosilanes followed by careful hydrolysis of the corresponding di- and trihalosilanes. As with their alkenyl counterparts, all three types can be activated with 1 equiv of Ag$_2$O in the presence of a palladium catalyst in THF at 60 °C to give cross-coupling products with



Ref. 26a,b

eq 12

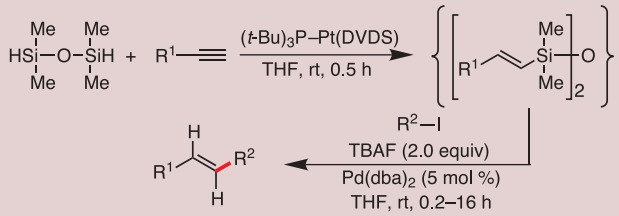


DPPB = 1,4-bis(diphenylphosphino)butane

eq 13

X	R	Aryl	Yield
I	4-MeO	4-MeC_6H_4	90%
I	4-MeO	2-MeC_6H_4	85%
I	4-MeO	4-$EtO_2CC_6H_4$	87%

Ref. 30



R^1	R^2	Yield
n-C_5H_{11}	4-$MeOC_6H_4$	84%
n-C_5H_{11}	4-AcC_6H_4	94%
n-C_5H_{11}	*n*-$C_5H_{11}CH{=}CH$	67%
Ph	4-$MeOC_6H_4$	74%
$HO(CH_2)_3$	4-$MeOC_6H_4$	89%

DVDS = 1,3-divinyl-1,1,3,3-tetramethyldisiloxane

Ref. 32

Scheme 1. One-Pot, *Inter*molecular Tandem Hydrosilylation/Cross-Coupling Reaction.

aryl iodides (**eq 12**).[26a,b] The coupling of arylsilanols with aryl iodides can also be achieved at 90 °C in dioxane by the action of 2 equiv of Cs_2CO_3•$2H_2O$ in the presence of 5 mol % of APC and 10 mol % of Ph_3As. The corresponding reaction of aryl bromides requires the use of 10 mol % of 1,4-bis(diphenylphosphino)butane (DPPB) instead of Ph_3As and is carried out at 90 °C in toluene (**eq 13**).[30] Both methods provide high yields of biaryls and little or no homocoupling byproduct.

3.4. Alkylsilanes

Protocols for the palladium-catalyzed cross-coupling of alkylsilanes with organic halides include highly activated organosilicon reagents which allow for methyl, allyl, or alkyl cross-coupling. Methyl transfer to aryl iodides is accomplished with 2 equiv of TASF and 1.3 mol % of APC in THF at 50 °C to provide methylated cross-coupling products in good yields.[31a] More interestingly, alkyltrifluorosilanes yield cross-coupling products with aryl iodides and bromides when activated with 4 equiv of TBAF and 5 mol % of $(PPh_3)_4Pd$ in refluxing THF.[31b] Allyltrifluorosilanes couple with aryl iodides and triflates under the action of TBAF or TASF and 5 mol % of a palladium catalyst.[31c] Overall, the cross-coupling of alkylsilanes is not as well established as those of alkynyl-, alkenyl-, or arylsilanes, and few general procedures have been identified.

4. Tandem Reactions of Organosilicon Compounds

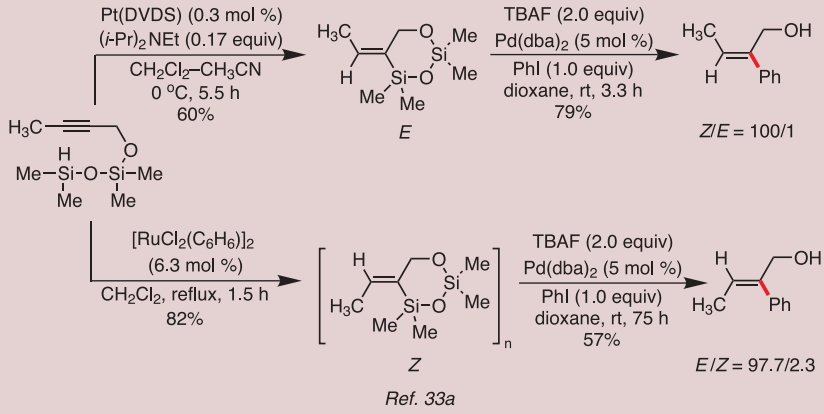
The diversity of organosilicon compounds that undergo palladium-catalyzed cross-coupling, as well as the different methods by which they can be synthesized enable a wide range of synthetic applications. Multistep or tandem reactions that harness the power of the organosilicon moiety can be effectively applied to create complex structures rapidly. These tandem reactions, terminating with palladium-catalyzed cross-coupling, highlight the advantages that silicon-based carbon–carbon-bond formation can offer to the realm of synthetic organic chemistry.

4.1. Intermolecular Hydrosilylation/ Cross-Coupling

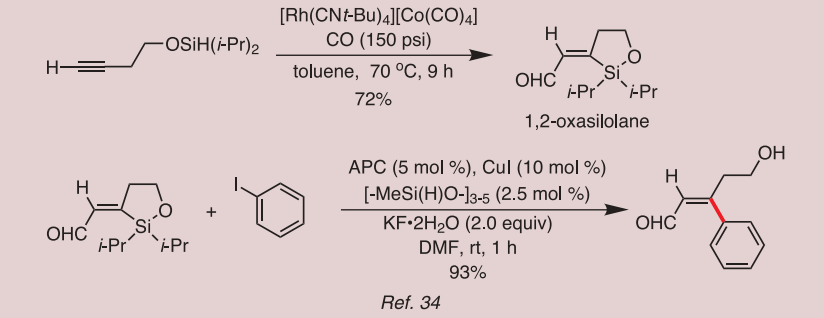
The hydrosilylation of terminal alkynes, followed by palladium-catalyzed cross-coupling of the alkenylsilane product, affords 1,2-disubstituted *E* alkenes in high yields and with high stereoselectivities. For example, a symmetrical alkenyldisiloxane can be generated by reaction of 0.5 equiv of tetramethyldisiloxane, $(t\text{-}Bu)_3P$–Pt(DVDS) with a terminal alkyne. The hydrosilylation is highly regio- and stereoselective for the production of the *E* 1-alkenyldisiloxane. The subsequent cross-coupling reaction can be performed directly on the in situ generated alkenyldisiloxane with aryl or vinyl iodide under the action of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ to yield the desired products (**Scheme 1**).[32] This efficient Pt–Pd system effects the net hydroarylation of terminal alkynes.

4.2. Intramolecular Hydrosilylation/ Cross-Coupling

Starting from simple propargylic and homopropargylic alcohols, highly functionalized trisubstituted allylic and homoallylic alcohols are obtainable through an intramolecular hydrosilylation followed by a rapid palladium-catalyzed cross-coupling of the intermediate cyclosiloxanes with aryl iodides. Propargylic alcohols can easily be converted to *E* or *Z* alkenylcyclodisiloxanes under Pt(DVDS) or $[RuCl_2(C_6H_6)]_2$ catalysis, respectively, in high yields and with excellent stereo- and regioselectivities. The palladium-catalyzed cross-coupling of these cyclodisiloxanes with a number of aryl iodides (in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in 1,4-dioxane at ambient temperature) leads to trisubstituted *Z* or *E* allylic alcohols (**Scheme 2**).[33a] The one-pot synthesis of trisubstituted homoallylic alcohols is accomplished by treating the corresponding homopropargylic alcohol with 1 equiv of tetramethyldisilazane (TMDS), and 0.3 mol % of Pt(DVDS) in THF at ambient temperature. This provides the intermediate alkylidene-1,2-oxasilolanes, which are then treated with aryl iodides, 2.2 equiv of TBAF, and 10 mol % of $Pd(dba)_2$ to afford the trisubstituted homoallylic alcohols.[33b]



Scheme 2. *Intra*molecular Tandem Hydrosilylation/Cross-Coupling Reaction.



Scheme 3. Tandem Silylformylation/Cross-Coupling Reaction.

4.3. Silylformylation/ Cross-Coupling

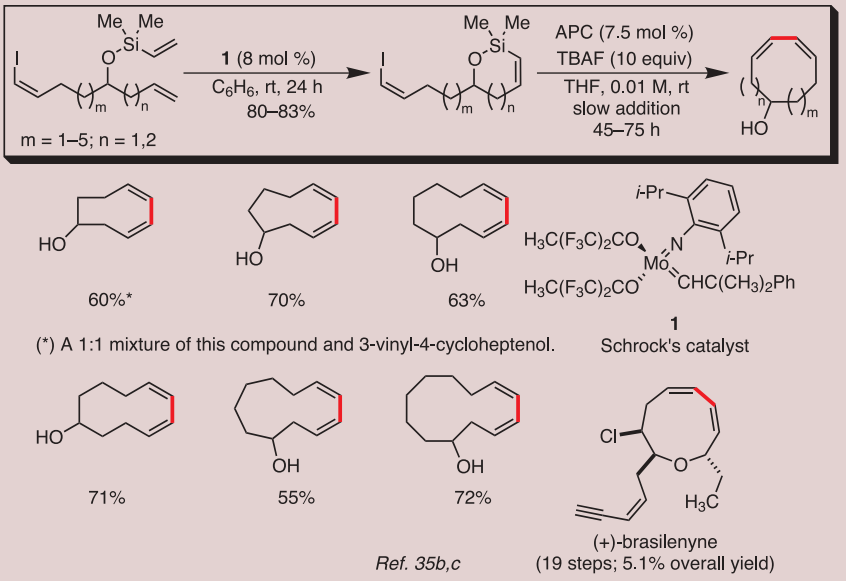
In the preceding two cases, hydrosilylation provided olefinic coupling precursors containing a newly formed carbon–silicon bond. Silylformylation, on the other hand, gives rise to new, vicinal carbon–silicon and carbon–carbon bonds to create an aldehyde-containing alkenylsilane. These compounds provide functionalized α,β-unsaturated aldehydes when subjected to the palladium-catalyzed cross-coupling. The realization of this tandem silylformylation/cross-coupling process begins with the intramolecular silylformylation of homopropargylic silyl ethers with 0.5 mol % of $[Rh(CNt\text{-}Bu)_4][Co(CO)_4]$ under 150 psi of carbon monoxide in toluene at 70 ˚C. The newly formed, aldehyde-containing, cyclic silyl ethers are competent cross-coupling partners with aryl iodides in the presence of 2 equiv of $KF•2H_2O$, 5 mol % of APC, 10 mol % of CuI, and 2.5 mol % of methylhydrocyclosiloxane in DMF at ambient temperature (**Scheme 3**). The use of both CuI and the hydrosilane are essential for the efficiency of the cross-coupling reaction and are thought to mediate the formation of the key reactive catalytic species.[34]

4.4. Mizoroki–Heck Reaction/Cross-Coupling

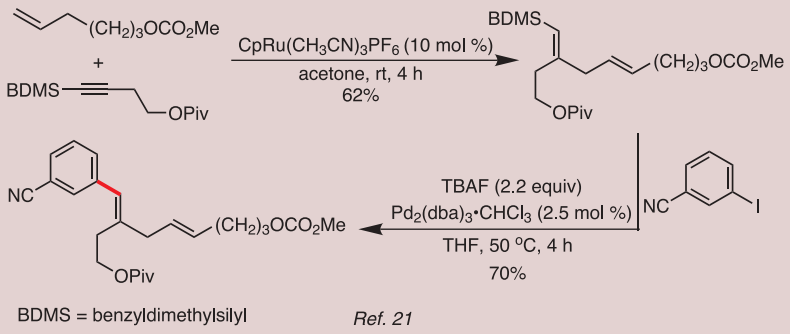
As mentioned in Section 3.2.1.2.2, the use of 2-pyridylsilanes as cross-coupling agents allows for the preservation of the silicon moiety through chemical manipulations prior to the palladium-catalyzed cross-coupling. A secondary property of the pyridyl group is that it can be employed as a directing group for the Mizoroki–Heck reaction. These two assets allow for a tandem Heck reaction/palladium-catalyzed cross-coupling reaction to afford highly substituted alkenes efficiently and in good yields. Exposure of dimethyl(hexenyl)-(2-pyridyl)silane to 0.5 mol % of $Pd_2(dba)_3•CHCl_3$, 2 mol % of tri(2-furyl)-phosphine (TFP), 1 equiv of Et_3N, and an aryl iodide in THF at 60 ˚C produces in situ the Mizoroki–Heck coupling product with retention of the 2-pyridylsilane unit. This intermediate, aryl-substituted dimethyl-(hexenyl)(2-pyridyl)silane can then undergo a subsequent cross-coupling reaction upon addition of 1 equiv of TBAF and a second aryl iodide to provide the olefinic products in good yields and excellent stereo- and regioselectivities.[20b,c] The selectivity of the Mizoroki–Heck process is proposed to be enhanced by the 2-pyridylsilane functionality, which directs the carbopalladation across the double bond of the alkenyldimethyl(2-pyridyl)silane.[20b]

4.5. Ring-Closing Metathesis/Cross-Coupling

The combination of ring-closing metathesis (RCM) and palladium-catalyzed cross-coupling constitutes a powerful sequence for the synthesis of substituted, unsaturated alcohols and medium-size rings with *cis*,*cis*-1,3-diene units. Alkenyl-(dimethyl)silyl ethers containing terminal alkenes undergo efficient ring closure in the presence of Schrock's catalyst to afford cycloalkenylsiloxanes of varying sizes. These siloxanes couple with aryl iodides in the presence of 2 equiv of TBAF and 5 mol % of $Pd(dba)_2$ in THF at room temperature to provide highly substituted styrenes in high yields.[35a] The intramolecular



Scheme 4. Tandem Ring-Closing Metathesis/Cross-Coupling Reaction (Yields Shown Are for the Cross-Coupling Step).



Scheme 5. Tandem Alder-Ene/Cross-Coupling Reaction.

variant of this reaction provides access to a number of medium-size rings,[35b] and has been exemplified in the synthesis of (+)-brasilenyne, an antifeedant isolated from *Aplysia brasiliana* (**Scheme 4**).[35c]

4.6. Alder-Ene/Cross-Coupling

The intermolecular Alder-ene reaction of benzyldimethylsilylalkynes, catalyzed by 10 mol % of $CpRu(CH_3CN)_3PF_6$, provides trisubstituted vinylsilanes in good yields and regioselectivities. These benzyldimethylsilyl-substituted alkenes can then be further functionalized through palladium-catalyzed cross-coupling with aryl iodides or bromides in the presence of 2.2 equiv of TBAF and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ in THF at 25 or 50 °C (**Scheme 5**).[21] Both the Alder-ene and cross-coupling reactions proceed efficiently to provide highly functionalized alkenes in good yields.

5. Summary and Outlook

The scope and generality of synthetic applications for which organosilanes can be employed in palladium-catalyzed cross-coupling reactions have grown substantially in the past five years. Nonetheless, the palladium-catalyzed cross-coupling of organosilanes with organic halides and pseudohalides is still an evolving field. Some of the major challenges that appear on the horizon are the development of (1) new, more reactive and more functional-group-tolerant organosilicon species, (2) new methods for activation of the cross-coupling process, (3) new methods for the introduction of organosilicon moieties into cross-coupling precursors, and (4) a better understanding of the mechanistic details[4,17,26c] of the activation and transmetalation steps in the process. Ongoing and future studies are certain to broaden the potential of these reactions and their applications in complex-molecule synthesis. We are confident that the burst in activity in this area over the past few years will continue unabated, and bring with it new and exciting advances in organosilicon chemistry.

6. Acknowledgements

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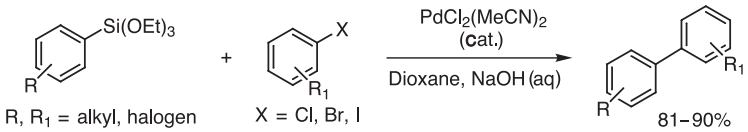
About the Authors

Scott E. Denmark was born in Lynbrook, NY, on June 17, 1953. He obtained an S.B. degree from MIT in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year, he began his career at the University of Illinois. He was promoted to associate professor in 1986, to full professor in 1987 and, since 1991, he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental carbon–carbon-bond-forming processes. Professor Denmark is currently on the Board of Editors of *Organic Reactions* and *Organic Syntheses.* He is Associate Editor of *Organic Letters* and Editor of *Topics in Stereochemistry.*

Michael Ober was born in Belleville, MI, on July 30, 1977. He graduated from Rose-Hulman Institute of Technology in 1999 with a B.S. degree in chemistry and minor degrees in chemical engineering and philosophy. He is currently a graduate student at the University of Illinois, working under the guidance of Professor Scott E. Denmark.

New Alkoxysilanes

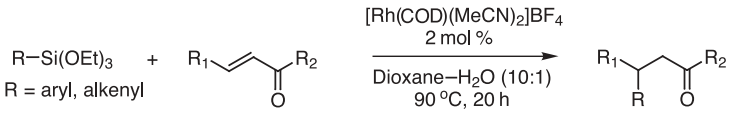
The use of silicon compounds as transmetalation reagents has attracted much attention as a viable alternative to the popular Stille and Suzuki coupling reactions, mainly due to the formation of nontoxic byproducts and the stability of the reagents to many reaction conditions.[1] Silicon-based coupling reactions can be carried out using aryl, heteroaryl, or alkenyl halides and alkoxysilanes in the presence of palladium or rhodium catalysts. Among the various types of silicon compounds available, alkoxysilanes are most effective in the coupling reactions.



R, R_1 = alkyl, halogen

X = Cl, Br, I

Recently, considerable attention has been paid to the rhodium-catalyzed addition of aryl(trialkoxy)silanes to carbonyl compounds, such as aldehydes, α,β-unsaturated ketones and esters.[2]



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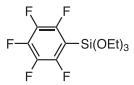

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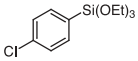
25g

17,556-0

100mL
500mL

59,791-0



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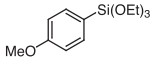
59,701-5



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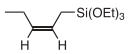

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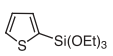

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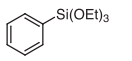

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1kg

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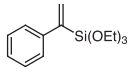

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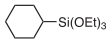

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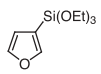

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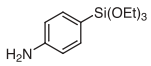

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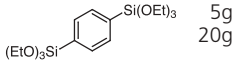

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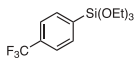
63,043-8



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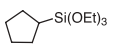

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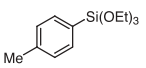

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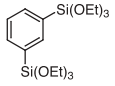

1g
10g

22,565-7 Bis(acetonitrile)dichloropalladium(II), 99%

$PdCl_2(MeCN)_2$

500mg
5g

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References: (1) For a review, see the preceding article in this issue: Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75. (2) Oi, S. et al. *Org. Lett.* **2002**, *4*, 667.

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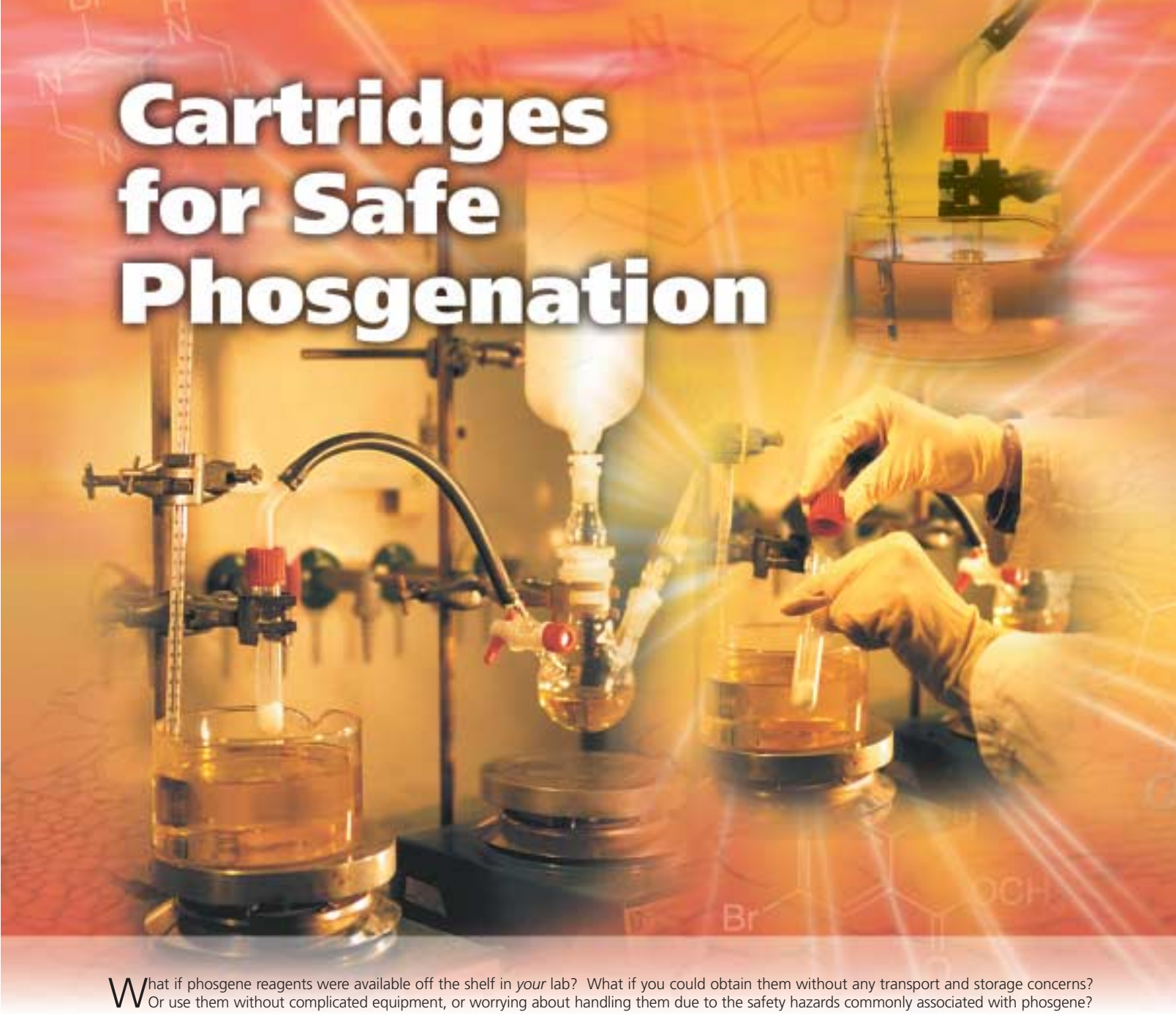

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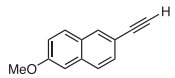
63,263-5

$C_{13}H_{10}O$ 182.22 — 1g, 5g



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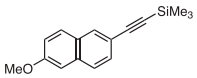
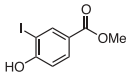
$C_{16}H_{18}OSi$ 254.41 — 1g, 5g



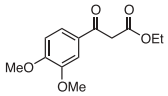
63,194-9

$C_8H_7IO_3$ 278.05 — 1g, 5g



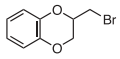
59,316-8

$C_{13}H_{16}O_5$ 252.27 — 1g, 5g



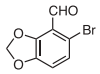
63,264-3

$C_9H_9BrO_2$ 229.07 — 1g, 5g



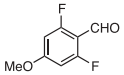
59,737-6

$C_8H_5BrO_3$ 229.03 — 1g, 5g



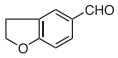
63,180-9

$C_8H_6F_2O_2$ 172.13 — 1g, 5g



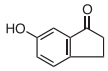
63,195-7

$C_9H_8O_2$ 148.16 — 1g, 5g



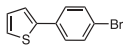
63,454-9

$C_9H_8O_2$ 148.16 — 5g



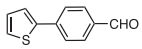
59,666-3

$C_{10}H_7BrS$ 239.13 — 1g



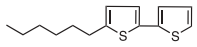
59,732-5

$C_{11}H_8OS$ 188.25 — 1g



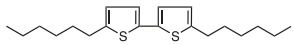
63,051-9

$C_{14}H_{18}S_2$ 250.43 — 500mg, 1g



63,295-3

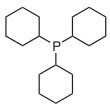
$C_{20}H_{30}S_2$ 334.59 — 1g, 5g



New Reagents

59,228-5

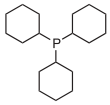
$C_{18}H_{33}P$ 280.44 — 100mL



Tricyclohexylphosphine
1M solution in toluene

59,239-0

$C_{18}H_{33}P$ 280.44 — 100mL



Tricyclohexylphosphine
1M solution in THF

59,370-2

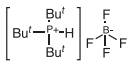
H_4AlLi 37.95 — 25mL, 100mL

$LiAlH_4$

Lithium
aluminum hydride
2.0M solution in THF

57,894-0

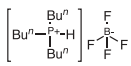
$C_{12}H_{28}BF_4P$ 290.13 — 1g, 5g



Tri-*tert*-butylphosphine
tetrafluoroborate

57,649-2

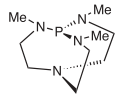
$C_{12}H_{28}BF_4P$ 290.13 — 1g, 5g



Tri-*n*-butylphosphine
tetrafluoroborate

46,355-8

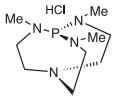
$C_9H_{21}N_4P$ 216.27 — 1g, 5g



N-Methyl Superbase

59,815-1

$C_9H_{22}ClN_4P$ 252.73 — 1g, 5g

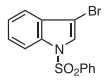


N-Methyl Superbase
hydrochloride

Heterocyclic Building Blocks

63,393-3

$C_{14}H_{10}BrNO_2S$ — 1g
336.21 — 10g

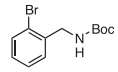


47,996-9

$C_5H_4N_4$ — 1g
120.11 — 5g

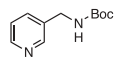
63,406-9

$C_{12}H_{16}BrNO_2$ — 1g
286.17



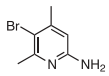
63,444-1

$C_{11}H_{16}N_2O_2$ — 1g
208.26 — 5g



63,420-4

$C_7H_9BrN_2$ — 1g
201.07 — 5g



63,215-5

C_6H_4ClNO — 1g
141.56 — 5g

63,276-7

$C_7H_7NO_3$ — 1g
153.14 — 5g

63,214-7

C_6H_4BrNO — 1g
186.01 — 5g

63,246-5

$C_6H_4BrNO_2$ — 1g
202.01 — 5g

63,341-0

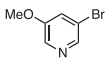
$C_6H_4ClNO_2$ — 1g
157.56 — 5g

59,317-6

$C_6H_4FNO_2$ — 1g
141.10 — 5g

63,181-7

C_6H_6BrNO — 1g
188.02 — 5g



Versatile Boronic Esters

56,814-7

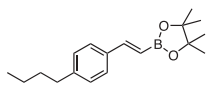
$C_{10}H_{21}BO_2$ — 1g
184.08 — 5g

63,334-8

$C_8H_{15}BO_2$ — 1g
154.02 — 10g

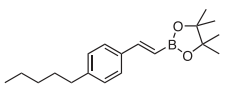
59,287-0

$C_{18}H_{27}BO_2$ — 1g
286.23 — 5g



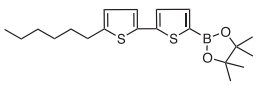
59,298-6

$C_{19}H_{29}BO_2$ — 5g
300.25 — 25g



63,296-1

$C_{20}H_{29}BO_2S_2$ — 1g
376.39 — 5g



63,156-6

$C_8H_{10}BNO_2$ — 1g
162.99 — 5g

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2003 Young Chemist in Industry Awards

Sigma-Aldrich is pleased to announce the winners of the *Young Chemist in Industry* awards, presented on April 30, 2003 at the 12th Young Chemists Meeting in London.

This annual, one-day meeting showcases organic chemistry research undertaken in an industrial setting by chemists under the age of 30 who do not hold a Ph.D. It represents a unique opportunity for younger chemists to present their research to an industry-wide audience. This year's gathering was attended by over 85 young scientists and featured 10 presentations by participants, and a guest lecture by Dr. Dave Tapokzay.

Sigma-Aldrich applauds the work of these talented young scientists. It is our honor to recognize the important contributions being made by young chemists throughout the industry. We congratulate the winners and commend all those who participated in the symposium.

First Prize:

Amanda Boase, *Merck, Sharp & Dohme (Harlow)*
GABA-A a5-Subtype Selective Inverse Agonists as Potential Cognition-Enhancing Agents

Second Prize:

James Peace, *Syngenta (Bracknell)*
Discovery of the Cyanotropanes, a Novel Class of Insecticides

Third Prize:

Colin Gray, *Organon (Newhouse)*
Web Based Chemoinformatics: Making the Drug Discovery Process More Efficient

Front row (left to right): Julia Lainton (Scientific Organizer), David Walker, Helen Feilden, Cedric Poinsard, and David Proctor (Scientific Organizer). *Back row (left to right):* Frederic Cordier, James Peace, Alex Smith (Scientific Organizer), Colin Gray, Peter Barton, and Robert Sheppard.

Cross Metathesis of Nitrogen-Containing Systems

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Outline

1. Introduction

Olefin metathesis is now firmly established as an important and general reaction in synthetic organic chemistry. One variant, known as cross metathesis (CM), uses a transition metal to catalyze the exchange of alkylidene groups on two independent alkenes to give a new, differently substituted alkene. The first reports of CM featured the coupling of allyl methyl sulfide with unfunctionalized alkenes using a tungsten–carbene complex,[1] and the use of Schrock's catalyst (**1**) in the cross metathesis of styrene.[2] Cross metathesis has since evolved into a highly practical synthetic tool, owing to the availability of advanced catalysts that provide excellent functional-group tolerance and the ability to conduct reactions under mild conditions.

A number of other types of metathesis reactions are known, including ring-closing, domino, ring-opening, ring-expansion, and polymerization metatheses. However, this review focuses on the cross metathesis of nitrogen-containing alkenes and alkynes, many of which are of biological significance. The review begins with a survey of the catalysts that are currently available for metathesis chemistry. Those catalysts that are most suited to cross metathesis are identified, as are practical considerations that need to be taken into account when carrying out these reactions. A number of other reviews have been written over the past few years in the area of metathesis chemistry: general reports,[3–7] the application of metathesis to carbohydrate chemistry,[8,9] sequential metathesis,[10] the ring-closing metathesis of nitrogen-containing compounds,[11] and a review of ruthenium complexes as metathesis catalysts.[12]

2. Catalysts

Numerous catalysts are available to facilitate metathesis reactions. However, only a few are used on a regular basis (**Figures 1** and **2**). The complexes shown in these two figures have alternately been called "precatalysts", "initiators", or "promoters" in the literature. To simplify the discussion in the rest of the review, complexes **1–24** will be called catalysts, with the understanding that they often are the precursors of the active catalytic species, which is formed by dissociation of a suitable ligand from **1–24**. Schrock's molybdenum–alkylidene catalyst (**1**), one of the first metathesis catalysts to be developed,[13] is known to tolerate β-lactam[14] and acrylonitrile functionalities, but is not compatible with unprotected amines, free alcohols, acetate groups, enones, and enoic esters. Despite these drawbacks, commercially available **1** is highly reactive toward a range of substrates that contain a variety of functional groups. In general, Schrock's catalyst gives shorter reaction times and higher yields than the more widely used ruthenium catalysts such as **9**. However, the general use of **1** remains somewhat problematic due to its sensitivity toward atmospheric oxygen. There are a number of other molybdenum catalysts available (see Figure 1); for example, chiral carbenes **2**[15]

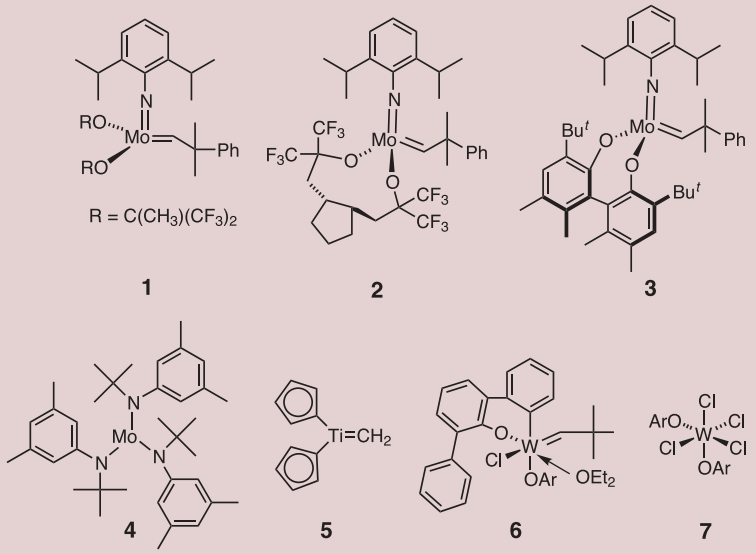


Figure 1. Molybdenum, Tungsten, and Titanium Metathesis Catalysts.

and **3**,[16] and achiral carbene **4**,[17] the latter of which is activated in situ by dichloromethane. Catalyst **4** has found use in the cross metathesis of alkynes that contain both electron-donating and electron-withdrawing substituents, and where tolerance of polar groups such as ethers, esters, nitriles, acetals, sulfones, and silyl ethers is required.[17]

Complex **8**, one of the first ruthenium–carbene catalysts reported,[18] effects the ring-closing metathesis (RCM) of suitably substituted precursors, leading to conformationally constrained amino acids and peptides.[19] However, its use has been somewhat superceded by what remains one of the most commonly used metathesis catalysts—Grubbs "first generation" catalyst, **9**.[20] Commercially available **9** initiates metathesis reactions more rapidly than the earlier catalyst **8**, and tolerates functionalities such as carbamate hydrogens,[21] unprotected carboxylic acids,[22] and a wide range of peptide protecting groups,[21] while remaining relatively air- and moisture-stable. Despite its widespread applications in metathesis reactions, catalyst **9** does have some drawbacks such as sluggish reactivity especially in the cross metathesis of unprotected homoallylic alcohols and allyltrimethylsilane,[23] and of substituted double bonds.[24] The bimetallic catalyst **10** was recently reported to have a catalytic activity that is similar to that of **9**, but with the advantage of increased stability, ease of storage, and the ability to be recovered and recycled.[25]

Water-soluble ruthenium catalysts such as **11** and **12** have been developed to allow metathesis reactions to be carried out in polar solvents, a feature that is particularly important if biological applications involving water-soluble substrates are to be fully realized. These catalysts, synthesized by a ligand-exchange reaction of catalyst **9**, show good RCM activity in solvents such as water and methanol.[26] Catalysts **11** and **12** have, however, found limited use to date due to their high air sensitivity in solution, decomposing rapidly to form a bright green solution in the presence of trace levels of oxygen. It is interesting to note that, while catalyst **12** is also soluble in dichloromethane, it does not show activity due to its rapid decomposition in this solvent.[27] A number of other ruthenium-based catalysts have also been developed, including the infrequently used photoinducible dimer **13**[28] and the chiral benzimidazolidene catalyst **15** that has an activity comparable to that of **9**.[29]

Hoveyda reported the first recyclable ruthenium-based catalyst, **14**. This complex can be purified in high yield by silica gel column chromatography for reuse.[30] However, while **14** is comparable to **9** in its catalytic activity, it is only reactive toward terminal alkenes. Other catalysts (e.g., **20**), that exhibit improved initiation rates as compared to **14**, have also been developed.[31]

The emergence in 1999 of the now commercially available Grubbs "second generation" catalyst, **16**, proved to be a particularly significant advance in metathesis chemistry.[32] The steric bulk and increased basicity of the dihydroimidazolidene ligand in **16** and **17** impart improved stability and activity as compared to the "first generation" catalyst **9**.[33] Catalyst **16**, which has a similar, if not improved, functional-group tolerance with respect to **9**, has been used to prepare functionalized trisubstituted double bonds by cross metathesis.[34] Catalyst **16** has found use in cross-metathesis reactions involving α,β-unsaturated esters, ketones, aldehydes, and a variety of other groups as detailed in this review.[35]

A "second generation recoverable", phosphine-free catalyst, **17,** has been developed by Hoveyda and co-workers.[36] This catalyst is highly reactive, recyclable via silica gel based chromatography, and extremely stable when exposed to water and/or air. Although not widely available commercially, its preparation has been published and its crystal structure determined. Catalyst **17** is very effective in cross-metathesis reactions, where one olefin is electron-deficient. For example, highly selective cross metathesis of α,β-unsaturated nitriles and acrylonitriles has been achieved using **17** but not **16**. Also, in contrast to **16**, catalyst **17** is reasonably soluble in methanol at room temperature and readily soluble at 50 °C; however, it remains completely inactive in water-based solvent systems.[37] In addition, catalyst **17** is compatible with unprotected alcohol[38a] and acid[33] groups, and has been used to synthesize unsymmetrical, functionalized, disubstituted olefins with good stereoselectivity under mild conditions.[38a] A variety of functionalities are tolerated including base-sensitive groups, and as such cross metathesis can be used to replace Wittig or Horner–Wittig reactions where substrates are base-sensitive. The dendrimeric **24** has been reported as an alternative to **17**, with an improved ability to be recycled by silica gel filtration.[36]

A variety of solid-phase catalysts related to **17** have also been reported, including **21**, **22**, and **23**. Deep-green resin **22**, synthesized from **16** and immobilized onto Wang resin, is a particularly stable and recyclable catalyst that shows good cross-metathesis activity even with highly electron-deficient olefins.[39] Solid-supported **21** shows high ring-closing metathesis activity, but much lower cross-metathesis activity as compared to **22**. Catalyst **23** has been used for cross-metathesis reactions in methanol or water in ambient air.[37]

Blechert and co-workers reported the novel ruthenium–alkylidene catalysts **18** and BINOL-based **19** as an addition to

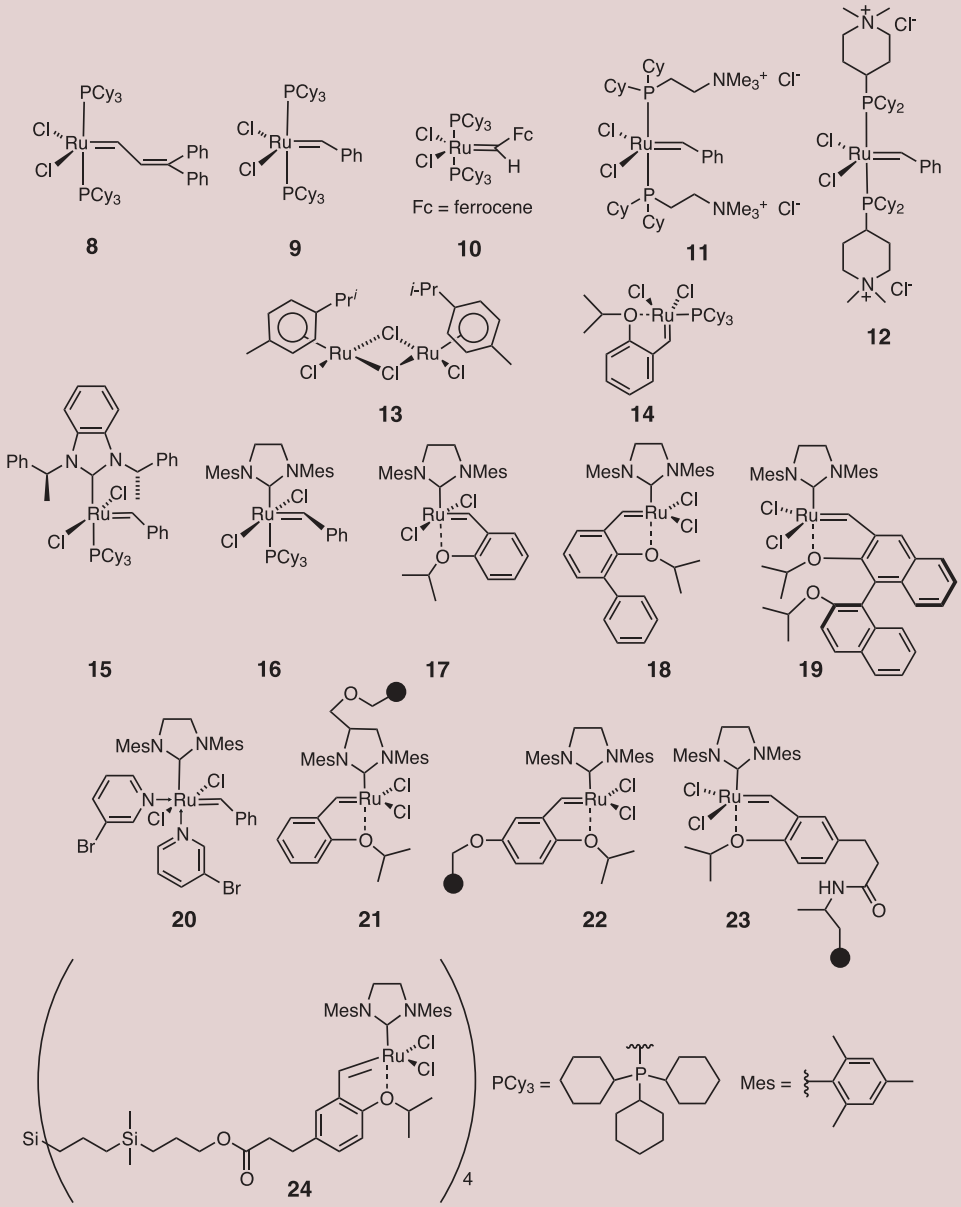


Figure 2. Ruthenium Metathesis Catalysts.

the growing list of second-generation catalysts.[40,41] These catalysts are significant in that they display increased activity, relative to **16** and **17**, while retaining stability even after exposure to air for one week. The improved reactivity and stability of these catalysts has been attributed to the increased steric bulk of the ligands.

Metals other than molybdenum and ruthenium can also form the basis of metathesis catalysts (see Figure 1). For example the titanium carbene **5**[42] and the tungsten catalysts **6** and **7** have found use in cross-metathesis reactions.[1,43]

3. Catalysis Mechanism

The generation of metallacyclobutane intermediates by alternating [2+2] cycloadditions and cycloreversions is the generally accepted mechanism for the cross metathesis of alkenes and alkynes.[44] A simplistic version of this, the so-called "Chauvin mechanism", is depicted in **Figure 3**. The choice of olefin that initially binds to the catalyst (step **A**) is dependent upon a variety of issues related to the electronic and steric properties of the alkene or alkyne.[45,46]

The key steps in the catalytic cycle are as follows: The cycle is initiated by coordination of an alkene to the ruthenium metal (step **A**) to form what has been termed a "ruthenacycle," which fragments rapidly (step **B**) to give a newly substituted alkylidene with the release of ethylene gas. A second alkene then reacts regio- and stereoselectively with this alkylidene (step **C**) to give a second metallacyclobutane (steps **D** or **D1**). The formation of the metalla ring shown in step **D** is highly favored over that in **D1**.[47] The favored metallacycle breaks down to regenerate the

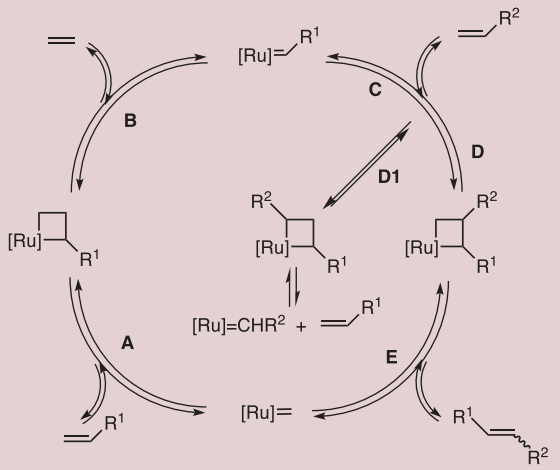


Figure 3. Schematic Representation of the Cross-Metathesis Mechanism.

active catalytic species and the desired cross-metathesis product (step **E**). It should be noted that phosphine-based catalysts coordinate to the alkene only after an initial pre-equilibrium dissociation of a PCy_3 group.[12,20,45]

Catalyst activity is directly related to the electron-donating ability of the phosphine ligands: σ donation of the phosphine ligands stabilizes the fourteen-electron metallacyclobutane intermediate; while the larger and the more strongly electron-donating the halide ligands (I<<Br<Cl) are, the lower the catalytic activity.[12] Catalytic activity also depends on catalyst initiation (related to the nature of the alkylidene moiety) and catalyst lifetime (decomposition rate of catalyst).

4. Reaction Scope and Conditions

While a variety of reaction conditions have been employed in metathesis chemistry, there are some standard techniques that generally improve reaction yields. A number of the factors that are known to influence the outcome of cross-metathesis reactions are discussed in this section.

The efficiency of formation of coupled alkene products in cross-metathesis reactions can be facilitated by removing the byproduct, ethylene, formed during the course of the reaction. For example, the conversion of vinylsilanes into cross-metathesis products is quantitative when ethylene is removed using a gentle stream of argon. In contrast, yields decrease considerably to around 20% in the absence of purging.[47] This simple procedure should be adopted in all cross-metathesis reactions. Where the substrates have a low viscosity, a static vacuum can be used to remove ethylene.[5]

There seems to be no advantage in using argon rather than nitrogen[22] in cross-metathesis reactions involving ruthenium-based carbene catalysts, or by working in a dry box rather than using Schlenk techniques for reactions involving common catalysts such as **9** and **16**.[21] However, the yield of the cross-coupled product can, in general, be improved by increasing the number of equivalents of one terminal alkene coupling partner (up to four equivalents). It has also been shown that the most effective molarity range of second-generation Grubbs catalyst **16** is 5–20 mol %. Lower levels of **16** generally result in sluggish reaction with very low yields of product, while higher levels tend to give rise to side products in which the benzylidene group from the catalyst is transferred to the alkene substrate.[48]

The most commonly used solvents in metathesis reactions are dichloromethane, carbon tetrachloride, benzene, or 1,2-dichloroethane at reflux or at room temperature. It is important to note that **16** is more thermally stable than **9**, such that reactions at reflux are best carried out using the former complex. The use of reflux conditions has the added advantage of better facilitating the removal of ethylene from the reaction.

Isolation of Grubbs ruthenium catalysts **9** and **16** from reaction mixtures is often difficult due to the presence of residual ruthenium byproducts and, as such, a number of experimental techniques have been developed to aid catalyst removal and subsequent purification. Georg and co-workers developed an effective method for removing catalyst **9** from crude ring-closing-metathesis reaction mixtures. Here, the crude product is stirred with triphenylphosphine oxide or dimethyl sulfoxide, and the resulting complex is removed by filtration through silica gel.[49a] Maynard and Grubbs also reported a method in which residual ruthenium byproducts from **9** are removed as water-soluble ruthenium–tris(hydroxymethyl)-phosphine complexes.[50] However, this method has the drawback that many equivalents of the expensive phosphine ligand are required. Residual ruthenium from catalyst **9** and other highly colored impurities have been effectively removed from crude reaction mixtures by oxidation with a small amount of $Pb(OAc)_4$ followed by filtration through a silica plug.[51] These experimental techniques for the removal of residual ruthenium from the crude reaction mixture have become somewhat redundant with the development of recyclable catalysts such as **17**, which can be separated from reaction mixtures by silica gel based chromatography and subsequently recycled for future use.

5. Cross Metathesis with Alkenes

Cross-metathesis reactions of alkenes have been carried out on a range of substrates, many of which contain nitrogen, an element that is often associated with biological activity. In the following sections, we have divided these examples of nitrogen-containing substrates into a number of useful and functional groupings.

5.1. Amino Acids and Peptides

The application of cross-metathesis methodology to amino acids and peptides has attracted considerable attention as a means to prepare modified amino acids and peptidomimetics that possess useful chemical and biological properties. A number of variants of cross metathesis have been reported, which differ in the point of attachment of the alkene to the amino acid participant in the metathesis reaction. For example, a substituent bearing a terminal double bond can be attached at either the (i) α carbon, (ii) amino acid side chain, (iii) amino terminus, or (iv) carboxyl end of an amino acid. Reactions can be further classified on the basis of the parent amino acid, e.g., glycine, tyrosine, and serine.

5.1.1. α-Carbon-Substituted

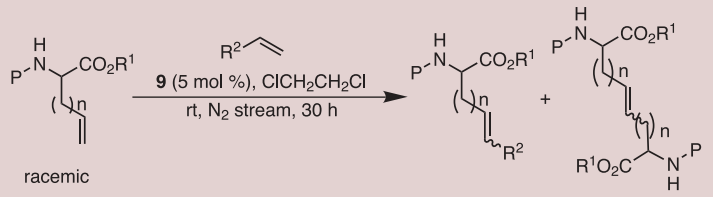
Modified glycine has proven to be a popular scaffold for cross-metathesis

chemistry. In 1997, Gibson and co-workers published the first examples of cross metathesis using protected amino acids.[22] This was followed soon after by further systematic studies (**eq 1**).[21] A variety of solvents, temperatures, reaction times, catalyst loadings, and substrate concentrations were investigated, as well as the effect of changing from a static pressure to a steady flow of nitrogen. In general, optimum conditions were achieved using a 0.25 M solution of amino acid substrate in 1,2-dichloroethane with two equivalents of styrene, 5 mol % of Grubbs first-generation catalyst **9** at room temperature, and with a steady flow of nitrogen for thirty hours. In all cases, both cross-coupled products and homodimers were isolated.

The outcome of these reactions seems to be relatively independent of the nature of the amine protection. The nature of the *C*-terminal group also seems to be relatively unimportant with methyl, benzyl, and *tert*-butyl esters giving similar results. A free acid also proved to be a suitable substrate, and homoallylglycine was generally more reactive than allylglycine.[21] However, vinylglycine does not undergo efficient cross metathesis, presumably due to the steric inaccessibility of the double bond to the catalyst. These findings illustrate the importance of the length of the alkene tether to the efficiency of cross-metathesis reactions. The applicability of this methodology to the solid phase has also been investigated using Wang resin.[21] Here, initial attempts at cross metathesis gave mixtures of cross-metathesis and self-metathesis products in relatively equal amounts, due to the lack of site isolation on the resin. It was subsequently found that "capping" the Wang resin allowed preparation of the desired cross-metathesis product in good yield.

Heterocycles have been successfully coupled to glycine derivatives. For example, racemic methyl *N*-acetylallylglycinate was coupled to 2,8-diallyldibenzothiophene as a key step in the production of antibiotic agents.[52] Two dibenzothiophene cross-metathesis products, the amino ester and the bis(amino ester), were isolated, along with two homodimeric products including a novel dibenzothiophenophane.

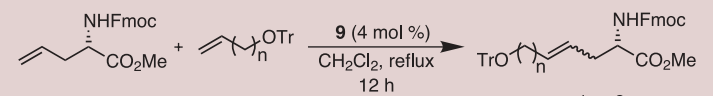
Cross-metathesis reactions have been employed by Blechert and co-workers as a preliminary step in developing a method for the catalytic cyclization and cleavage of tetrapeptide-derived macrocycles from solid supports.[53] Here, the side chain of Fmoc-allylglycine methyl ester was selectively coupled to *O*-trityl-protected alkenols of



n	P	R^1	R^2	Yield, % Cross Metathesis	Yield, % Self-Metathesis
0	Boc	Me	Hex	7	–
1	Boc	Bu^t	Hex	49	16
1	Boc	Me	Hex	45	17
1	Boc	Me	Ph	15	21
2	Boc	Me	Hex	66	28
2	Ac	Me	Ph	43	48
2	Boc	Me	Ph	52	40
2	Boc	Bn	Ph	53	44
2	Fmoc	Me	Hex	58	25
2	Fmoc	H	Hex	58	18
2	Phth	Me	Ph	55	35

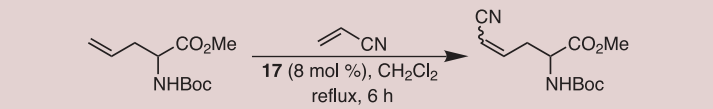
Ref. 21

eq 1



Ref. 53

eq 2



Ref. 33

eq 3

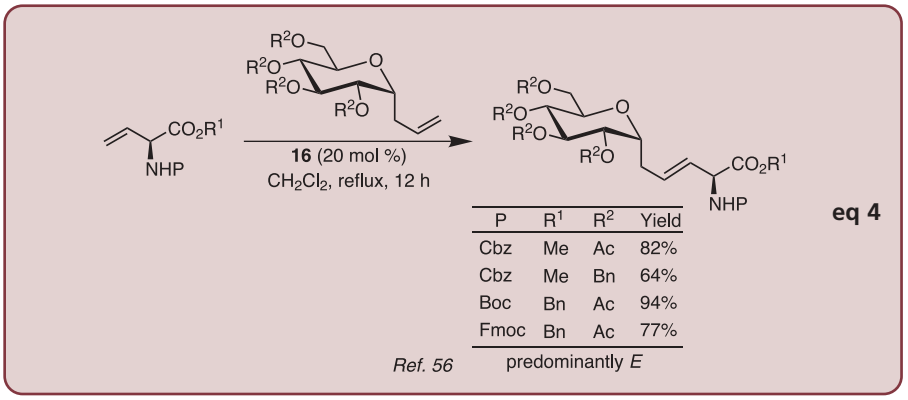
differing chain lengths, to give cross-metathesis products that were deprotected, resin-linked, and subsequently incorporated into tetrapeptides (**eq 2**).

The application of cross metathesis to allylsilanes has been developed as a basis for subsequent side-chain elaboration via the silyl group. In one example, a protected glycine derivative was functionalized using allyltrimethylsilane in excellent yield and with good stereoselectivity.[54] More recently, Blechert and co-workers utilized second-generation catalyst **17** for a highly selective cross metathesis between acrylonitriles and protected amino acids—reactions that could previously only be achieved using sensitive molybdenum catalysts (**eq 3**).[33] Again, this allows for subsequent side-chain modification.

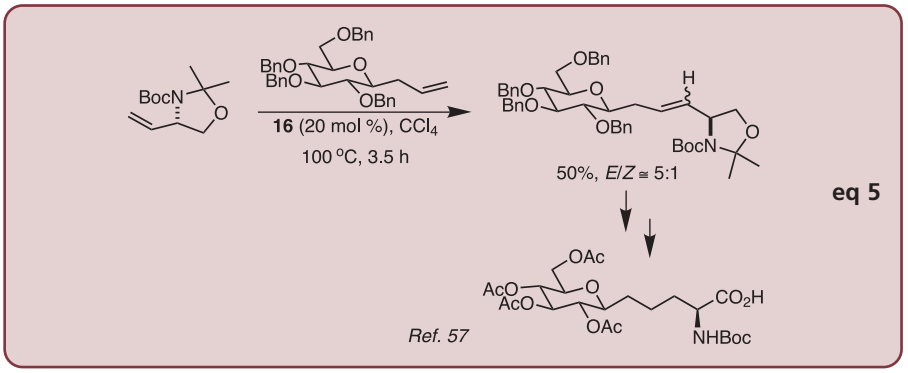
Roy and co-workers carried out the cross metathesis of a protected homoallylamine and a protected glycine derivative with suitably substituted monosaccharides to give *C*-linked carbohydrates that possess enhanced stability towards enzymatic and metabolic cleavage.[55] Reactions of this type provide convenient access to important glycopeptidomimetics, where the parent glycopeptides are known to play an important role in a number of important biological processes including tumor metastasis and chemotaxis.

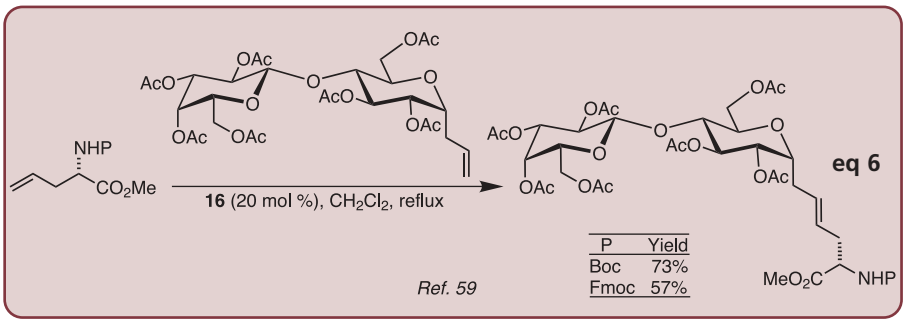
Nolen and colleagues reported related work using Grubbs second-generation catalyst **16** to give improved overall yields of *C*-glycosyl amino acids (**eq 4**).[56] Here, cross metathesis of a tetra-*O*-protected-glucose with a vinylglycine derivative proceeded efficiently, and the products obtained were hydrogenated to give *C*-glycosyl asparagines for use in enzyme assays. *C*-Glycosyl amino acids have also been prepared by reaction of *N*-Boc-vinyloxazolidine, a vinylglycine equivalent, and a sugar using Grubbs second-generation catalyst **16**; **9** does not catalyze these reactions (**eq 5**).[57] The resulting metathesis products were hydrogenated, acylated, and the oxazolidine ring oxidatively cleaved to afford a versatile building block for the synthesis of modified glycopeptides.

In a related study, Danishefsky and co-workers developed a mild and efficient

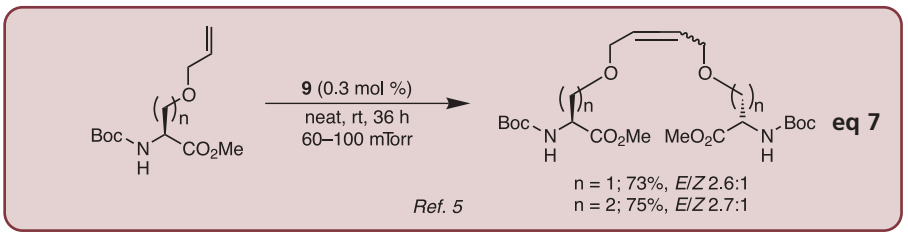


P	R^1	R^2	Yield
Cbz	Me	Ac	82%
Cbz	Me	Bn	64%
Boc	Bn	Ac	94%
Fmoc	Bn	Ac	77%





P	Yield
Boc	73%
Fmoc	57%



cross-metathesis synthesis of a hexasaccharide glycosyl amino acid that was suitable for incorporation into polymeric antitumor vaccines.[58] Here, Fmoc-L-allylglycine benzyl ester was coupled to a range of *O*-allyl glycosides to give the desired cross-metathesis products in good yields.

Other reports on the synthesis of stable glycopeptide analogues using cross-metathesis methodology have appeared with a view to identify potential therapeutic agents.[59] For example, protected *C*-allyl-glycosides have been coupled to protected allylglycine using second-generation Grubbs catalyst **16**—introduced in two equal portions at 24-hour intervals—to give moderate-to-good overall yields of coupled products. Both Boc and Fmoc protecting groups seem to function equally well in these reactions. This initial work was extended to allow the conjugation of *C*-allyllactose as a first step in the development of a co-translational glycopeptide synthetic strategy (**eq 6**).[59]

The amino acid serine has also been used as a basis for developing cross-metathesis methodologies. For example, Grubbs and colleagues explored a number of cross-metathesis reactions of serine derivatives with both terminal and substituted alkene coupling partners.[5] Allyl ethers of protected serine residues were dimerized by cross metathesis under reduced pressure (**eq 7**), while treatment of Boc-L-serine(*O*-allyl) methyl ester with bis(9-nonenyl acetate), itself made by cross metathesis, generated a lipophilic amino acid in high yield and with good stereoselectivity.[5] Larger and more complex architectures also appear to be compatible with cross-metathesis chemistry. For example, a hydrophobic pentapeptide framework has been elaborated.[5] The dimerized pentapeptide represents an example of side chain to side chain cross-linking via a non-native *C–C* linkage.

Aryl-substituted *C*-fucopeptides have been synthesized using cross-metathesis methodology These products are important in that they mimic tetrasaccharide sialyl Lewis X, a carbohydrate-based terminal unit found in cell-surface glycoproteins and glycolipids, which interacts with E- and P-selectin to mediate the early stages of an inflammatory response. It was found that cross metathesis at room temperature failed to give the desired coupled products. However, reaction at reflux afforded an array of products in reasonable yields, with the electron-poor pentafluorostyrene giving the lowest yield of cross-metathesis product (**eq 8**).[60] The authors noted that activated aromatic and nonaromatic olefins gave mixtures of *E* and *Z* isomers, while nonactivated aromatic olefins produced only the *E* isomers. The final products were screened for E- and P-selectin binding.

Tyrosine-based systems have been used in cross-metathesis reactions, where the *O*-allyl tether is of sufficient length to allow cross metathesis to proceed.[5] By contrast, the analogous dimerization of Boc-L-allylglycine methyl ester does not proceed well, because the close proximity of the double bond to the amino acid backbone appears to hinder catalyst binding.

5.1.2. N-Substituted

There are comparatively far fewer examples of cross-metathesis reactions of an olefin attached to the α nitrogen of an amino acid or peptide. Nevertheless, cross metathesis of *N*-alkenylpeptoids and *O*-allyl glycosides has been reported by Hu and Roy to give mixtures of *E* and *Z* metathesis products (**eq 9**).[61] The reaction is tolerant of free carboxylic acids, but not of secondary amine functionalities. It was found that a shorter tether between the nitrogen and the double bond results in a lower yield of the desired cross-metathesis product.

5.1.3. O-Substituted

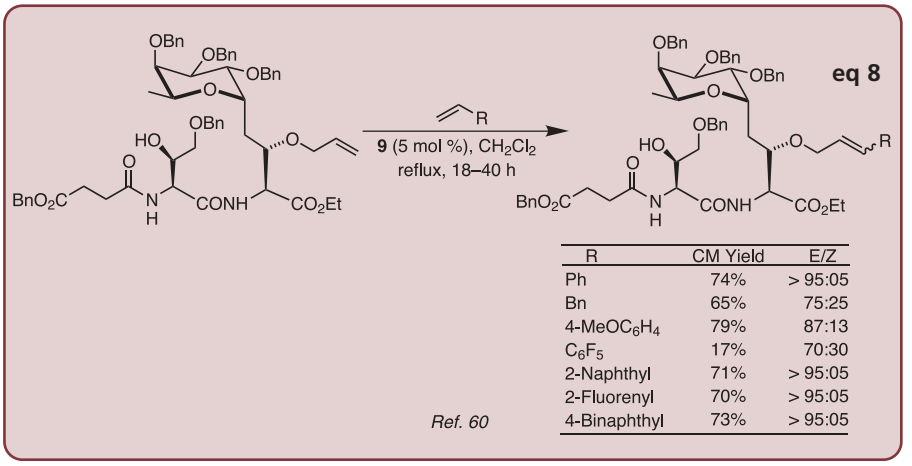
Cross metathesis at the *C* terminus of suitably substituted amino acids and peptides has also been reported. For example, 9-decen-1-yl Boc-glycinate reacts with 9-decen-1-yl acetate homodimer, in the presence of catalyst **9**, to give a differently functionalized 9-octadecene-1,18-diol (**eq 10**).[5] This glycine derivative also undergoes self-metathesis to give a novel amino acid homodimer in excellent yield.[5]

Cross-metathesis reactions of this type have also been extended to the solid phase using a polystyrene (1% DVB) resin.[62] These resin-bound amino acids and peptides can be chemically manipulated and subsequently cleaved from the resin. In another solid-phase example, Schreiber and colleagues carried out "intra-site" cross-metathesis reactions in near quantitative yields on individual polystyrene polymer beads with a silyl linker (**eq 11**),[63] and found that the alkyl chain length had little effect on the reaction efficiency. Here, the metathesis step can be viewed as a ring-closing metathesis, despite the net overall result being the same as that from a solution-phase cross metathesis.

5.2. Carbamates

There are numerous non-amino acid based examples of cross metathesis in which an amine nitrogen is protected by a carbamate (e.g., Cbz, Boc, and Fmoc). (The protection of an amine is especially important in cross-metathesis chemistry since most catalysts are poisoned by this functional group.) For example, carbamates have been utilized to synthesize functionalized allylsilanes using cross metathesis.[54] In addition, Fmoc-protected amines, which are potential starting materials for the synthesis of nonnatural amino acids, have been prepared by cross metathesis of an allylstannane using molybdenum catalyst **1** (**eq 12**).[64] The fact that cross-metathesis chemistry is compatible with allylstannanes is of particular significance, because allylstannanes are valuable reagents for nucleophilic additions and radical reactions.

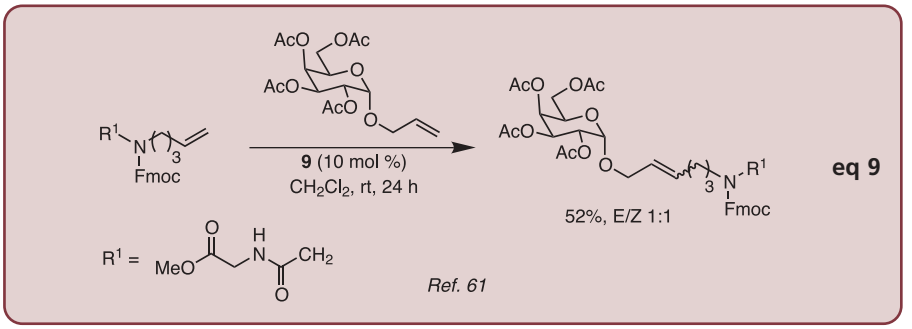
Second-generation Grubbs catalyst **16** has been used to promote the cross metathesis of a number of non-amino acid carbamates. A key step in a reported synthesis of (–)-prosophylline, a prosopis alkaloid with antibiotic and anesthetic properties, involves a cross-metathesis-based side-chain extension (**eq 13**).[65] The cross-coupling step was followed by hydrogenation and deprotection to give the final



eq 8

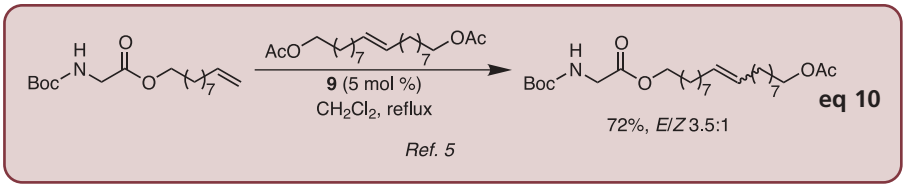
R	CM Yield	E/Z
Ph	74%	> 95:05
Bn	65%	75:25
4-MeOC$_6$H$_4$	79%	87:13
C$_6$F$_5$	17%	70:30
2-Naphthyl	71%	> 95:05
2-Fluorenyl	70%	> 95:05
4-Binaphthyl	73%	> 95:05

Ref. 60



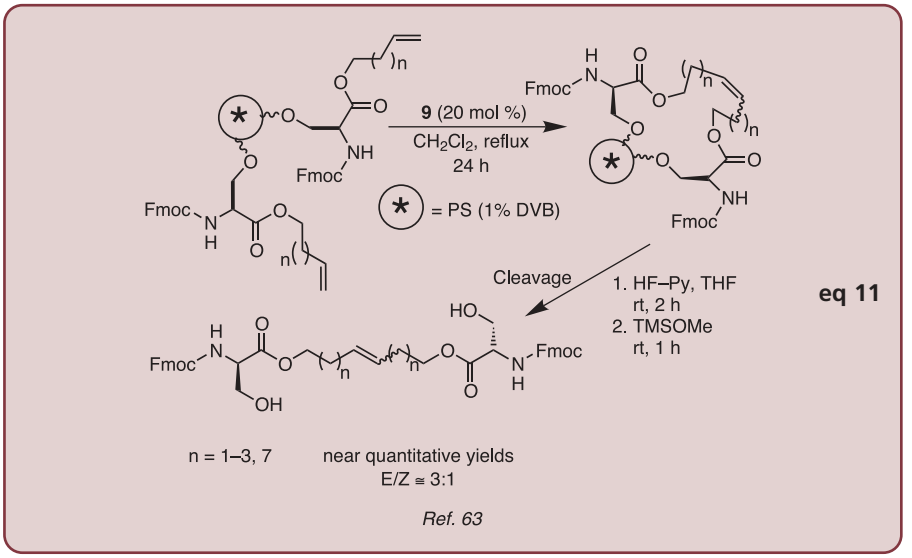
eq 9

Ref. 61



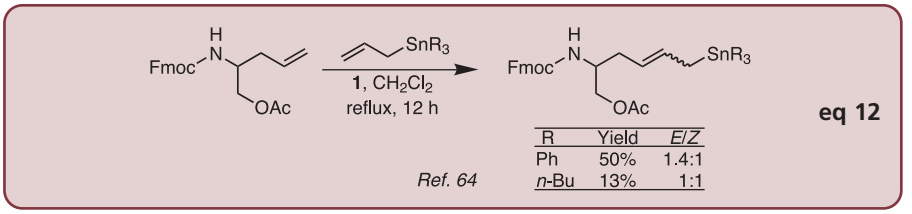
eq 10

Ref. 5



eq 11

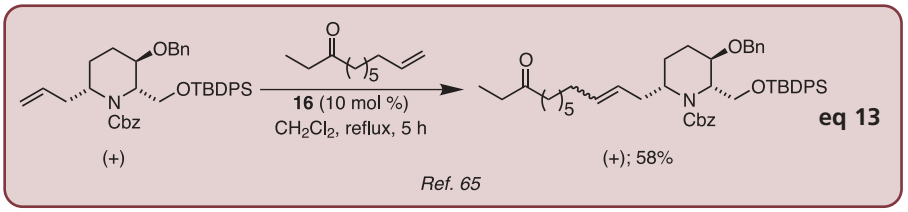
Ref. 63

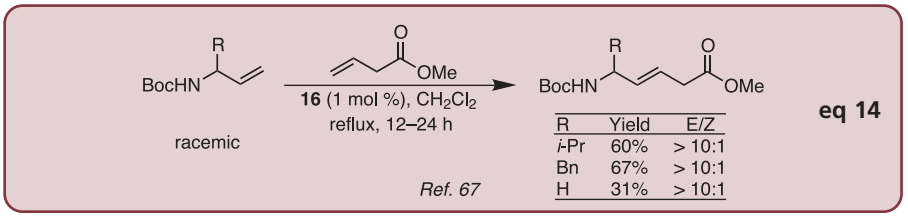


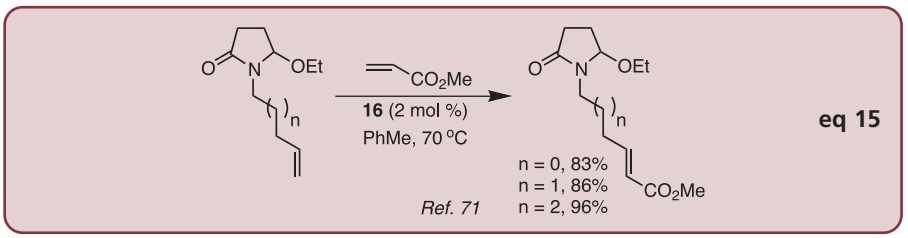
R	Yield	*E/Z*
Ph	50%	1.4:1
n-Bu	13%	1:1

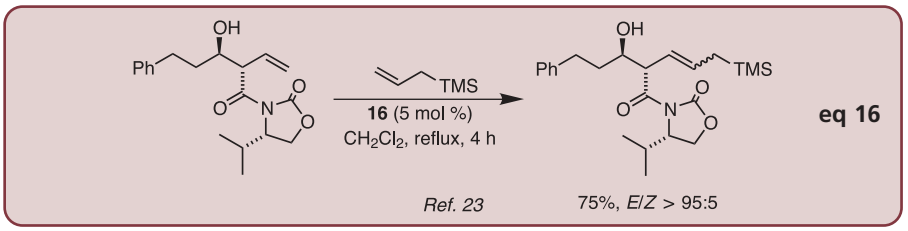
eq 12

Ref. 64









natural product. Roy and co-workers have also used catalyst **16** to facilitate the cross metathesis of allyl halides and terminal olefins in good yield and with excellent *E*/*Z* selectivity.[66] This sequence was extended to N-protected allylglycine to provide convenient access to useful peptidomimetics.

In an interesting piece of work, Vasbinder and Miller explored the isosteric replacement of peptide bonds using a convergent, cross-metathesis synthetic strategy.[67] The isosteric replacement of amide bonds to give β,γ-unsaturated δ-amino acids results in useful structural peptidomimetics that are less susceptible to biodegradation via proteolytic cleavage and, as such, have proved valuable in pharmaceutical drug design.[68] Allylic amines derived from either valine, phenylalanine, or glycine were coupled to methyl 3-butenoate to afford the isosteres in moderate yields (**eq 14**).[67] In another example of this methodology, a Pro-Gly dipeptide isostere was formed in 83% yield from vinyl-substituted pyrrolidine, itself prepared from Boc-protected proline methyl ester.[67]

A stereodiversified library of *trans*-1,4-enediols has been synthesized and subsequently screened for mu opioid receptor affinity. Eight enediol diastereomers were synthesized by cross metathesis in yields ranging from 51 to 81%. These were then separated into a total of sixteen stereoisomers using reverse-phase HPLC.[69]

5.3. Amides

Suitably substituted amides, other than those that constitute a peptide bond, have also proven to be useful substrates for cross metathesis. For example, Piva and co-workers submitted oxoamides to cross metathesis with trimethyl(allyl)silane to produce novel allylsilane derivatives.[70] Functionalized allylsilanes have also been prepared in excellent yields from chlorinated substrates containing amide linkages.[54] In addition, *N*,*O*-acetals bearing an olefinic side chain undergo cross metathesis with methyl acrylate in excellent yields—the longer the tether, the higher the yield (**eq 15**).[71]

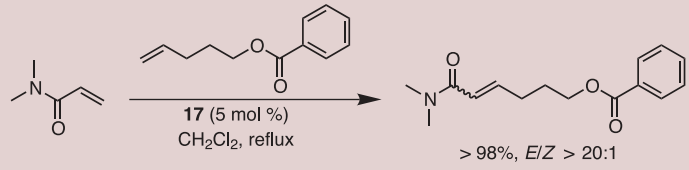
The ability to dimerize resin-bound, amide-containing olefins in good yields has been demonstrated using metathesis chemistry.[72] The initial metathesis reaction is strictly an example of ring-closing metathesis, since both coupling partners are attached to the solid support. However, the net result after cleavage from the solid support is analogous to a solution-phase cross-metathesis reaction. (This approach is similar to that depicted in equation 11 for resin-bound amino acids.)

There are a number of cross-metathesis reactions on systems that are not true amides. These reactions are included here for convenience. A key step in a recently reported enantioselective total synthesis of (+)-amphidinolide T1 involves a cross-metathesis coupling of two key fragments, in the presence of catalyst **16**, to give a 60% yield of the desired cross-metathesis product as a 1:1 mixture of *E* and *Z* isomers in addition to some alkene dimers.[73] These alkene dimers were then exposed to catalyst **16** in a second metathesis reaction, affording an additional 36% yield of the cross-metathesis product (96% overall). In a related example, a cross-metathesis reaction was carried out that gave high *E*-olefin selectivity (**eq 16**).[23] This selectivity is thought to be due to the formation of a five-membered chelate ring between the homoallylic hydroxyl group and the ruthenium in a metallacyclic intermediate, thus giving rise to kinetically controlled products highly selectively.

There are numerous examples of nitrogen-containing cross-metathesis reactions that involve α,β-unsaturated amides. Grubbs and co-workers conducted a systematic study on the cross metathesis of α,β-unsaturated amides with terminal olefins using the second-generation catalyst **16**.[74] Cross metathesis was shown to be compatible with Weinreb amides and oxazolidinone imides, both of which are widely utilized in organic synthesis. All reactions afforded products with excellent *E*/*Z* diastereoselectivities. The authors report that electron-donating substituents on the amide nitrogen, such as alkyl groups, gave lower yields, whereas electron-withdrawing groups afforded higher cross-metathesis yields. It has been suggested that the amide carbonyl group chelates to the metal center, the extent of which is dependent on the electron density at the oxygen atom.[36,74,75] The amide nitrogen substituent greatly affects the outcome of the metathesis reaction, since chelation of the amide carbonyl group to the metal center results in a decrease in catalyst turnover. This is demonstrated by the electron-donating *N*,*N*-dimethylacrylamide giving a significantly lower cross-metathesis yield than that of the electron-deficient *N*,*N*-diphenylacrylamide.[74]

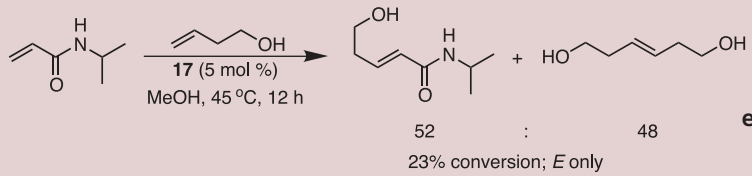
Recyclable catalyst **17** has been used in a related cross-metathesis transformation involving an α,β-unsaturated amide and a terminal olefin (**eq 17**).[76] The solid-phase catalyst **22** has also been used to facilitate the cross metathesis of *N*,*N*-dialkylacrylamides as examples of electron-deficient alkenes.[39]

Despite the obvious potential for cross metathesis in biological systems, little progress has been made in developing methods applicable to protic solvents such as methanol and water. To date, attempts to carry out selective cross-metathesis reactions in these environments have proven to be problematic. For example, cross metathesis between *N*-isopropylacrylamide and 3-butenol in methanol gave a mixture of cross-coupled and homodimer products in almost equal amounts (**eq 18**).[37] Connon and Blechert postulated that the particularly electrophilic alkylidene intermediates in these reactions are of insufficient stability in nucleophilic solvents, thus giving unselective reactions and poor yields of cross-metathesis products.[37]



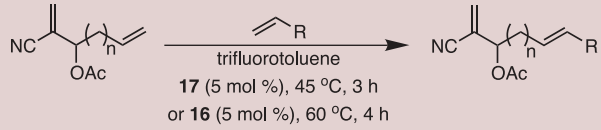
eq 17

Ref. 76



eq 18

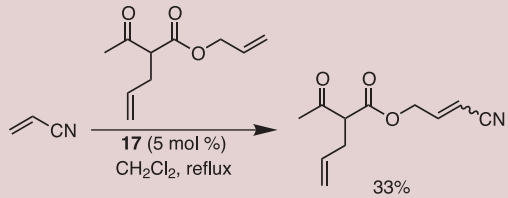
Ref. 37



n	R	CM Yield with **16**	CM Yield with **17**	*E*/*Z*
2	CF_3	16%	50%	≥ 20:1
8	CF_3	> 95%	≥ 95%	≥ 20:1
2	C_4F_9	13%	57%	≥ 20:1
8	C_4F_9	24%	≥ 95%	≥ 20:1

eq 19

Ref. 77



eq 20

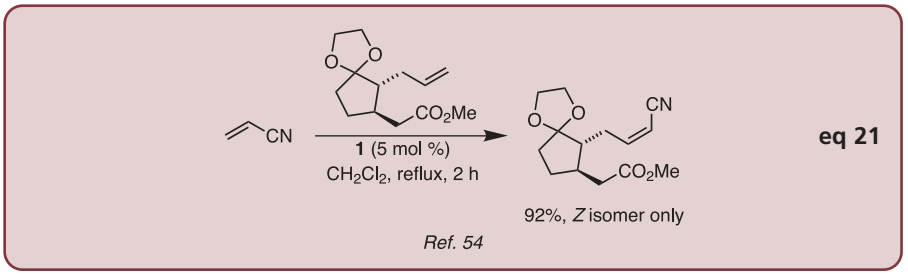
Ref. 76

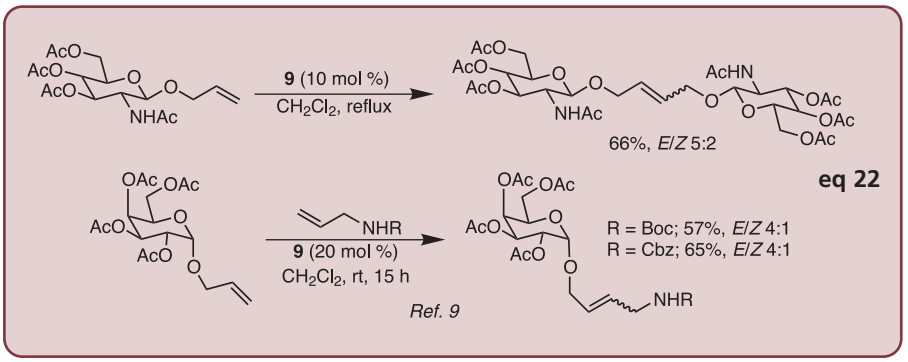
5.4. Acrylonitriles

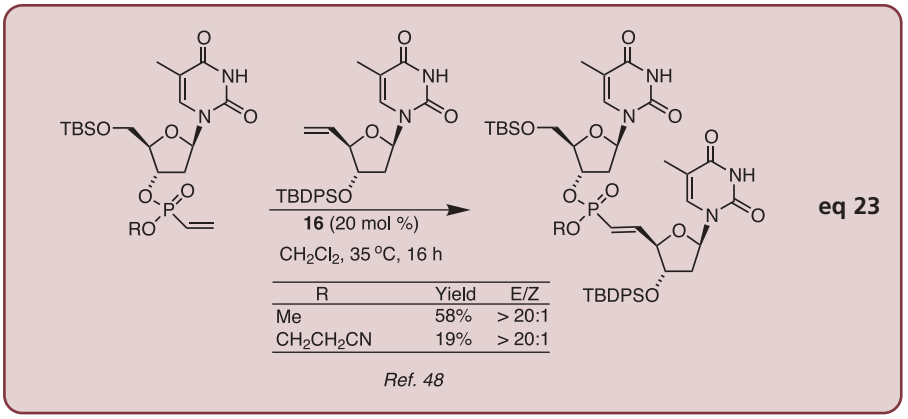
Organonitriles are useful synthetic intermediates that can be reduced to an amine or aldehyde, or hydrolyzed to the corresponding acid. These derivatives can, in theory, be prepared by cross metathesis of a suitable acrylonitrile. However, acrylonitriles tend to be unreactive in cross metathesis and, in some cases, cross metathesis of an olefin can even take place in the presence of a hindered acrylonitrile (**eq 19**).[77] Cross metathesis only occurs with the relatively electron-rich terminal double bond and not the hindered, electron-deficient nitrile double bond, when using these particular catalysts. However, the acrylonitrile functionality does participate in a competitive intramolecular RCM reaction to give a 5-membered ring. In addition, Grubbs first-generation catalyst **9** does not generally tolerate this functionality, and molybdenum catalysts are particularly sensitive and their use is often impractical. However, the emergence of second-generation, recyclable catalysts has made these reactions possible.

Hoveyda and co-workers carried out studies on acrylonitriles using catalyst **17**, with a resulting intriguing product selectivity:[38a] a homodimer was isolated in an *E*/*Z* ratio of 4:1 and the cross-metathesis product exclusively as the *Z* isomer. The authors postulate that the *Z* selectivity is the result of kinetic control, probably related to either the small size or the electron-withdrawing properties of the cyano substituent. By comparison, cross metathesis of acrylonitrile using **9** gave a product with high *E* stereoselectivity.[38b] (This is thought to be the only example reported, where first-generation Grubbs catalyst **9** promotes cross metathesis of an acrylonitrile.) Blechert and co-workers have also used catalyst **17** to facilitate cross metathesis of acrylonitriles (**eq 20**);[76] Grubbs second-generation catalyst **16** proved to be unsuitable, as it does not facilitate cross metathesis with electron-deficient alkenes.

The molybdenum complex **1** has been used in cross-metathesis reactions of acrylonitrile with a series of alkenes to give predominantly the substituted *Z* acrylonitrile products in 18–90% yields.[78] The poor nucleophilicity of an acrylonitrile dictates that its participation in cross-metathesis reactions requires a reaction partner that is more nucleophilic. This is why reactions involving styrene do not take place: both substrates (styrene and acrylonitrile) are good alkylidene donors but poor nucleophiles. In contrast to other studies,[74] yields were lower for alkyl-substituted olefins bearing a polar group in the alkyl substituent. Catalyst **1** has also been employed to prepare a chain-extended, α,β-unsaturated nitrile with high *Z* stereoselectivity (**eq 21**).[54] Crowe and co-workers have also reported the cross metathesis of unsaturated aliphatic nitriles of variable tether length between the C=C and CN groups with allylsilanes using catalyst **1**.[79] Here, the coordinating solvent dimethoxyethane was used, since it is known to stabilize reactive methylene complexes formed as intermediates in the Mo-catalyzed olefin metathesis reactions.[13]







5.5. Carbohydrates

The application of cross-metathesis chemistry to carbohydrate-based systems has generated considerable interest (see section 5.1.1 for a discussion of amino acid and peptide-based examples). Oligosaccharides are critical components of synthetic vaccines, drug-delivery systems and the like, and the ability to tether small, organic molecules onto these backbone structures is critical to the development of applications in these and related areas. Cross metathesis is now an important tool in this field. For example, cross metathesis has been used to provide a route to 1,4-butanediol-linked head-to-head dimers derived from daunosamine, the amino sugar group present in daunomycin, the RNA groove-binding antibiotic natural product.[80] Reaction to form the dimeric product proceeded in good yield; however, cross metathesis was sluggish for substrates containing an unprotected hydroxyl group. Roy and Das have also utilized cross metathesis in the carbohydrate arena by forming homodimers of sugar substrates and by coupling N-protected terminal allylamines with *O*-allyl glycosides (**eq 22**).[9]

5.6. Other Functionalities

Cross metathesis is a particularly versatile reaction that seems to tolerate a number of functional groups within the olefinic substrates. Lera and Hayes investigated the formation of vinylphosphonate-linked nucleotide dimers via a cross-metathesis reaction employing **16** as catalyst (**eq 23**).[48] The reaction proceeded in moderate yield to afford the *E* isomer as a 1:1 mixture of diastereoisomers at phosphorus. In contrast, no reaction occurred when first-generation Grubbs catalyst **9** was used. Some interesting side products, in which the benzylidene group from catalyst **16** had been transferred to the starting material, were also isolated. The cross-metathesis product had previously been prepared using palladium(0)-catalyzed P–C=C cross-coupling methodology; however, the cross-metathesis-based synthesis is significantly more effective.

Dinucleosides have been synthesized by linking an olefinic chain at the 3' position of the glycosidic moiety using cross-metathesis chemistry.[81] Yields of these dinucleotide analogs were independent of the amount of catalyst used; however, coupling was sluggish when the amine group of the heterocyclic base was unprotected. The *E* isomer was marginally favored over the *Z*, and the thymine analogue gave a noticeably lower yield than the other nucleotides.

Disubstituted olefins have been successfully employed in cross-metathesis reactions.[5,82] For example, Boc-protected *cis*-1,4-diamino-2-butene underwent cross metathesis with 9-decen-1-yl benzoate in good yield; however, an attempt to introduce a Weinreb amide gave a poor yield attributed by the authors to the coordination of the amide to catalyst **9**, consistent with observations made by Crowe and Goldberg.[78] Problems arising from the use of a Weinreb amide in cross-metathesis reactions have been overcome with the development and use of second-generation Grubbs catalyst **16**.[74]

There are other examples of cross metathesis of nitrogen-containing systems, including the reaction of allyl cyanide with allylstannanes.[64] Cross metathesis has also been used to prepare *N*,*N*'-alkenyl-substituted bis(hydrazino carbenes), a class of Fischer-type carbenes.[83] To date, there have been limited applications of cross-metathesis chemistry to this type of compound, but again the versatility and tolerance of the metathesis reaction is apparent.

Grela and Bieniek have shown that phenyl vinyl sulfone can participate in cross-metathesis reactions using second-generation catalyst **16** (**eq 24**).[24] Despite the low yield, presumably due to steric crowding in the indole starting material, this remains an efficient way to access functionalized α,β-unsaturated sulfones with excellent stereoselectivity under mild conditions.

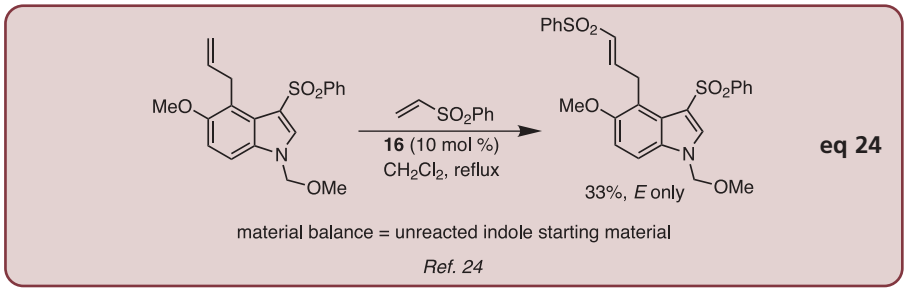
A small family of chiral 2-(2'-oxazolyl)phenols, which offer potential as novel tridentate ligands, has been synthesized using cross metathesis by Grubbs and co-workers (**eq 25**).[6] A related oxazoline underwent cross metathesis using Grubbs second-generation catalyst **16** to give the corresponding salen-like dimer in 32% yield.[6]

6. Ring-Opening Cross Metathesis

Ring-opening cross metathesis (ROCM or ROM-CRM) is an important strategy for assembling complex structures from readily available bicyclic substrates, since the chiral information inherent in the ring system is transformed into the stereochemistry of the cyclic product.[49b] However, metathesis reactions of this type remain relatively unexplored due to problems with lack of regioselectivity. In addition, ring-opening cross-metathesis reactions must be carried out in relatively dilute solutions to suppress competing ring-opening polymerizations. An example of the basic strategy can be seen, where a strained 2-azanorbornene derivative gives rise to a γ-lactam product in good yield in the presence of Grubbs first-generation catalyst **9** (**eq 26**).[49b] Resin-bound norbornene derivatives have also been shown to undergo metathesis with styrene to give 50/50 mixtures of regioisomers.[49b]

In another example, 4-vinylanisole reacts with a symmetrical bicyclic substrate to afford diastereomeric, cis-substituted, cyclic hydrazines in near quantitative yield (**eq 27**).[84] An analogous addition of an unsymmetrical cycloadduct to 4-vinylanisole gave four cyclic hydroxylamine products in nearly equal amounts.[84] Hydroxylamines of this type are important intermediates to conformationally restricted peptidomimetics.

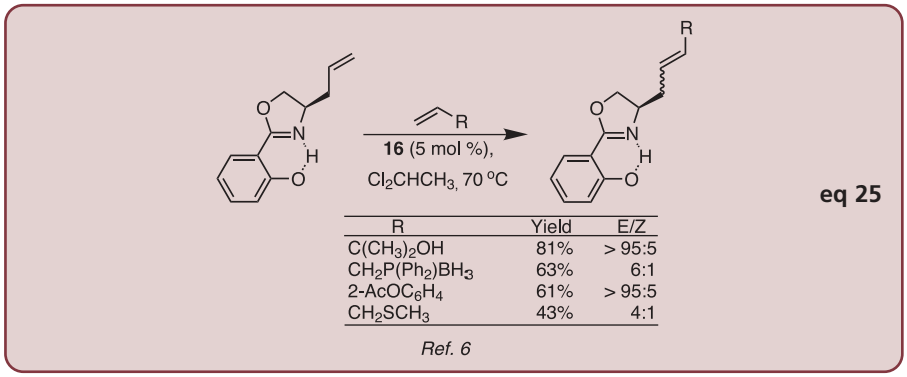
Ishikura and co-workers have reported a ring-opening cross metathesis of a 2-azabicyclo[2.2.1]hept-5-en-3-one that gives rise to two regioisomeric products, which were purified by HPLC.[85] This example reinforces the earlier point that cross-metathesis reactions tolerate a number of nitrogen-protecting groups within the substrate, e.g., Boc, Cbz, and Ac. Some work has also been done to develop the ring-opening cross-metathesis reactions of bicyclic alkenes with terminal aryl alkenes on the solid phase in an attempt to suppress competing cross-metathesis polymerizations.[86] Ring-opening polymerizations compete with the desired cross metathesis, and although this can be somewhat controlled in solution phase by using very dilute concentrations, solid-phase synthesis offers a means of preventing polymerization by isolating the bicyclic or fused alkene on a resin. The solution-phase chemistry proceeded in moderate-to-excellent yields to give two regioisomers.[86] A Wang resin bound bicyclic substrate was also reacted with an electronically diverse range of aryl alkenes, including 4-vinylanisole, to give 60–77% yields of two regioisomeric metathesis products (**eq 28**).[86]



material balance = unreacted indole starting material

Ref. 24

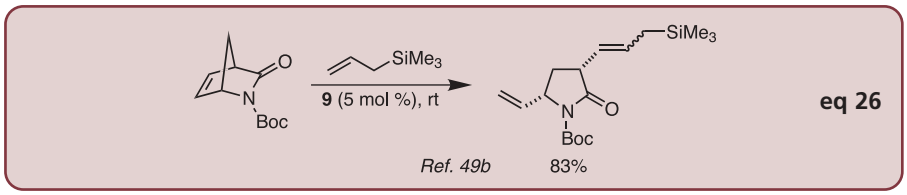
eq 24



R	Yield	E/Z
$C(CH_3)_2OH$	81%	> 95:5
$CH_2P(Ph_2)BH_3$	63%	6:1
$2\text{-}AcOC_6H_4$	61%	> 95:5
CH_2SCH_3	43%	4:1

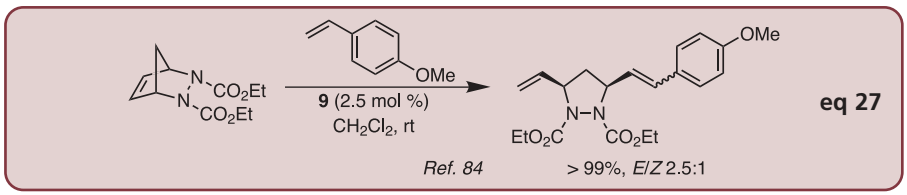
Ref. 6

eq 25



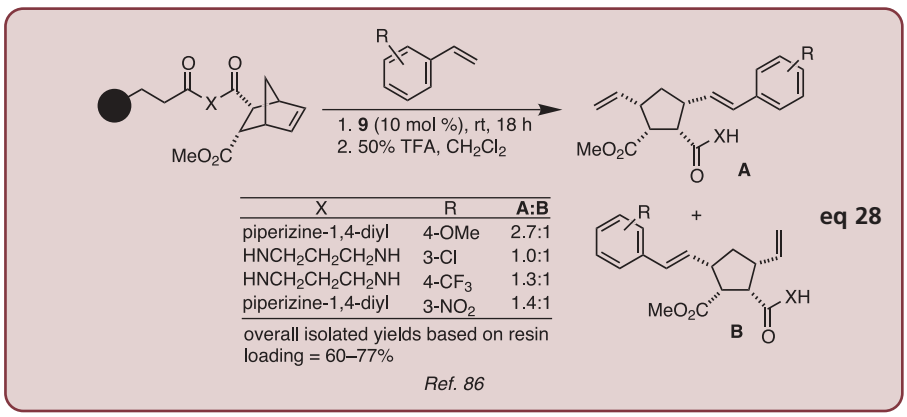
Ref. 49b 83%

eq 26



Ref. 84 > 99%, *E*/*Z* 2.5:1

eq 27



X	R	A:B
piperizine-1,4-diyl	4-OMe	2.7:1
$HNCH_2CH_2CH_2NH$	3-Cl	1.0:1
$HNCH_2CH_2CH_2NH$	$4\text{-}CF_3$	1.3:1
piperizine-1,4-diyl	$3\text{-}NO_2$	1.4:1

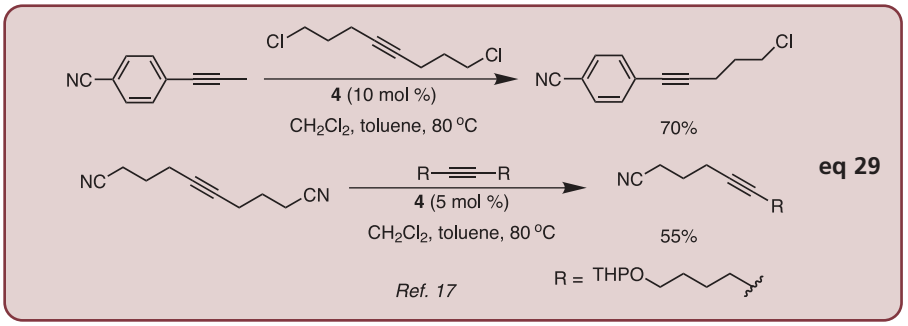
overall isolated yields based on resin loading = 60–77%

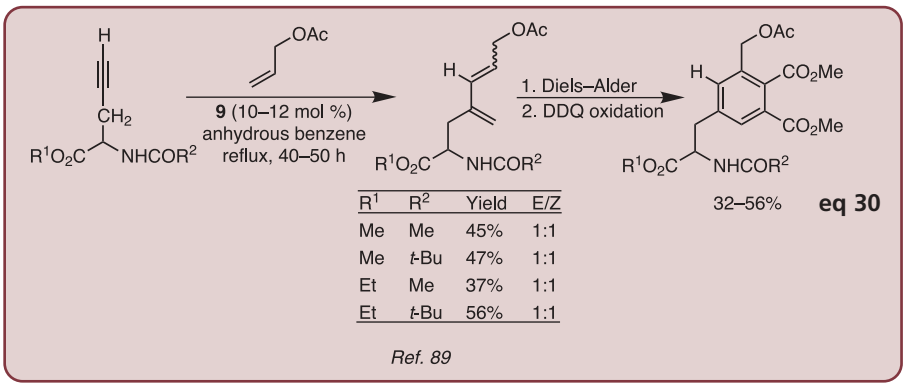
Ref. 86

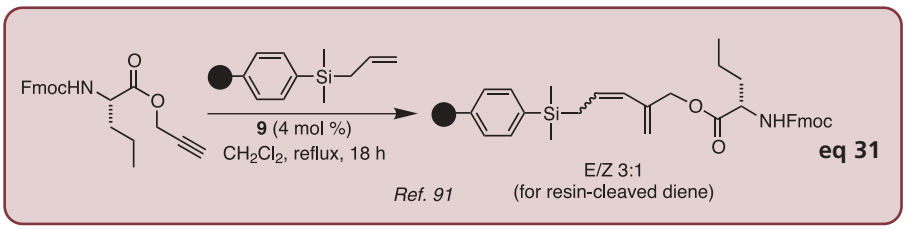
eq 28

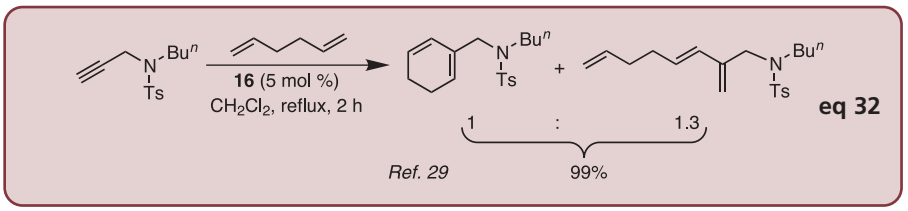
7. Cross Metathesis with Alkynes

Alkyne-based cross metathesis is a comparatively unexplored area of metathesis chemistry with few nitrogen-containing systems having been reported (**eq 29**).[17] One important general application of alkyne-based cross metathesis is the reaction of an alkyne and an alkene to generate a disubstituted butadiene for use in Diels–Alder chemistry. This combination of cross metathesis and Diels–Alder chemistry provides straightforward and versatile access to some structurally quite complex systems.[87,88] For example, α-amino acid









based dienes, prepared by enyne cross metathesis, undergo the Diels–Alder reaction to give functionalized phenylalanine derivatives (**eq 30**).[89] Despite the moderate yields, this method is synthetically viable, since the acetylene building blocks used are readily obtainable from glycine-derived starting materials. The lack of *E*/*Z* stereoselectivity observed in these reactions, although not desirable, is of no consequence to the final target molecule. Highly substituted tetrahydropyridines, important structural components of numerous alkaloids, have also been prepared by enyne cross metathesis followed by an aza-Diels–Alder synthetic step.[90]

Other examples include a selective, enyne cross metathesis of solid-phase-supported allylsilylpolystyrene (1% DVB) with Fmoc-protected norvaline propargyl ester—itself formed from the free carboxylic acid, Fmoc-Nva-OH (**eq 31**).[91] Reactions of this type, in which an alkyne is coupled to an alkene through cross metathesis avoid problems of homodimer formation. Blechert's group demonstrated other applications in this area with the synthesis of pseudooligosaccharides.[92] There is significant scope in this methodology, since a range of sugars and dienophiles can be employed.[92]

Tandem enyne cross metathesis between an alkyne and 1,5-hexadiene, followed by in situ ring-closing metathesis, has also been carried out using second-generation catalyst **16** (**eq 32**).[29] The crude diene products were subsequently subjected to a Diels–Alder reaction with *N*-methylmaleimide to give bicyclic products of substantially greater molecular complexity than the alkene and alkyne starting materials.

8. Conclusions

While cross-metathesis chemistry is yet to reach the maturity level of other metathesis-based methodologies, it has already made a significant impact in the area of nitrogen-containing systems. The mild conditions under which these reactions can be performed, along with the high functional-group tolerance of the current catalysts, mean that cross metathesis will clearly be of significant value in many areas of chemistry. There are numerous other cross-metathesis-based methodologies, including domino metathesis, which is a combination of ring-opening (ROM), ring-closing (RCM), and cross (CM) metatheses. Although domino metathesis is a useful method for the synthesis of various novel cyclic compounds, it is not discussed in this review. Original articles and reviews of this topic, including discussions of stereospecificity and regiocontrol, have recently been published.[10,93]

9. Acknowledgments

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10. References and Notes

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About the Authors

Andrea Vernall was born in 1981 in Wellington, New Zealand. In 2002, she obtained a Bachelor of Science with First Class Honours in Chemistry from the University of Canterbury. Currently a member of Professor Abell's research group, she is in her second year of a Ph.D. research program investigating metathesis reactions in biological systems.

Andrew Abell was born in 1960 in Adelaide, South Australia. He obtained a Bachelor of Science with First Class Honours in Organic Chemistry from the University of Adelaide in 1982 and, in 1986, he received his Ph.D. from the same university under the supervision of Dr. Ralph Massy-Westropp. Two years were then spent working as a postdoctoral fellow with Professor Sir Alan Battersby at Cambridge, UK and, in 1987, he took a faculty position at the University of Canterbury, Christchurch, New Zealand. His current research interests include the design, synthesis, and biological properties of peptidomimetics.

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Grubbs Catalyst 1st Generation

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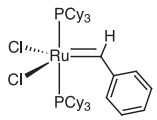

The first metathesis catalyst to be widely utilized in organic synthesis, Grubbs First Generation Catalyst effects ring-closing metathesis, olefin cross-metathesis, and ROMP with high activities and tolerance for functional groups and protic media.[1,2]

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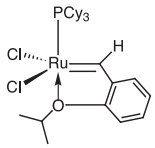
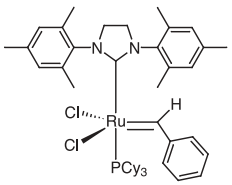


An efficient, recyclable catalyst for RCM of terminal olefins.[6,7]

Grubbs Catalyst 2nd Generation

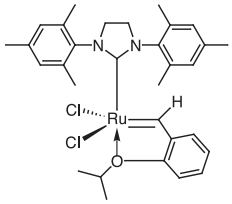
56,974-7 — 100mg, 500mg, 2g



Grubbs Second Generation Catalyst is a more active analog of the first-generation Grubbs catalyst for ring-closing metathesis, cross metathesis, and ROMP,[3] and can lead to trisubstituted olefins via cross metathesis;[4] it ring-closes olefins with excellent functional-group tolerance and selectivity.[5]

Hoveyda–Grubbs Catalyst 2nd Generation

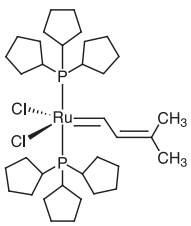
56,975-5 — 100mg, 500mg, 2g



The Hoveyda–Grubbs Second Generation catalyst shows efficiencies similar to those of second-generation Grubbs catalyst, but with different substrate specificities. The catalyst is unique in catalyzing the ring-closing, ring-opening, and cross-metathesis reactions of highly electron-deficient substrates.[7,8]

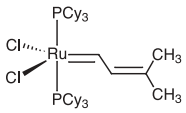
Dichloro(3-methyl-2-butenylidene)bis(tricyclopentylphosphine)ruthenium(II)

57,870-3 — 1g, 5g



Dichloro(3-methyl-2-butenylidene)bis(tricyclohexylphosphine)ruthenium(II)

57,868-1 — 1g, 5g



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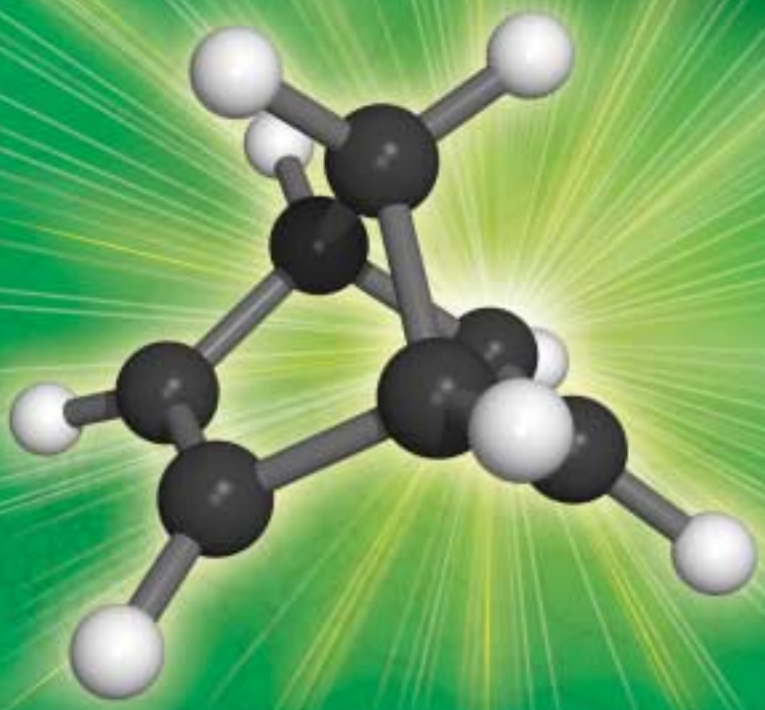

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8.0	10	10/30	Z51,216-8	Z51,217-6	Z51,264-8
9.5	11.5		Z51,249-4	Z51,256-7	Z51,265-6
11.0	13		Z51,250-8	Z51,257-5	Z51,266-4
12.5	14.5	14/20	Z51,211-7	Z51,212-5	Z51,267-2
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19.0	21		Z51,252-4	Z51,259-1	Z51,271-0
20.5	23	24/40	Z51,213-3	Z51,214-1	Z51,272-9
22.0	25		Z51,253-2	Z51,260-5	Z51,273-7
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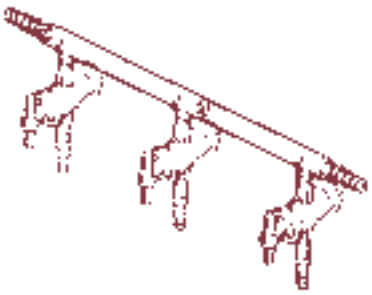
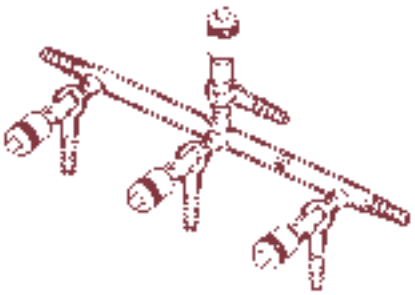


Glass Stopcock

Positions	Overall L (mm)	Cat. No.
Standard manifold		
3	300	Z53,213-4
4	400	Z53,214-2
5	500	Z53,215-0
Manifold with vacuum-gauge port		
3	300	Z53,216-9
4	400	Z53,217-7
5	500	Z53,218-5



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Positions	Overall L (mm)	Cat. No.
Standard manifold		
3	300	Z53,219-3
4	400	Z53,220-7
5	500	Z53,221-5
Manifold with vacuum-gauge port		
3	300	Z53,222-3
4	400	Z53,223-1
5	500	Z53,225-8

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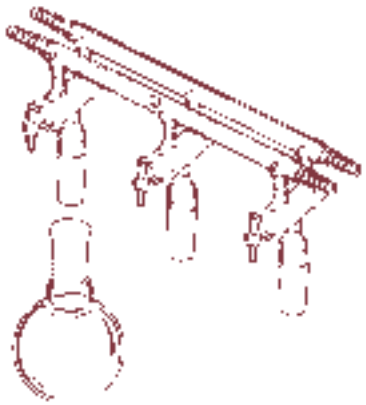

Positions	Overall L (mm)	Ʇ*14/20* Cat. No.	Ʇ*24/40* Cat. No.	Ʇ*29/32* Cat. No.
3	300	Z53,066-2	Z53,069-7	Z51,752-6
4	400	Z53,067-0	Z53,070-0	Z51,753-4
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Solutions for Oligonucleotide Synthesis

Precisely Blended Capping, Deblocking, and Activator solutions for oligonucleotide synthesis.

Catalog No.	Product Name	Unit
55,534-7	**Cap Mix A** (Contains 90% tetrahydrofuran: 10% acetic anhydride)	1L 2L
55,531-2	**Cap Mix A, with 2,6-lutidine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% 2,6-lutidine)	1L 2L
55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L

Catalog No.	Product Name	Unit
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L
56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L
55,404-9	**Activator** (1*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L

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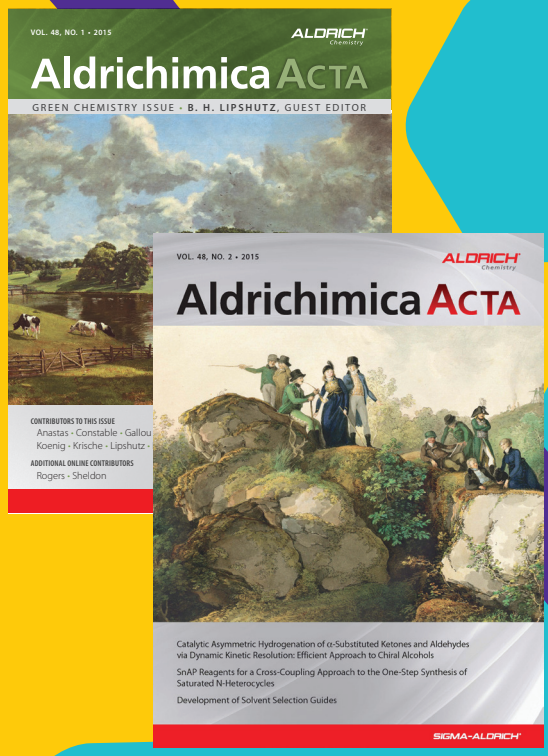

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