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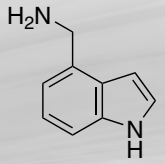

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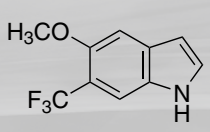

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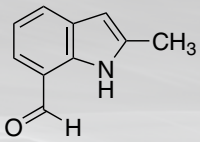

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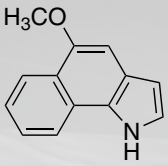

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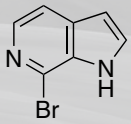

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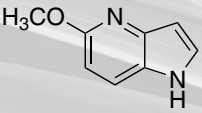

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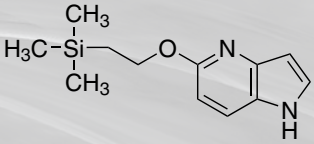

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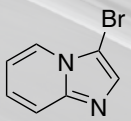

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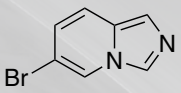

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References: (1) Horton, D. A. et al. *Chem. Rev.* **2003**, *103*, 893 and references therein. (2) (a) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 8689. (c) Song, J. J. et al. *Chem. Soc. Rev.* **2007**, *36*, 1120. (d) Huang, W.-S. et al. *J. Med. Chem.* **2010**, *53*, 4701. (e) Buckley, G. M. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3656. (f) Buckley, G. M. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3291.

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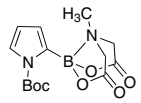

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River Landscape with a Resting Traveller (oil on panel, 46×66.5 cm) was painted most likely in the mid-1650s by Jan Lievens (1607–1674), who was one of the most prominent painters of the Dutch Golden Age. He is usually mentioned in the same breath as Rembrandt, because the two artists shared much during their early years. Because of Rembrandt's greater achievement, Lievens was long assumed to have been his follower, but recently it has become clear that he was initially the leader. Although younger, he was a celebrated child prodigy who established himself years before his colleague.

Detail from ***River Landscape with a Resting Traveller***. Photo courtesy of Dr. David de Witt, Queen's University.

Lievens's later success lay in following and interpreting the grand figurative style of Flemish masters such as Peter Paul Rubens and Anthony van Dyck, much favored among the elite. He could study such works while in Antwerp, where he also saw the contemplative landscapes by Rubens and other artists. These reflected the Flemish tradition of rich, lively, and decorative fantasy landscapes, in contrast to the more sober realism exercised by Dutch landscapists. In his own landscapes, Lievens tried a more fluid brush handling and rolling forms. In this late scene, he places a weary traveler reclining against a tree in a lush forest. He also betrays his penchant for arranging a screen of trees against a light background that pierces between the trunks to generate drama and rhythm. The result is slightly otherworldly, an invitation to escape from the urban confines and daily pressures, that would have appealed to many collectors in both Flanders and Holland.

This painting is part of the Bader Collection of Dutch and Flemish Paintings, whose future home will be the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.

ALDRICH Chemistry

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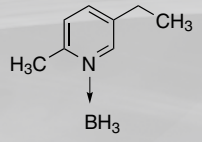

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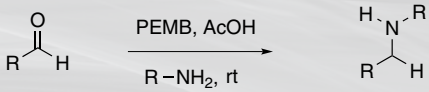

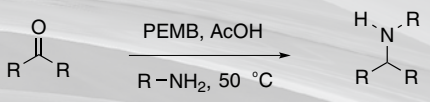

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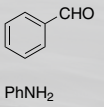
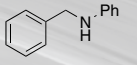
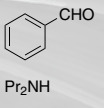
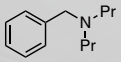
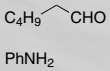
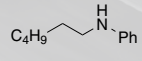
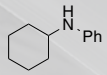
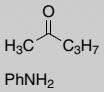
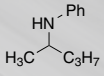
	PEMB, AcOH MeOH, 25 °C		72 (80)
	PEMB, AcOH MeOH, 25 °C		0 (96)
	PEMB MeOH, 25 °C		92 (94)
	PEMB, AcOH MeOH, 25 °C		92 (93)
	PEMB, AcOH MeOH, 50 °C		74 (94)

For more examples and experimental details, please see: Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152.

Asymmetric N-Heterocyclic Carbene (NHC) Catalyzed Acyl Anion Reactions

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Keywords. N-heterocyclic carbene; NHC; acyl anion; organocatalysis; polarity reversal; umpolung.

Abstract. In recent decades, N-heterocyclic carbenes (NHCs) have been shown to facilitate a wide variety of nontraditional asymmetric transformations. This article reviews the utility of these nucleophilic species in the generation of acyl anion equivalents from aldehydes and their application in the Stetter, α-redox, and cascade-catalysis reactions.

Outline

1. Introduction

The generation of acyl anion equivalents has been of interest to the synthetic community since the early 1960s. Of the numerous methods available to generate acyl anions (or acyl anion equivalents), their catalytic production from aldehydes has been through the use of cyanide and N-heterocyclic carbenes (NHCs). The latter method has emerged as a prominent way to catalyze the formation of acyl anion equivalents from aldehydes in a polarity-reversal or "umpolung" process, thus facilitating the discovery of new transformations and the development of asymmetric variants of existing ones. This rapidly growing field of organocatalysis[1] has been the subject of several reviews that detail the contributions of numerous researchers in this area.[2] The present review will discuss the advent and development of NHCs for the generation of acyl anion equivalents and their use in synthesis.

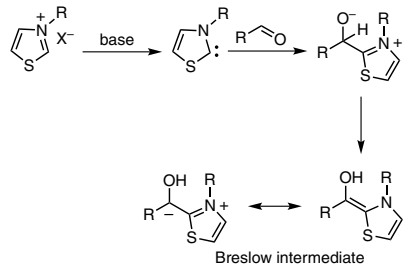
2. Carbenes

In 1832, Wöhler and Liebig reported the homodimerization of aldehydes in the presence of cyanide to provide benzoin products.[3] In 1943, Ukai demonstrated that stoichiometric amounts of thiazolium salts in the presence of base are capable of generating acyl anion equivalents from aldehydes to yield benzoin products.[4] Breslow subsequently demonstrated that thiazolium salts undergo ready deprotonation by weak bases, generating the ylide or carbene which then adds to the aldehyde and forms the acyl anion equivalent, now commonly called the Breslow intermediate **(Scheme 1)**.[5]

Carbenes have long been studied, but our understanding of their stability and reactivity has dramatically improved in recent decades.[6] They have typically been considered highly reactive intermediates, and only recently has it been shown that their reactivity can be harnessed and controlled through the manipulation of steric and electronic parameters. Carbenes are neutral compounds bearing a divalent carbon with six electrons in the valence shell. The two nonbonding electrons can either be spin-paired (singlet) or unpaired (triplet).

Stabilizing effects in the ground state can be broken down into the π and σ types.[7] In the ground state, the nonbonding electrons of a singlet carbene occupy a σ orbital, leaving a vacant p orbital available for π donation by atoms attached to the divalent carbon. This π donation results in an overall increase of the s character and nucleophilicity of the carbene, and aids in its stabilization. An additional, plausible stabilizing factor involves electron withdrawal from the carbene center through the σ-bond framework with a concomitant increase in the s character of the carbene. This is typically indicated in the crystal structures of isolable carbenes by a decrease in the X–C–X bond angle and an increase in the C–X bond length **(Figure 1)**.[8]

The advent of nucleophilic singlet carbenes in organic synthesis has been premised on the seminal work of Wanzlick[9] and Arduengo.[10] In 1962, Wanzlick reported the synthesis of bis(1,3-diphenyl-2-imidazolidinylidene), a dimer obtained from the reaction of two molecules of the carbene. He also noted that this dimer has a high affinity to dissociate and react with a variety of different electrophiles and nucleophiles.[9] In 1991, Arduengo's report of an isolable NHC renewed interest in the use of such compounds as ligands and catalysts.[10]



Scheme 1. Formation of Acyl Anion Equivalent. *(Ref. 5)*

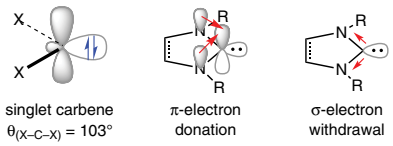
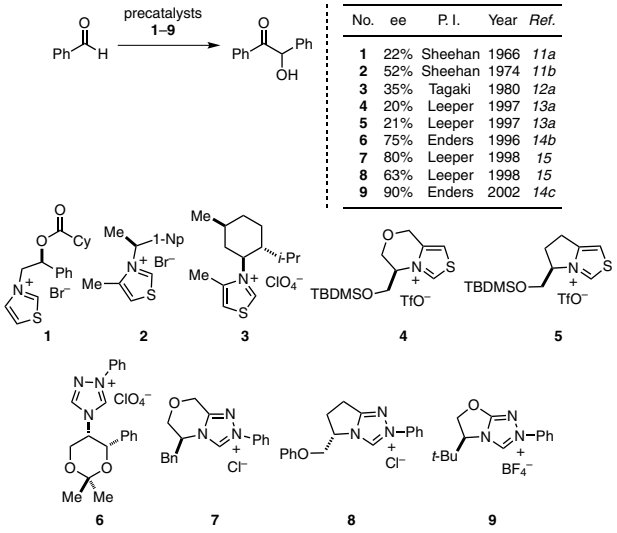
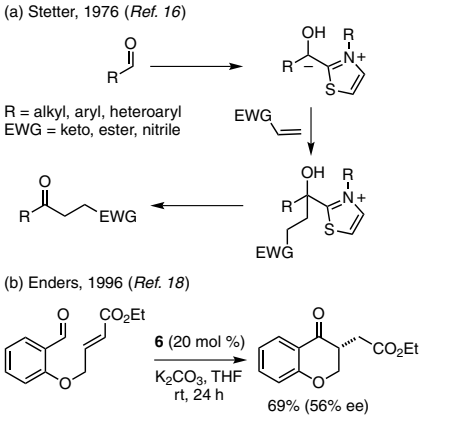


Figure 1. Stabilization of Singlet Carbenes. *(Ref. 8)*



No.	ee	P. I.	Year	Ref.
1	22%	Sheehan	1966	*11a*
2	52%	Sheehan	1974	*11b*
3	35%	Tagaki	1980	*12a*
4	20%	Leeper	1997	*13a*
5	21%	Leeper	1997	*13a*
6	75%	Enders	1996	*14b*
7	80%	Leeper	1998	*15*
8	63%	Leeper	1998	*15*
9	90%	Enders	2002	*14c*

eq 1



Scheme 2. The Stetter Reaction.

3. Benzoin Reaction

The benzoin condensation became the model reaction by which the efficiency of novel chiral azolium carbenes would be measured. In 1966, Sheehan and Hunneman were first to use a chiral thiazolylidene carbene derived from **1** to facilitate benzoin formation in 22% optical purity.[11] The chiral thiazolylidene carbenes that were developed in the ensuing three decades all had a common structural characteristic: free rotation was feasible around the chiral center, which was believed to give rise to the low enantioselectivities observed with these carbenes.[12] The introduction of bicyclic thiazolium salts only led to modest improvements in enantioselectivity.[13] The emergence of triazolylidene carbenes, developed by Enders and Teles,[14] and bicyclic triazolylidene carbenes, developed by Leeper,[15] resulted in acceptable enantioselectivities for the benzoin product (**eq 1**).

4. Stetter Reaction

The application of NHCs to other areas of acyl anion chemistry was pursued concurrently with the development of the benzoin reaction. In 1976, Stetter demonstrated that thiazolylidene carbenes could be employed to facilitate the addition of an aldehyde via its acyl anion equivalent to activated double bonds to generate functionalized ketones (**Scheme 2**, Part (a)).[16] Although Stetter had previously demonstrated this process with cyanide, the use of a thiazolylidene carbene displayed improved proficiency for aliphatic aldehydes, which were not compatible with the cyanide reaction conditions. In 1995, Ciganek illustrated an intramolecular Stetter reaction to generate chromanones.[17] The asymmetric Stetter reaction did not receive much attention from the synthetic community for many years, and the only example prior to our work was that of Enders, who showed that triazolium precursor **6** provides the desired chromanone product in 69% yield and 56% ee (**Scheme 2**, Part (b)).[18]

4.1. Catalyst Development

In 2000, our laboratory began a program to study chiral NHCs for use in organic synthesis. We envisioned accessing structurally and electronically diverse carbene precursors from readily available starting materials. The triazolium scaffold was prioritized over the thiazolium and imidazolium ones based on the number of sites available for structural and electronic modifications and on their proficiency as bicyclic carbenes in the benzoin reaction. In the thiazolium-derived carbene, only one quadrant of the steric space around the carbene center is blocked, while three quadrants are effectively blocked in the corresponding triazolium-derived system (**Figure 2**). This presumably leads to improved selectivities in cases catalyzed by the latter system.

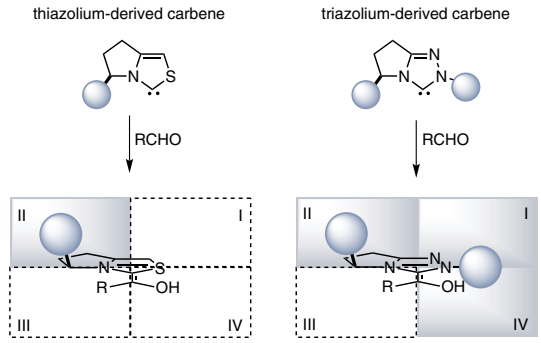


Figure 2. Mapping of the Steric Space around the Carbene Center.

We conceived that the chiral backbone could be readily introduced from amino alcohols (morpholine series) or amino acids (pyrrolidine series) and would provide steric blocking of quadrant II (see Figure 2). We also envisaged that substitution in quadrants I and IV could arise from the hydrazine component, which would enable additional modulation of electronic and steric parameters (**Figure 3**). The use of substituted aryl hydrazines would give rise to differences in reactivity given the proximity of the aromatic ring to the carbene carbon.

We chose the intramolecular Stetter reaction to test the effectiveness of our catalysts. We quickly identified 1-amino-2-indanol as the optimal chiral amino alcohol starting material in the morpholine series, which could be coupled with a variety of structurally and electronically diverse hydrazines to furnish bench-stable triazolium salts **10**–**13** (**Figure 4**).[19] In the pyrrolidine series, a variety of side chains (ultimately derived from amino acids such as phenylalanine and valine) were identified as efficient chiral scaffolds which could also incorporate a variety of hydrazines to furnish additional bench-stable triazolium salts (**14**–**16**).

4.2. Asymmetric Intramolecular Stetter Reaction

Our work on the intramolecular Stetter reaction has been reviewed extensively and therefore will not be the focus of this review.[20] A variety of salicylaldehyde-derived substrates and aliphatic aldehydes bearing a range of linkers—including ether, thioether, sulfone, and protected amines—are effective in this process. An electron-withdrawing group on the prochiral alkene is still a requirement[21] and can be an ester, thioester, amide, ketone, aldehyde, nitrile, phosphine oxide, or a phosphonate.[22]

Michael acceptors bearing a second β substituent also participate in the intramolecular reaction in the presence of precatalyst **12** to furnish quaternary stereocenters.[23] Contiguous stereocenters can also be generated by using precatalyst **15** with a variety of salicylaldehyde substrates in a highly enantioselective and diastereoselective process. The reaction is not limited to salicylaldehyde-derived substrates, as aliphatic aldehydes also partake in the reaction with high levels of enantio- and diastereoselectivity. This diastereoselectivity has been attributed to an intramolecular proton-transfer event.[24] Next, highly substituted cyclohexadienones, bearing a 4-formylmethoxy substituent and which are readily accessible in two steps, undergo the optimized intramolecular Stetter reaction in the presence of triazolium salt **11** to provide hydrobenzofuranones with excellent enantio- and diastereoselectivity.[25] With these successes in the intramolecular Stetter reaction in hand, we turned our attention to the intermolecular version.

4.3. Asymmetric Intermolecular Stetter Reaction

The intermolecular addition of acyl anion equivalents to activated double bonds had been thoroughly studied by Stetter,[26] but the asymmetric variant of this reaction has been nearly nonexistent. The use of chiral NHCs in this process has not been fruitful as benzoin products dominate. One solution to the benzoin product predominating is the use of acylsilanes to generate acyl anion equivalents via Brook rearrangement. Johnson has shown that, in the presence of a chiral metallophosphite, acylsilane, and an activated prochiral olefin, one can obtain sila-Stetter products.[27] Scheidt has also reported that the addition of acylsilanes to chalcones gives rise to racemic products in the presence of an NHC.[28] In 2006, Scheidt's group rendered this process enantioselective by generating the acyl anion in the presence of stoichiometric carbene and chiral thiourea.[29] While the use of acylsilanes is an elegant solution, it does not address the problem at hand directly.

Prior to our work in this area, only three examples were known of an asymmetric intermolecular Stetter reaction, all reported by Enders. The reaction of butanal and chalcone in the presence of precatalysts **17** provides the 1,4-dicarbonyl product in low yield and poor ee.[30] Enders later introduced an improved triazolium catalyst for the Stetter reaction of aromatic aldehydes and chalcones (**eq 2**).[31] The benzyl substituent on the triazolium was found to be key to providing observable yields.

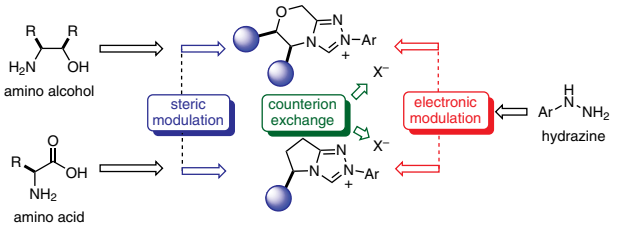
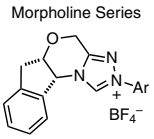
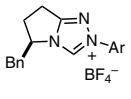


Figure 3. NHC Catalyst Design.

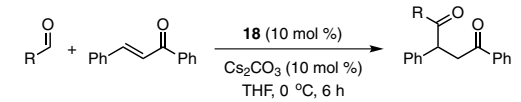


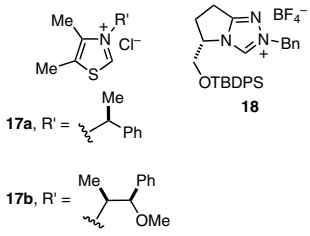
No.	Ar
10	Ph
11	4-MeOC$_6$H$_4$
12	C$_6$F$_5$
13	4-F$_3$CC$_6$H$_4$



No.	Ar
14	Ph
15	4-F$_3$CC$_6$H$_4$
16	C$_6$F$_5$

Figure 4. Bench-Stable Triazolium Salts as Carbene Precursors. *(Ref. 19)*

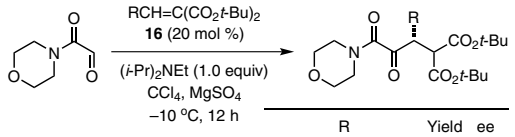




R	Yield	ee
n-Pr[a]	30%	40%
n-Pr[b]	29%	30%
Ph	65%	66%
4-MeC$_6$H$_4$	43%	78%
3-MeC$_6$H$_4$	50%	70%
4-ClC$_6$H$_4$	55%	67%
4-BrC$_6$H$_4$	68%	56%
2-Np	65%	70%
2-Fur	98%	56%
Ph[c]	55%	64%
Ph[d]	57%	56%

[a] **17a** (20 mol %) used. [b] **17b** (20 mol %) employed. [c] β substituent = 4-MeC$_6$H$_4$ instead of Ph. [d] β substituent = 4-ClC$_6$H$_4$ instead of Ph.

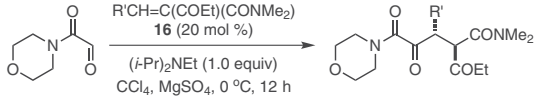
eq 2 *(Ref. 30,31)*



R	Yield	ee
Me[a]	68%	87%
Et	84%	90%
n-Pr	83%	90%
n-Bu	70%	90%
$BnCH_2$	81%	88%
i-Bu[b]	51%	91%
$BnO(CH_2)_2$	91%	80%
$Cl(CH_2)_3$	84%	81%
$[S(CH_2)_3S]CH(CH_2)_2$	88%	84%
$H_2C{=}CH(CH_2)_2$	97%	89%

[a] For 3 h. [b] For 28 h.

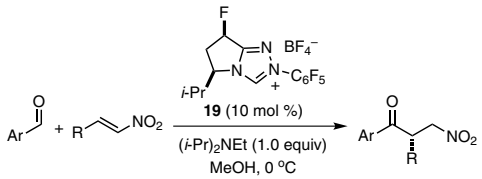
eq 3 *(Ref. 33)*



R'	Yield	dr	ee
Me	95%	7:1	89%
Et	90%	12:1	92%
n-Pr	81%	6:1	90%
n-Bu	71%	12:1	92%
i-Bu[a]	44%	11:1	87%
$BnCH_2$	65%	19:1	83%
$BnO(CH_2)_2$	87%	11:1	98%
$Cl(CH_2)_3$	83%	10:1	81%
$H_2C{=}CH(CH_2)_2$	83%	14:1	90%
$HC{\equiv}CH(CH_2)_2$	78%	4:1	92%
$[S(CH_2)_3S]CH(CH_2)_2$	77%	9:1	86%
Et[b]	92%	11:1	92%
4-$ClC_6H_4(CH_2)_2$[b]	64%	5:1	94%
Et[c]	94%	9:1	90%

[a] For 20 h. [b] CO(*n*-Pr) used instead of COEt in the alkylideneketo amide. [c] $CO[H_2C{=}CH(CH_2)_2]$ employed instead of COEt in the alkylideneketo amide.

eq 4 *(Ref. 34)*



Ar	R	Yield	ee
2-Py	Cy	95%	95%
2-Py	*c*-Pent	98%	90%
2-Py	*c*-Pr	72%	87%
2-Py	*i*-Pr	85%	95%
2-Py	*n*-Pr	82%	83%
2-Py	*i*-Bu	99%	83%
2-Py	*a*	62%	96%
pyrazin-2-yl	Cy	99%	96%
pyridazin-3-yl	Cy	88%	94%
4-Me-thiazol-2-yl	Cy	70%	96%
furan-2-yl	Cy	75%	87%
oxazol-4-yl	Cy	76%	86%

[a] 1-Nitrocyclohexene was used.

eq 5 *(Ref. 35)*

Based on Stetter's extensive work,[26] we identified glyoxamides as competent aldehyde partners and β-substituted alkylidenemalonates as reactive electrophiles. During catalyst optimization, we noted that, while precatalyst **16** produces the desired Stetter product in 50% yield and 51% ee, the phenyl analogue, **14**, does not provide any product. These results again stress the significance of the N-aryl substituent in impacting carbene-catalyzed reactions.[32]

Of the glyoxamides tested, 4-glyoxylmorpholine results in superior reactivity with a variety of alkylidenemalonates, including ones with substituents at the β position, to provide the corresponding α-keto amides (**eq 3**).[33] Under the reaction conditions, the glyoxamide is rapidly consumed to generate the benzoin product, which simply serves as a reservoir of the aldehyde, which then participates in the desired Stetter process after being released in situ via a retro-benzoin reaction.[33]

This reaction was further developed to generate contiguous stereocenters in a highly enantioselective and diastereoselective manner. We hypothesized that a highly diastereoselective protonation event should result in a second stereocenter if the two activating carbonyls in the olefin are different. The resultant stereocenter would be difficult to maintain under the basic reaction conditions unless one of the activating carbonyls was a tertiary amide which would insulate the stereocenter due to $A_{1,3}$ strain. The use of alkylidineketo amides with 4-glyoxylmorpholine in the presence of **16** leads to the desired Stetter product in 68–97% yields, 81–97% ee's, and high diastereoselectivities (**eq 4**).[34]

The above studies, although limited to the glyoxamide functional group as the sole nucleophile, demonstrated that electron-deficient aldehydes and activated Michael acceptors provide higher yields with the triazolium systems. Consequently, we investigated next nitroalkenes as electrophiles and heteroaryl aldehydes as nucleophiles. We found that pyrrolidine-series triazolium salts bearing the electron-deficient pentafluorophenyl (C_6F_5) group are necessary for reactivity, and that a sterically demanding substituent, such as an isopropyl group, is required in quadrant II to obtain moderate enantioselectivity. Further modification of the pyrrolidine core with a fluorine atom, as in **19**, provides optimal reactivity and selectivity. It was further observed that the cis diastereomer of **19** provides the β-nitro ketone in 95% yield and 95% ee, while the trans diastereomer provides the product in only a 22% yield and 88% ee. The difference in selectivity between diastereomers is currently hypothesized to arise from a conformational pucker (exo/endo) induced via a stereoelectronic effect. The scope of the reaction is restricted to heteroaromatic aldehydes, while a variety of aliphatic substituents can be tolerated on the nitroalkene (**eq 5**).[35]

5. Redox Reactions

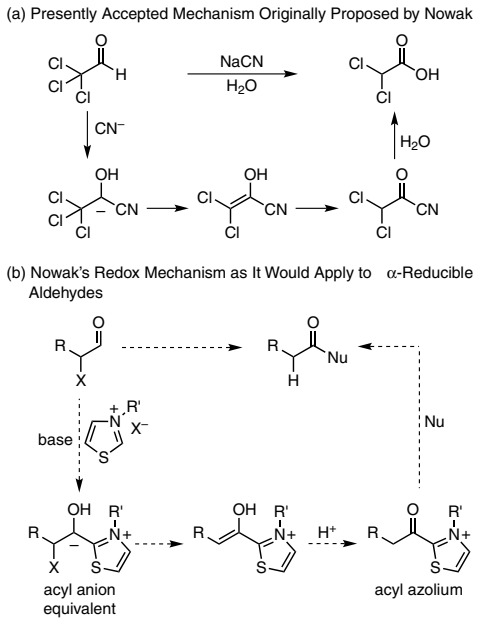
In the course of investigating the intramolecular Stetter reaction, we inadvertently discovered a unique reactivity of acyl anion equivalents which is reminiscent of Wallach's observation that chloral generates dichloroacetic acid when treated with aqueous cyanide.[36] The mechanism of the Wallach method was long debated, and the currently accepted version is that proposed by Nowak (**Scheme 3,** Part (a)).[37] The net process is an internal redox wherein one functionality gets reduced while a second is oxidized. An acylation of this type would thus be an example of redox economy.[38]

5.1. Redox Esterification

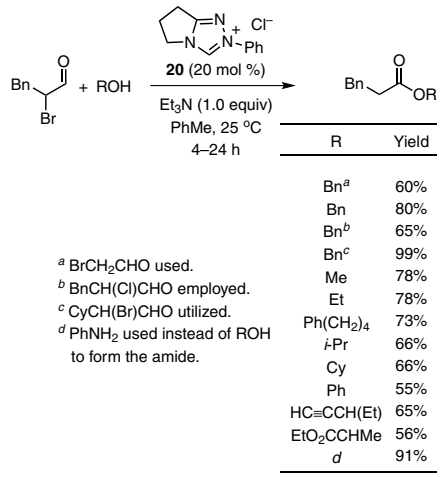
We saw in Wallach's observation an opportunity to implement this methodology as a mild acylating process using α-reducible aldehydes and NHCs (**Scheme 3**, Part(b)). A resurgence in the development of α-halogenation of aldehydes[39] has led to their use as substrates with alcohols as nucleophiles. Investigation of the halogen leaving group revealed that bromide is more facile to eliminate than chloride, with a variety of alcohols participating in the acylation process (60–99%) (**eq 6**).[40] Enantioenriched ethyl lactate may also be used, with acylation proceeding with only minor epimerization. Moreover, the reaction of racemic lactate and a chiral carbene occurs with enantioenrichment, suggesting acylation occurs on the acyl azolium (see eq 6).

Independently and concurrently, Bode showed that epoxy aldehydes are viable substrates in the NHC-catalyzed redox reaction with a variety of alcohol nucleophiles to furnish β-hydroxy esters (**eq 7**).[41] Since the two initial reports by our group and Bode's, the carbene-catalyzed redox process has been developed to include other α-reducible aldehydes that participate in the esterification process. Bode[42] and Scheidt[43] have independently shown that enals, in the presence of imidazolium salt **22** or triazolium salt **23**, can either generate a lactone dimer or a saturated ester depending on the choice of reaction conditions (**eq 8**).[42] The use of a strong base such as *tert*-butoxide leads to the lactone dimer, presumably due to the absence of an efficient proton source (pK_a of *tert*-butanol = 29.4 in DMSO). However, when a base whose conjugate acid is sufficiently acidic is employed, one obtains the protio-acylation product (pK_a of $(i\text{-Pr})_2EtNH^+$ = 13 in THF); in this case, a variety of alcohols are tolerated in the reaction, leading to the saturated esters in 63–99% yields.

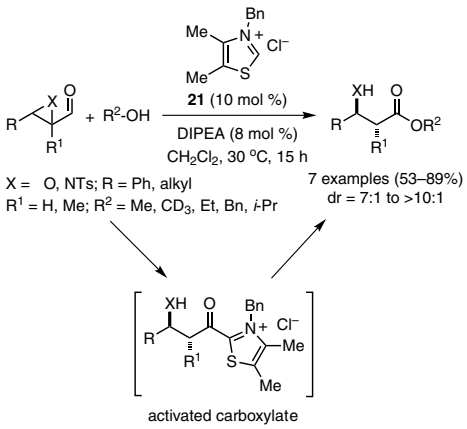
The synthesis of (*E*)-α,β-unsaturated esters can also be accomplished via redox esterification of propargylic aldehydes. Zeitler had reported imidazolium salt **22** to be efficient in this process in the presence of DMAP as the base, furnishing 45–90% yields and high levels of *E:Z* selectivity (typically >95:5).[44] A variety of alcohols participate in the reaction and aromatic, heteroaromatic, and aliphatic substituents are tolerated in the propargylic aldehyde. Bode has also found that formylcyclopropanes are competent partners in the redox esterification with a variety of nucleophiles including alcohols, thiols, and water. Subjecting the chiral formylcyclopropane substrates to the optimized reaction conditions with precatalyst **23** furnishes the 1,5-dicarbonyl adducts in 84–99% yields and with only minor epimerization (**eq 9**).[45]



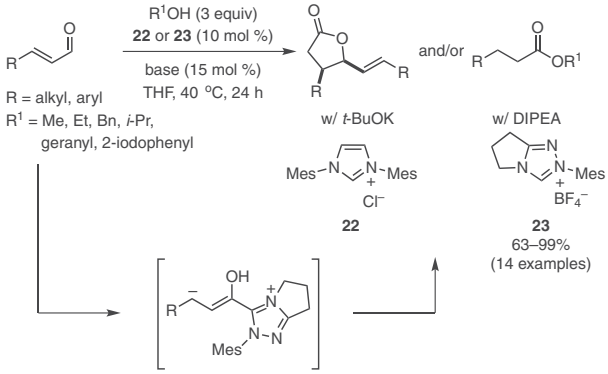
Scheme 3. Redox Mechanism. *(Ref. 36,37)*



eq 6 *(Ref. 40)*

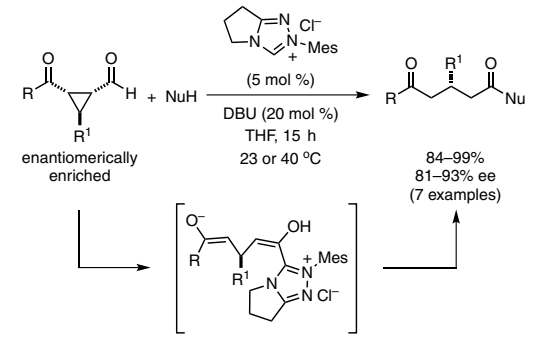


eq 7 *(Ref. 41)*

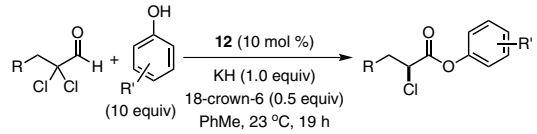


eq 8 *(Ref. 42)*

Treatment of α,α-dichloro aldehydes with phenols in the presence of NHC precursor **12** allows access to enantioenriched α-chloro aryl esters, via asymmetric protonation[46] of the enol intermediate.[47] A variety of α,α-dichloro aldehydes and substituted phenols participate in the reaction, providing the respective esters in good-to-high yields and enantioselectivities, with the current limitation being β branching on the aldehyde (**eq 10**).[47] The reaction provides distinct advantages and complements other methods[48] of generating enantioenriched α-chloro aryl esters.

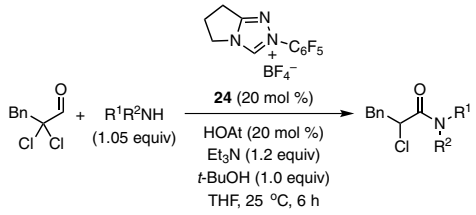


eq 9 *(Ref. 45)*



R	R'	Yield	ee	R	R'	Yield	ee
Ph	H	79%	93%	Ph	4-Me	71%	89%
4-MeOC$_6$H$_4$	H	76%	90%	Ph	4-MeO	71%	91%
Bn	H	73%	85%	Ph	4-Cl	75%	83%
Ph(CH$_2$)$_2$	H	68%	89%	Ph	2-Me	62%	90%
cis-*n*-PentCH=CH	H	74%	90%	Ph	2-Cl	75%	91%
cis-EtCH=CH(CH$_2$)$_3$	H	71%	88%	Ph	2,6-Cl$_2$	65%	82%
Cy	H	65%	93%	Ph	2,6-Br$_2$-4-Me	85%	76%
n-Pr	H	65%	89%	Ph	2,4,6-Me$_3$	0	----
MeO$_2$C(CH$_2$)$_6$	H	75%	84%	Ph	3,4-Me$_2$	80%	89%
BnO(CH$_2$)$_2$	H	71%	84%				

eq 10 *(Ref. 47)*



R^1	R^2	Yield
Et	H	89%
t-Bu	H	73%
Cy	H	85%
Ph	H	87%
3-ClC$_6$H$_4$	H	82%
4-MeOC$_6$H$_4$	H	83%
a	*a*	85%
Me	MeO	72%
Et	Et	89%

[a] R^{1}R^{2}NH = *tert*-butyl ester of alanine. Product diastereomeric ratio = 2:1.

eq 11 *(Ref. 52))*

5.2. Redox Amidation

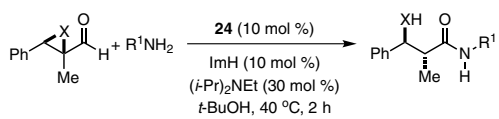
Expanding the scope of this mild acylation process to incorporate amine nucleophiles would afford amides. Amines had been previously studied as coupling partners with acyl azoliums derived from thiazolium and imidazolium carbenes, and were determined to be less competent when compared to alcohols and hydroxide.[49] We had initially shown that aniline was an effective nucleophile with 2-bromo-3-phenylpropanal and carbene **20**, furnishing the desired amide in 91% yield (see eq 6, last table entry);[40] however, other amines failed in the reaction or only provided the amides in low yields. Others working in this area expressed similar sentiments,[42,44] and further investigation into this process revealed that two byproducts of the reaction are an imine and a hydration product arising from incorporation of water into the redox reaction.

This problem was solved by introducing a nucleophilic additive, such as imidazole or HOAt, which acts as an acyl transfer agent and liberates the carbene from the acyl azolium.[50] The acylated additive in turn reacts with the amine to yield the respective amide. Common peptide coupling reagents were identified to participate in this process with HOAt displaying optimal reactivity.[51] Exclusion of water was key to prevent hydration. A variety of primary and secondary amines, as well as their respective hydrochloride salts, participate as nucleophiles in the acylation process (**eq 11**).[52] The scope of the reducible aldehyde includes α,α-dichloro aldehydes, epoxy aldehydes, and enals (**eq 12**).[52]

Concurrently, Bode and Sohn reported a similar concept whereby N-acylation in the redox reaction is facilitated by using stoichiometric imidazole and triazolium carbene precursor **23**.[53] Imine formation is suppressed by stoichiometric generation of the acyl imidazole, followed by sequential addition of the amine to generate the amide. Primary and secondary amines are tolerated; however, amine hydrochloride salts are not compatible. The reducible aldehyde substrate scope includes formylcyclopropanes, α-chloro aldehydes, and α,β-unsaturated aldehydes to generate the respective amides (**Scheme 4**).[53] More recently, Bode and co-workers have extended the substrate scope to include α'-hydroxyenones as surrogates for α,β-unsaturated aldehydes with 1,2,4-triazole used in substoichiometric quantities to facilitate amidation (see Scheme 4, Part (c)).[54]

5.3. Redox Azidation

We also sought to generate carbamoyl azides and oxazolidinones from epoxy aldehydes in the presence of NHCs and azide as the nucleophile. Using triazolium salt **24**, we were able to



R^1	X	Yield	dr
Bn	O	86%	>19:1
a	O	75%	15:1
Bn	NTs	72%	>19:1

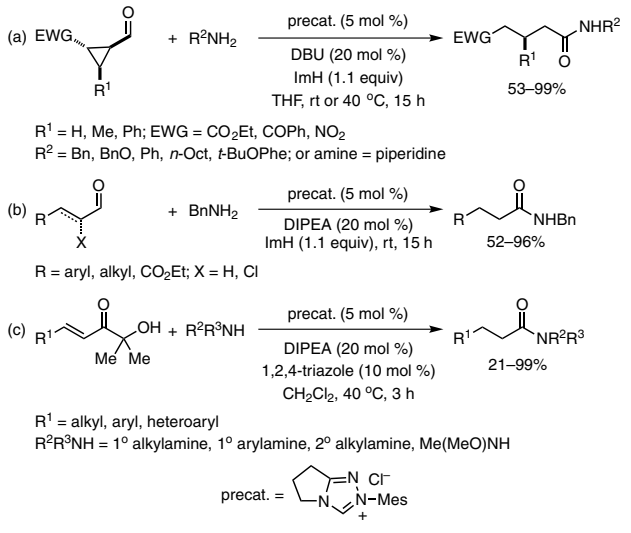
[a] R^{1}NH$_2$ = *tert*-butyl ester of alanine.

eq 12 *(Ref. 52)*

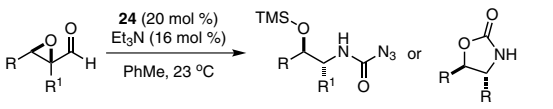
modulate product selectivity by varying the reaction conditions. Combining azidotrimethylsilane and sodium azide in a 2.5:1 ratio provides the carbamoyl azide selectively in 20–84% yields and diastereoselectivities of 2.6:1 to 6.5:1. The use of pseudo HN_3 conditions, which require a $TMSN_3$:NaN_3:EtOH ratio of 1:1:1, affords the oxazolidinone products in 53–83% yields and moderate diastereoselectivities (1:1 to 6.5:1). The varying levels of diastereoselectivities are attributed to epimerization occurring at the acyl azide, as the α proton is significantly acidic (**eq 13**).[55]

5.4. Redox Hydration

In recent years, the generation of α-halo acyl derivatives has received considerable attention. To the best of our knowledge, however, no catalytic asymmetric method is available to generate α-halo acids directly.[56] We found that chiral NHC precatalyst **25**[57] promotes the redox hydration of α,α-dichloro aldehydes with 1M potassium carbonate in water. The reaction can also generate α-deuterio-labeled chloro acids by simply using D_2O (**eq 14**).[58] The hydration process has been extended to α-fluoro-α,β-enals to generate enantioenriched α-fluorocarboxylic acids (**eq 15**).[58] The α-deuterio-α-fluoro acids can also be obtained from α-fluoro-α-bromo aldehydes as the reducible aldehyde partners.



Scheme 4. Bode's N-Acylation by Use of a Nucleophilic Additive. *(Ref. 53,54)*



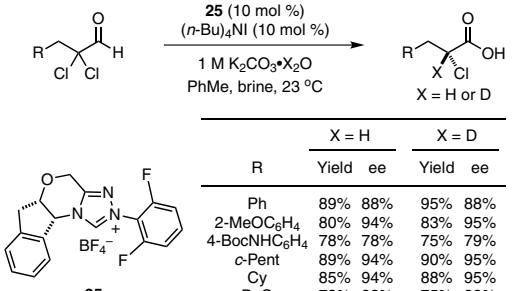
R	R¹	A Yield	A dr	B Yield	B dr
Ph	Me	75%	4:1	75%	4:1
Ph	*n*-Pent	83%	6.5:1	83%	6.5:1
Ph	Ph	84%	2.6:1	47%	1:1
4-ClC$_6$H$_4$	Me	79%	3.6:1	53%	3.5:1
2-Np	Me	52%	5.6:1	53%	3:1
1-Np	Me	20%	2.6:1	60%	5:1
Cy	Me	78%	2.7:1	78%	3:1

eq 13 *(Ref. 55)*

6. Cascade Catalysis

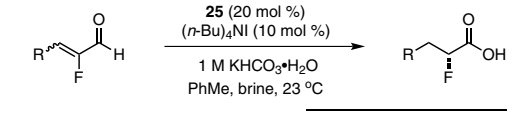
Having shown cooperative catalysis to be fruitful in our amidation chemistry, we turned our attention to coupling other branches of organocatalysis with carbene catalysis.[59] Our group successfully prepared substituted cyclopentanones by coupling secondary-amine catalysis with carbene catalysis of readily available starting materials in a Michael–Benzoin cascade reaction. Substitution is tolerated on the enal and the 1,3-dicarbonyl partners, which react to provide the corresponding cyclopentanones in excellent enantioselectivities and modest diastereoselectivities (**eq 16**).[60] Importantly, both catalysts are present throughout the course of the reaction and the protocol involves immediate charging of all reactants and reagents with no slow addition necessary.

Our laboratory has also extended the Michael–benzoin cascade to a Michael–Stetter cascade reaction with salicylaldehydes and activated acetylenes to provide hydrobenzofuranones. The reaction scope is tolerant of substitution on the salicylaldehyde with dimethyl acetylenedicarboxylate (DMAD) as the Michael acceptor to provide the respective benzofuranones in good yields



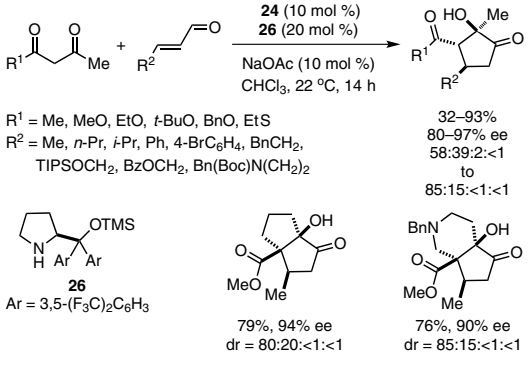
R	X = H Yield	X = H ee	X = D Yield	X = D ee
Ph	89%	88%	95%	88%
2-MeOC$_6$H$_4$	80%	94%	83%	95%
4-BocNHC$_6$H$_4$	78%	78%	75%	79%
c-Pent	89%	94%	90%	95%
Cy	85%	94%	88%	95%
BnO	78%	88%	75%	89%
Bn	86%	88%	78%	89%
EtO$_2$C(CH$_2$)$_2$	75%	90%	77%	91%

eq 14 *(Ref. 58)*



R	Yield	ee
2-MeOC$_6$H$_4$	80%	96%
4-MeOC$_6$H$_4$	74%	93%
1-Np	77%	94%
thiazol-3-yl	70%	90%
Cy	65%	96%

eq 15 *(Ref. 58)*



eq 16 *(Ref. 60)*

(62–80%) and enantioselectivities (85–94% ee's). The Michael acceptor is currently limited to acetylenedicarboxylates and activated allenes (**eq 17**).[61]

Córdova's[62] and Jørgensen's[63] groups have independently demonstrated secondary amine catalysis using **26**, coupled with carbene catalysis using **24**, in the realm of redox reactivity to furnish β-hydroxy and β-amino esters. The optimized reaction conditions rely on the consumption of the enal with secondary amine catalysis to furnish the epoxy or aziridinyl aldehyde prior to addition of azolium salt and alcohol to furnish the β-hydroxy esters (34–84%, 92–98% ee's)[62] and β-amino esters (77–96%, 93–96% ee's),[63] respectively.

7. Conclusion

We have presented here an overview of NHC-catalyzed formation of acyl anion equivalents from aldehydes and their reactivity in the Stetter, α-redox, and cascade catalysis reactions. Although this field is still in its infancy compared to other areas of organocatalysis, the further development of novel carbene precursors will pave the way to new reactivity and to its utilization in natural product synthesis and industrial processes.

8. Acknowledgments

We gratefully acknowledge our many co-workers without whose intellectual and experimental contributions none of this would have been possible. Special thanks go to Mark Kerr and Javier Read de Alaniz who initiated the early work with these catalysts. We thank NIGMS (GM72586) for support. H.U.V. thanks Lilly for a graduate fellowship. T.R. thanks Amgen and Roche for support. We thank Donald Gauthier (Merck) for a generous gift of 1-amino-2-indanol.

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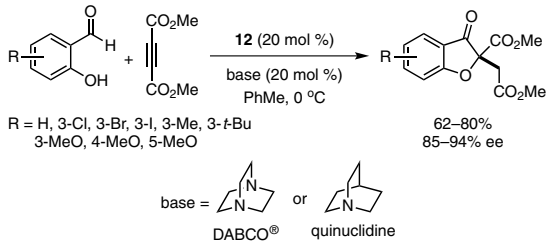

eq 17 *(Ref. 61)*

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Harit U. Vora was born in 1979 in Calcutta, India, and raised in Tobyhanna, PA. He received his undergraduate education at the University of Pittsburgh, where he carried out research under the guidance of Professor Paul E. Floreancig. He then joined the Medicinal Chemistry division of Roche USA in Palo Alto, CA. He is now pursuing the development of new synthetic methods involving N-heterocyclic carbenes (NHCs) as part of his graduate studies under the guidance of Professor Tomislav Rovis at Colorado State University.

Tomislav Rovis was born in Zagreb in the former Yugoslavia, but was largely raised in Southern Ontario, Canada. Following his undergraduate studies at the University of Toronto, he earned his Ph.D. degree at the same institution in 1998 under the direction of Professor Mark Lautens. From 1998 to 2000, he was an NSERC postdoctoral fellow at Harvard University with Professor David A. Evans. In 2000, he began his independent career at Colorado State University, and was promoted to Associate Professor in 2005 and to Professor in 2008. He currently holds the John K. Stille Chair in Chemistry.

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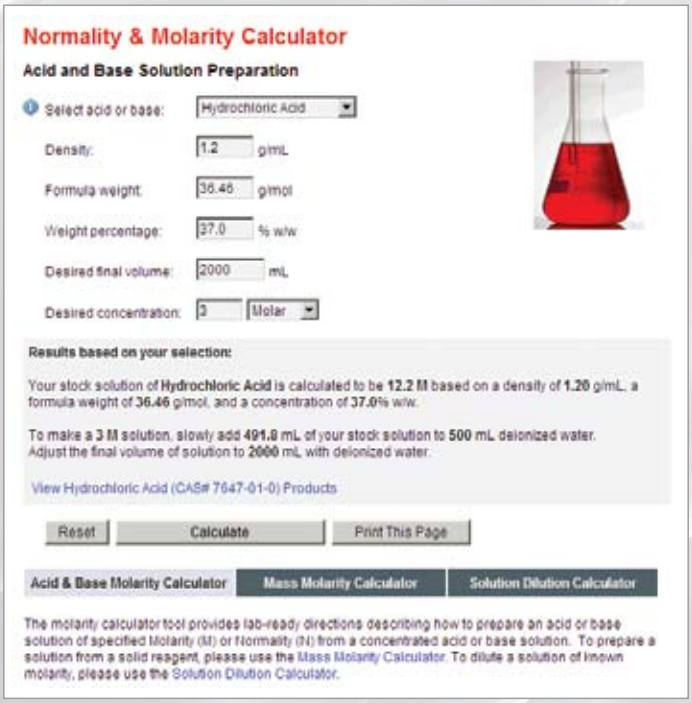

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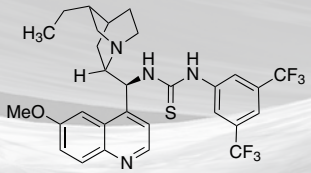

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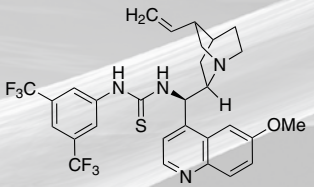

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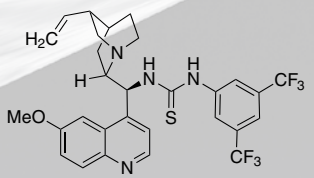

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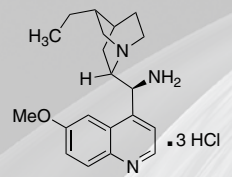

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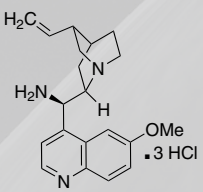

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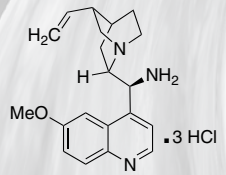

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Keywords. Mannich reaction; intermolecular; asymmetric; organocatalysts; organometallic catalysts.

Abstract. Significant, recent developments in the enantioselective Mannich reaction, catalyzed by organic and organometallic compounds, are reviewed. In particular, advances that have led to the development of new asymmetric methodologies that overcome some of the traditional limitations of the Mannich reaction are highlighted.

Outline

1. Introduction

In 1903, van Marle and Tollens observed that the reaction of acetophenone with formaldehyde and ammonium chloride leads to the formation of a tertiary amine.[1] However, it was not until 1917 that the tertiary amine was isolated by Carl Mannich by subjecting antipyrine to the same reaction conditions (**Scheme 1**).[2]

The intermolecular Mannich reaction thus became a classic method for preparing β-amino carbonyl compounds, known as Mannich bases. These bases are obtained through the condensation of a compound containing an activated C–H bond (usually aldehyde and ketone) with a primary or secondary amine or ammonia and a nonenolyzable aldehyde or ketone (**eq 1**).[3,4]

Overall, the Mannich adduct can be prepared through addition of a resonance-stabilized nucleophilic carbon to an electrophile, which can be an iminium salt, an imine, an aminal, or an aza ketal. The enolyzable component is usually an aromatic or aliphatic aldehyde or ketone, but it can also be a derivative of a carboxylic acid, β-dicarbonyl, nitroalkane, aromatic compound with high electron density, or a terminal alkyne.

Mannich bases are versatile synthetic intermediates that can be converted into a number of derivatives, including Michael acceptor **1** (by eliminating HNR_2), 1,3-amino alcohol **2** (by reduction or by addition of organometallic compounds), functionalized carbonyl compound **3** (by replacing NR_2 with nucleophiles), and six-membered-ring heterocycles **4** and **5** (by amine elimination followed by cyclization) (**Scheme 2**).[4b,5–8] Mannich adducts and their derivatives have had numerous applications in several fields of chemistry, the most important of which has been the synthesis of products with biological activities.[9]

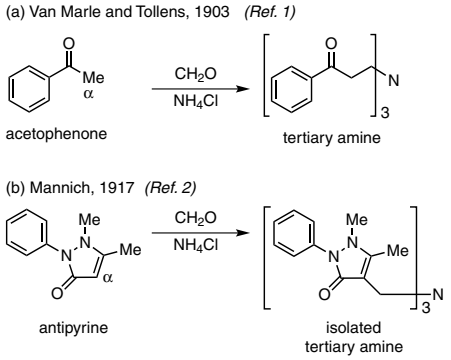
2. Catalytic, Enantioselective, Intermolecular Mannich Reactions

In the 1990s, a series of independent studies opened the way for the current development of the catalytic, asymmetric Mannich reaction.[10] These contributions include all the studies with preformed enolates and imines such as the discovery by Tomioka and co-workers of the activation of lithium enolate addition to imines through the intermediacy of a ternary complex involving catalytic amounts of chiral ether **6** (**eq 2**).[11]

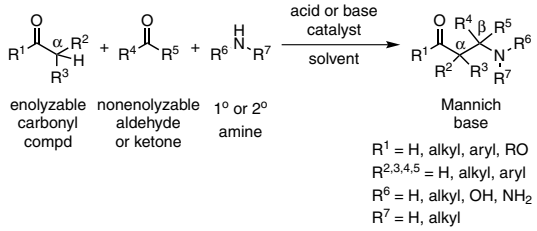
2.1. Use of Chiral Organometallic Catalysts

Kobayashi's group reported the first enantioselective, Mannich-type reaction catalyzed by a chiral Lewis acid, Zr(IV)BINOL (**7**), which activates the receptor imine, **8**, towards addition of silicon enolates, and in silyl transfer, which facilitates catalyst recovery.[12] This synthetic protocol was applied to the synthesis of syn and anti amino alcohols. The use of α-alkoxy silyl ketene acetals as nucleophiles permits control of the product stereochemistry by the choice of the alkoxy substituent. Thus, reaction of imine **8** with silyl ketene acetal **9** generates the syn product, whereas reaction with silyl ketene acetal **11** provides the anti product (**Scheme 3**).[13,14]

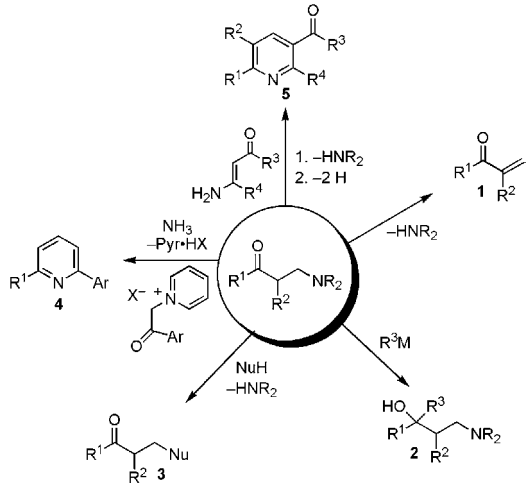
Other BINOL-derived catalysts have been described for the same type of reaction.[10c,15] Yamamoto, Ishihara, and co-workers employed a catalyst, containing a Tf_2CH and a phenolic OH group, to activate the imine starting material through hydrogen bonding.



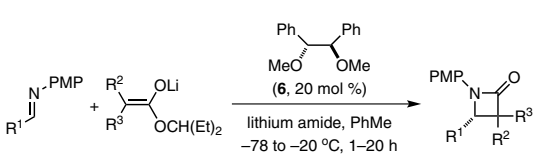
Scheme 1. First Publications on the Mannich Reaction.



eq 1 *(Ref. 3,4)*



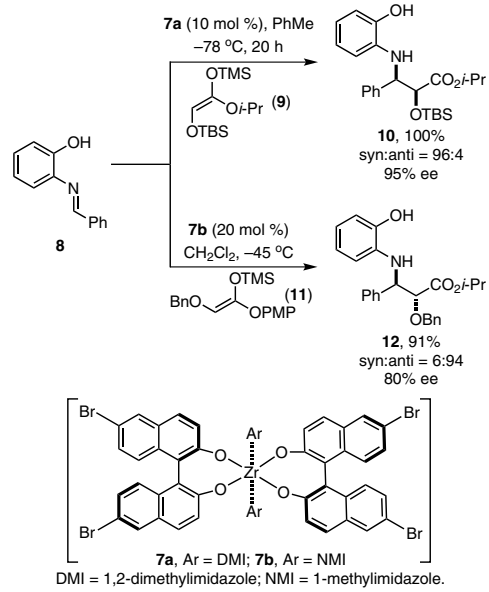
Scheme 2. Mannich Bases as Versatile Synthetic Intermediates. *(Ref. 4b, 5–8)*



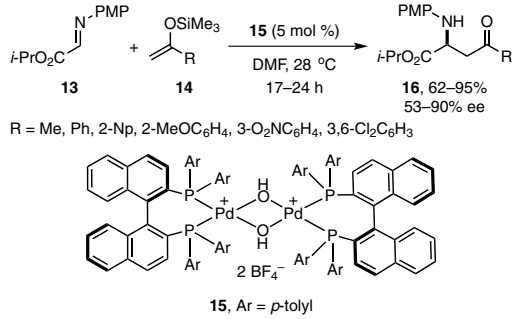
eq 2 *(Ref. 11)*

This has given rise to the concept of "Brønsted Acid Assisted Chiral Brønsted Acid" catalysis (BBA), in which the hydrogen bond R*OH•••N has restricted rotation around the catalyst R*–O axis, as its proton is activated by intramolecular OH•••OH hydrogen bonding.[16] Collin's group was the first to report that a BINOL-derived samarium complex catalyzes the reaction of glyoxylic imines with silyl ketene acetals in the presence of aniline as additive to provide, under optimized conditions, the Mannich adduct in excellent yields and enantioselectivities.[17]

Sodeoka's[18] and Lectka's[19] groups published two similar studies on organometal-catalyzed Mannich reactions of imines derived from glyoxylate. Sodeoka's team employed a new binuclear palladium complex prepared from chiral TolBINAP (**eq 3**).[18a] A palladium enolate was proposed as the main intermediate, stabilized by an η_2 coordination with the second palladium atom.[18b] The choice of this catalyst was justified by its lower nucleophilicity, thus avoiding the formation of byproducts, which is common in reactions of ketones with imines. Lectka and co-workers studied several complexes of phosphorus with transition metals as catalysts for the alkylation of α-imine esters and N,O-acetals with silyl enol ethers and silyl ketene acetals.[19] The best results were achieved with a BINAP-derived Cu(I) complex.[19]



Scheme 3. Controlling the Stereochemistry of the Mannich Product by Varying the Nature of the α-Alkoxy Substituent. *(Ref. 13)*



eq 3 *(Ref. 18a)*

Kobayashi's group reported that a complex of diamine **19** with $Cu(OTf)_2$ is a very effective catalyst (yields and enantiomeric excesses higher than 90%) for the reaction of *N*-acylimino esters with mono- and disubstituted silyl enol ethers and alkyl vinyl ethers. The synthesis of HPA-12 (**21**), a ceramide receptor inhibitor at the endoplasmic reticulum level, from *N*-acylimino ester **17** and alkyl vinyl ether **18** is a good application of this approach (**Scheme 4**).[20]

Carretero's group described the addition of *N*-(2-thienyl)-sulfonyl aldimines to silyl enol ethers and silyl enol thioethers, catalyzed by an iron–copper complex that is activated by silver perchlorate. The addition leads to the formation of β-amino esters or thioesters.[21]

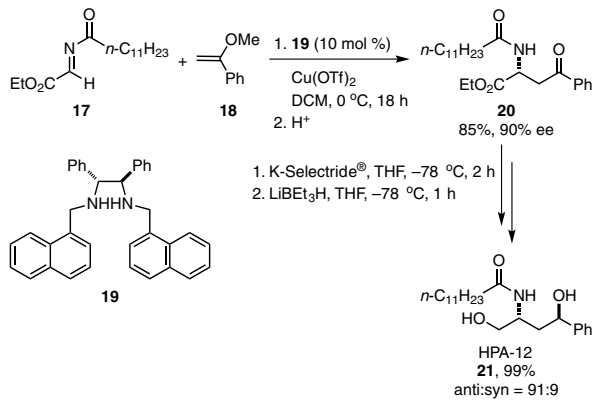
Shibasaki's group reported the first direct, catalytic Mannich reaction of unmodified ketones, in which a heterobimetallic $LaLi_3$tris(binaphthoxide) (LLB) complex served as catalyst.[22] This one-pot, three-component reaction between propiophenone, paraformaldehyde, and pyrrolidine gave only a 16% yield and 64% ee of the Mannich product. The low yield was explained by the reaction coming to an end due to the formation of $H_2C(NC_4H_8)_2$, which is inactive under the reaction conditions. The chemoselectivity of the reaction was enhanced with the use of diethylaminomethyl methyl ether and cooperative catalysis between lanthanum triflate and AlLibis(binaphthoxide) complex ((*R*)-ALB, **23**). β-Aminoalkyl aryl ketones **24** were obtained in good yields and moderate enantioselectivities (**eq 4**).[22]

Shibasaki and co-workers also described the use of a complex—formed between Et_2Zn or yttrium and an ether-linked (*S,S*)-BINOL—as catalyst for the Mannich reaction of *N*-diphenylphosphonyl (*N*-dpp) imines and α-hydroxy ketones.[23] The initial Mannich adducts, α-hydroxy-β-amino ketones, are formed as mixtures of syn and anti isomers, with both diastereoisomers obtained in high enantiomeric purity.[23] The stereoselectivity of the process is explained by approach of the electrophile from the *re* face of the zinc enolate in the transition state, in which steric repulsions with the bulky dpp group are minimized. The α-hydroxy-β-amino ketones can be elaborated in three steps into highly useful protected α-hydroxy-β-amino acids.

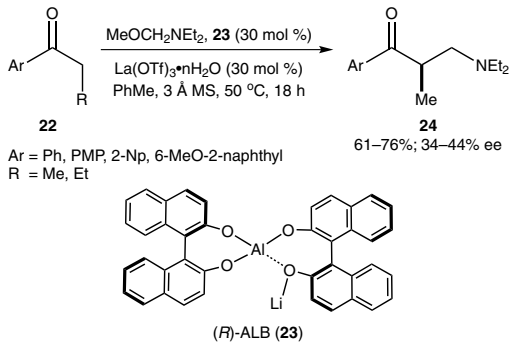
As an alternative, Trost's group reported the use of dinuclear catalytic complex **27** in the synthesis of *syn*-1,2-amino alcohols.[24] This catalyst is very effective with *ortho*-methoxy-substituted aromatic imines, likely because of the additional chelation of the imine with the catalyst, which makes the *E/Z* isomerization of the C=N bond difficult.[10b,25] This synthetic protocol was applied to the preparation of *syn*-α-hydroxy-β-amino ketones **28** from imines **25** and α-hydroxy ketones **26** (**eq 5**).[24] A dinuclear zinc catalytic complex that is very similar to **27**, but with Ar' = biphenyl, was employed by the same group in the synthesis of a protected α-hydroxy-β-amino acid from a glyoxylic imine and 2-hydroxy-1-(2'-methoxyphenyl)ethanone.[24]

Jørgensen's group reported an approach to asymmetric Mannich reactions that utilizes copper(II) complexes with bisoxazolines as catalysts. α-Carbonyl esters can be employed as nucleophiles, which makes this method an excellent choice for obtaining functionalized α-amino acid derivatives enantio- and diastereoselectively. For example, α-amino-γ-lactone **33** was obtained from the reaction of α-carbonyl ester **30** with glyoxylic imine **29** in the presence of catalyst **31** (**Scheme 5**, Part (a)).[10b,26] These same authors investigated the Mannich reaction between α-imino esters derived from glycine and several tosyl imines, with several chiral Lewis acid complexes. The reaction of **34** with **35**, using a catalytic complex of copper(I) with ligand **36**, provided the vicinal diamine Mannich adducts **37** in good diastereo- and moderate-to-high enantioselectivities (**Scheme 5**, Part (b)).[27]

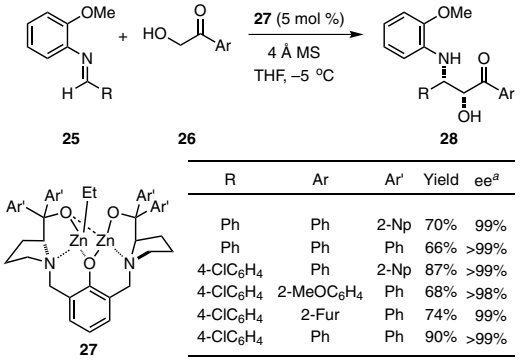
Kobayashi and co-workers reported that catalytic amounts of in situ generated niobium complex **38** effectively promotes the addition of silyl enol ethers to imines, providing the corresponding β-amino carbonyl compounds in moderate-to-good yields and high-to-excellent enantioselectivities (**eq 6**).[28] They observed that enantioselectivities were improved when the reactions were carried out in a mixture of PhMe–CH_2Cl_2 (1:1) and using 3 Å molecular sieves as additive.



Scheme 4. The Organometal-Catalyzed Mannich Reaction as a Key Step in the Synthesis of HPA-12, a Ceramide Receptor Inhibitor. *(Ref. 20)*



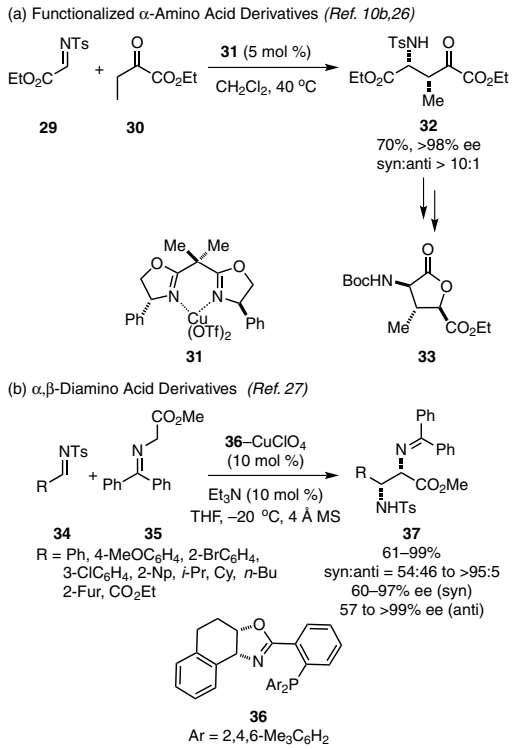
eq 4 *(Ref. 22)*



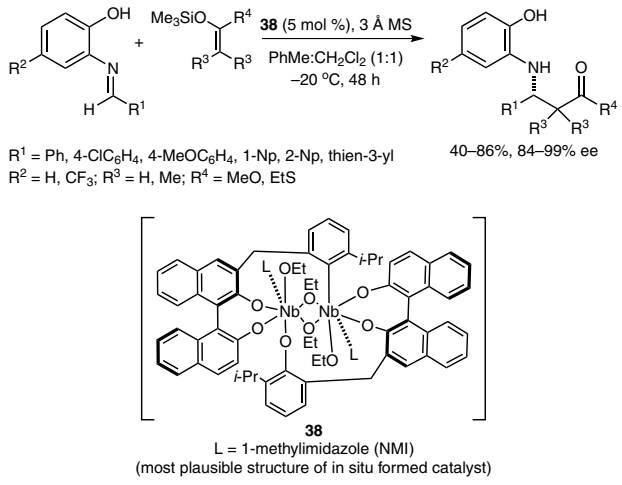
R	Ar	Ar'	Yield	ee[a]
Ph	Ph	2-Np	70%	99%
Ph	Ph	Ph	66%	>99%
4-ClC_6H_4	Ph	2-Np	87%	>99%
4-ClC_6H_4	2-$MeOC_6H_4$	Ph	68%	>98%
4-ClC_6H_4	2-Fur	Ph	74%	99%
4-ClC_6H_4	Ph	Ph	90%	>99%

[a] dr ≥15:1 in all cases.

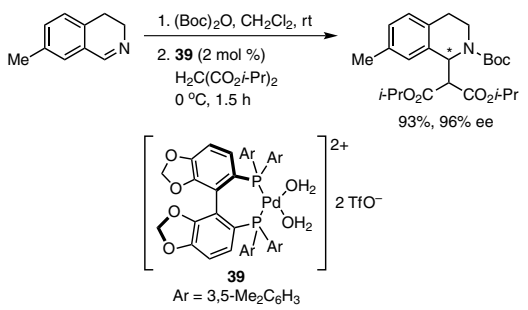
eq 5 *(Ref. 24a)*



Scheme 5. Asymmetric Mannich Reaction Catalyzed by Copper Complexes. *(Ref. 26,27)*



eq 6 *(Ref. 28b)*



eq 7 *(Ref. 30)*

Sodeoka's group reported an asymmetric Mannich reaction of β-keto esters with acyclic imines catalyzed by a chiral Pd(II) complex.[29] The same group later described the synthesis of tetrahydroisoquinolines, important biologically active alkaloids, for example by reaction of 7-methyl-3,4-dihydroisoquinoline (DHIQ) with isopropyl malonate as nucleophile. Again, a chiral Pd(II) complex, **39**, was employed as catalyst (**eq 7**).[30]

A number of other chiral organometallic complexes have also been utilized to catalyze the asymmetric Mannich reaction of enolates, silyl enol ethers, silyl ketene acetals, aldehydes, and ketones as nucleophiles with a variety of electrophiles, in particular with imines.[31]

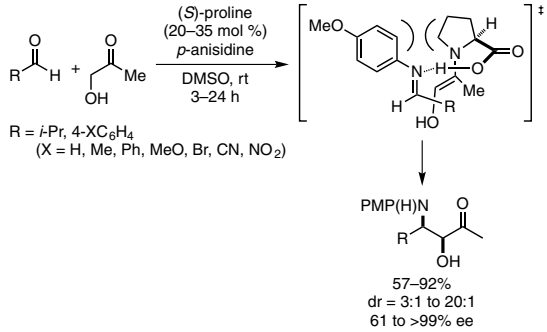
2.2. Use of Chiral Organocatalysts

The use of small organic molecules as catalysts has become a powerful tool to build chiral intermediates and products. The development of chiral organocatalysts such as prolines, pyrrolidines, cinchona-type alkaloids, and thioureas has had a profound influence on the Mannich reaction.[10a,b,31a,32] This effect has been amplified by the existence of a diversity of nitrogen-containing structural elements in biologically active substances and natural products.

2.2.1. Syn-Selective Organocatalysis

List and co-workers reported the first organocatalytic direct asymmetric Mannich reaction using (*S*)-proline as chiral catalyst to produce 1,2-amino alcohols with high distereo- and enantiomeric purities from aliphatic and aromatic aldehydes (**eq 8**).[33] This reaction was based on studies published by Shibasaki's group on the three–component, single-stage Mannich reaction,[22] as well as studies carried out on the asymmetric direct aldol reaction using catalytic amounts of proline as catalyst.[34] The stereochemical path of the direct asymmetric Mannich reaction catalyzed by L-proline can be explained by a *si*-facial attack on the imine by the *si* face of the enamine, both with trans configurations. The six-membered-ring transition state is stabilized by a hydrogen bond between the imine nitrogen atom and the hydroxyl hydrogen of the proline carboxylic acid group.[33]

The first computational study of the stereoselectivity of the proline-catalyzed direct Mannich reaction was carried out by Bahmanyar and Houk using density functional theory (DFT; B3LYP/6-31G*).[35] The transition-state geometry was optimized and characterized through frequency analysis to show the possible activation of the *E* and *Z* imines by the proline enamine. The lowest energy transition state for the reaction of the ketone proline enamine with *N*-phenylacetaldimine involves an anti



eq 8 *(Ref. 33b)*

conformation of the enamine, with a double bond away from the carboxylic acid group of proline.

Shortly thereafter, Barbas and co-workers published results similar to those obtained by List's group regarding the proline-catalyzed asymmetric Mannich reaction.[36] However, their objective quickly shifted to reactions involving preformed imines. For example, this group described a highly enantioselective proline-catalyzed reaction of ethyl *N*-(*p*-methoxyphenyl)iminoglyoxylate (**40**) with ketones **41**, forming the corresponding γ-keto-α-amino acids **42** in moderate-to-good yields and stereoselectivities (**eq 9**).[36] When asymmetric methyl ketones were employed, the reaction occurred with the most substituted enamine intermediate. Barbas's group also extended this reaction to aldehydes as donors in place of ketones.[37]

At about the same time, Barbas's, Córdova's, and Hayashi's groups reported a three-component, one-pot asymmetric Mannich reaction between two different aldehydes (crossed-Mannich reaction).[37,38] The scope of this reaction was extensively investigated by these groups, with several aliphatic aldehydes employed as Mannich donors and several aromatic and heteroaromatic aldehydes utilized as Mannich acceptors. For example, the L-proline-catalyzed addition of aldehydes **43** to *p*-anisidine (**44**) and an acceptor aldehyde, **45**, followed by an in situ reduction, produces 1,3-amino alcohols **46** in good-to-high yields, excellent enantioselectivities, and good diastereoselectivities. The reduction step is necessary in many cases in order to avoid epimerization of the β-amino aldehyde during the isolation stage (**eq 10**).

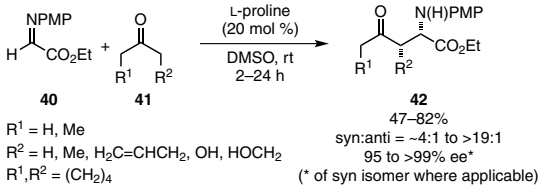
Subsequently, Hayashi et al. developed a new methodology for the stereoselective synthesis of secondary syn or anti 1,3-amino alcohols.[39] Instead of reducing the initial 3-amino aldehyde Mannich product with $NaBH_4$, it is reacted directly with a nucleophile (e.g., Ph_2CuLi or Ph_3ZnLi) to form a secondary alcohol. Since this stage occurs with low selectivity, the resulting secondary alcohol is oxidized to the ketone and then reduced with $LiAlH(Ot\text{-}Bu)_3$ or catecholborane to generate the syn or anti 1,3-amino alcohol.

Córdova and co-workers described the first asymmetric three-component Mannich reaction, catalyzed by proline and derivatives, that employs the dihydroxyacetone phosphate (DHAP) mimetic ketone **47** to form amino and aza sugars, which are of great interest in glycobiology and for the development of carbohydrate-based pharmaceuticals, especially the inhibitory action of glycosidases that have been employed or tested in the treatment of diabetes and HIV infection and as antifungal agents (**eq 11**).[40,41] This reaction took place with excellent chemoselectivity, and the corresponding products were isolated in moderate-to-good yields and, in several cases, with ee's >92%. The observed stereochemical course of this reaction is explained in terms of an attack from the enamine *si* face onto the *si* face of the imine with the trans configuration. The six-membered-ring transition state is stabilized by hydrogen bonding between the imine nitrogen and the hydroxyl hydrogen of the proline carboxyl group. The facial selectivity of the imine is explained by the fact that *re*-facial attack onto the imine would lead to steric repulsion with the pyrrolidine ring of the enamine. Consequently, the syn β-amino ketones are produced.

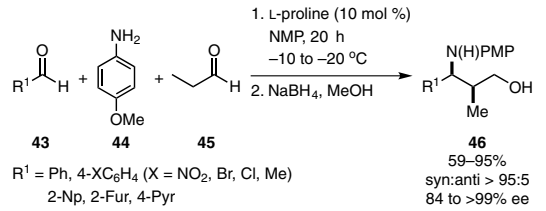
Fustero, Sanz-Cervera, and co-workers have described a highly diastereo- and enantioselective synthesis of *syn*-3-fluoroalkyl-1,3-amino alcohols by an indirect, proline-catalyzed Mannich reaction between fluoroakyl-substituted aldimines and propanal, followed by reduction of the resulting amino aldehydes with $NaBH_4$ (**eq 12**).[42] Although yields were low to moderate, stereoselectivities were consistently high to excellent. The stereochemical path proposed for this reaction is analogous to that suggested for the reaction with nonfluorinated aldimines.

The L-proline-catalyzed reaction of protected dihydroxyacetone and DHAP-mimic **47** with protected imine **40** was investigated by Westermann and Neuhaus.[43] In formamide and CF_3CH_2OH, the Mannich product was obtained in 54% and 72% yield, respectively. The syn:anti ratios were 95:5 and 97:3, while ee's were 96% and 99%, respectively. The reaction was accelerated by microwaves: after 10 minutes of irradiation at 300 W, the product was obtained in 72% yield and with high diastereo- and enantioselectivity (dr = 9:1, 94% ee).

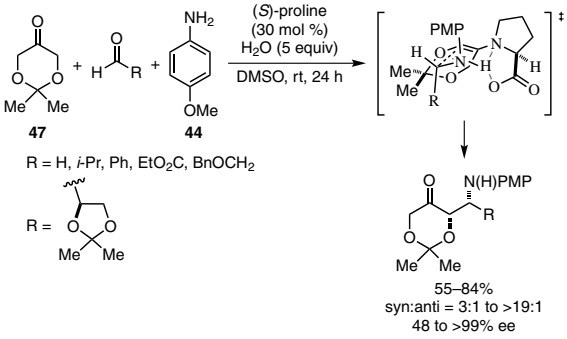
Enders and co-workers have also reported a direct organocatalytic synthesis of several carbohydrates and protected



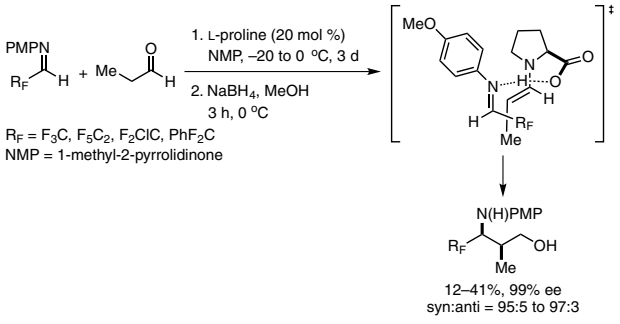
eq 9 *(Ref. 36)*



eq 10 *(Ref. 38b)*



eq 11 *(Ref. 40)*



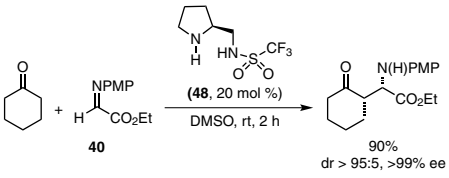
eq 12 *(Ref. 42)*

amino sugars in a highly diastereo- and enantioselective manner.[44] This L-proline-catalyzed reaction utilizes protected dihydroxyacetone **47** with a series of aldehyde starting materials. The reactive imine is formed in situ from the addition of *p*-anisidine (**44**) to an acceptor aldehyde. When a 4-TBSO derivative of L-proline was employed as the catalyst, a higher reaction rate was observed, presumably as a result of the higher solubility of the catalyst in the reaction medium.

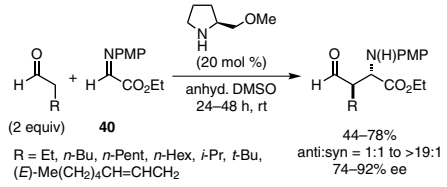
A series of chiral amino acids have been used to catalyze the Mannich reaction of cyclohexanone with *p*-anisidine and *p*-nitrobenzaldehyde highly enantioselectively.[45a] Improved yields, diastereomeric ratios, and ee's were observed as compared to the ones obtained with proline as catalyst. Moreover, the use of a chiral, more soluble aminoalkyltetrazole as catalyst resulted in a more efficient synthesis of the Mannich product. Amino acids have also been utilized as organocatalysts in the first example of an enantioselective Mannich reaction of ferrocenecarboxaldehyde to form β-arylamine-β-ferrocenyl ketones.[45b]

Ley and co-workers have identified L-proline derivatives ((*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole and L-proline methanesulfonamide) as efficient organocatalysts of the Mannich reaction between ketones and glyoxylate ethyl ester in apolar solvents.[46] Similarly, Wang, Wang, and Li reported that chiral pyrrolidine triflamide **48** effectively catalyzes the Mannich reaction between cyclohexanone and ethyl *N*-(*p*-methoxyphenyl)iminoglyoxylate (**40**), leading to functionalized α-amino acid derivatives highly stereoselectively (**eq 13**).[47]

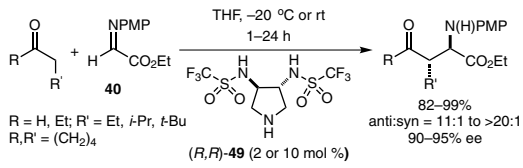
Kim and Park synthesized (+)-epi-cytoxazone in four steps starting with the reaction of benzyloxyacetaldehyde with *N*-Boc-4-methoxybenzaldimine. This asymmetric Mannich reaction was effectively catalyzed by chiral 5-benzyl-3-methyl-4-imidazolidinones differently substituted at the 2 position.[48]



eq 13 *(Ref. 47)*



eq 14 *(Ref. 49)*



eq 15 *(Ref. 53a)*

2.2.2. Anti-Selective Organocatalysis

The desire to synthesize all possible stereoisomers in asymmetric catalysis has served as an impetus for developing other protocols for the Mannich reaction. Thus, Córdova and Barbas reported the first anti-selective, (*S*)-2-(methoxymethyl)pyrrolidine-catalyzed, asymmetric Mannich reaction of aldehydes with protected glyoxylate ester **40** (**eq 14**).[49] However, yields of the *anti*-*N*-PMP-β-alkyl-α-amino ester products were moderate to good and enantioselectivities ranged from good to high (74–92% ee's). To improve the yield and selectivity of the reaction, Barbas's group developed a new pyrrolidine catalyst, (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid. With only 1–5 mol % loadings of this catalyst, much higher yields and excellent stereoselectivities were achieved.[50] However, (3*R*,5*R*)-5-methylpyrrolidine-3-carboxylic acid proved inefficient when the reaction was extended to ketones. For the latter substrates, (*R*)-pyrrolidine-3-carboxylic acid was far more effective, providing the anti N-protected β-substituted α-amino-γ-keto esters in high yields and stereoselectivities.[51]

Jørgensen and co-workers have demonstrated that (*S*)-α-trimethylsilyloxy-α,α-di(3,5-di(trifluoro)phenyl)pyrrolidine produces anti:syn ratios greater than 92:8 and 94–98% ee's.[52a] Other, structurally similar organocatalysts have also been evaluated.[52b]

Maruoka's group developed an (*S*)-BINAP-based aminosulfonamide as catalyst for the anti-selective, direct, asymmetric Mannich reaction of aldehydes with α-imino esters.[53] For aldehydes with primary alkyl groups, 1 mol % of this catalyst was sufficient to synthesize the corresponding Mannich products in excellent yields and selectivities (>92% yields; dr's > 11:1, and >99% ee's). However, sterically hindered aldehydes gave the corresponding Mannich products in only moderate yields, probably due to the low nucleophilicity of the aminosulfonamide. To improve the results for sterically hindered aldehydes and ketones, the same group tested a novel, more efficient, pyrrolidine-based aminosulfonamide (*R*,*R*)-**49**, which they synthesized from inexpensive and readily available L-tartaric acid (**eq 15**).[53]

α-Amino acid **50** was reported to catalyze the reaction of α-hydroxy ketones with aldehydes to provide the corresponding anti α-hydroxy-β-amino ketones in moderate-to-high yields and good diastereo- and enantioselectivities (**eq 16**).[54] Threonine-based organocatalysts were reported by Lu's group as being effective in aqueous systems.[55] For example, *O*-TBDS threonine catalyzes the reaction of benzyloxyacetone with a number of in situ generated aldimines in moderate-to-good diastereo- and enantioselectivities.

Recently, Gong's group employed phosphoric acid derived Brønsted acids as effective catalysts of the anti-selective, three-component, asymmetric Mannich reaction of aldehydes with six-membered-ring ketones in the presence of aniline.[56] The anti β-amino carbonyl products were formed in high yields, excellent enantioselectivities (up to 98% ee), and high diastereomeric ratios (up to 98:2).

2.2.3. Chiral Brønsted Bases

In the previous examples, the key carbon–carbon bond-forming step occurs through the reaction of a nucleophilic enamine with a protonated imine. Imine protonation is essential for making the imine electrophilic enough to react with an enantiomerically pure enamine. However, it is also possible to carry out Mannich reactions with neutral imines. In these cases, it is usually necessary to have electron-withdrawing substituents on the imine nitrogen atom in order to render the imine more electrophilic. The nucleophile

typically contains an active methylene that, after deprotonation with a chiral amine, provides a chiral ionic pair, whose anion reacts with the Mannich acceptor in a stereoselective way.

In this regard, Schaus and co-workers employed cinchona-type alkaloids in the direct, asymmetric Mannich reaction of cyclic 1,3-dicarbonyl compounds with *N*-carbamoyl arylimines to afford products containing an α-quaternary carbon (**eq 17**).[57] The stereoselectivity of the reaction was explained by proposing complexation of the chiral alkaloid with the nucleophile. Deng's group employed a cinchona-alkaloid-derived, bifunctional catalyst containing a thiourea group at position 9 to effect a highly enantioselective Mannich reaction with in situ generated carbamate-protected imines from stable α-amido sulfones. This reaction provides a short and highly enantioselective route to optically active aryl and alkyl β-amino acids from aromatic and aliphatic aldehydes (**eq 18**).[58] Another quinine-derived alkaloid has been successfully employed by Ricci's group in the asymmetric Mannich-type reaction of in situ generated, Cbz-protected azomethines and malonates in the presence of potassium carbonate.[59] The β-amino diester adducts, which are obtained in excellent yields and with ee's up to 98%, can serve as precursors of optically pure β-amino acids.

A number of other organocatalysts derived from cinchona alkaloids have also been successfully employed in several Mannich reactions,[60] including the reaction of methyl isocyanoacetate with *N*-sulfonyl imines to form imidazolines,[60a] and in the reaction of phenyl acetates, thio esters, and *N*-sulfonyl imines.[60b] Structurally simpler thioureas modeled after cinchona-derived, thiourea organocatalysts have also been investigated in the Mannich reaction.[61]

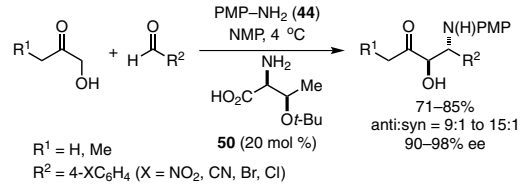
2.2.4. Chiral Brønsted Acids

A third approach for carrying out organocatalyzed, enantioselective Mannich reactions relies on the use of chiral Brønsted acids, instead of an enantiomerically pure nucleophile (reaction via enamine formation). Here, the Brønsted acid protonates the imine, forming an iminium ion containing an enantiopure counterion. This counterion directs the addition of the nucleophile and leads to the formation of an optically active Mannich adduct.

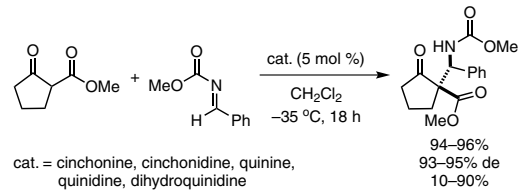
One of the first studies in this regard was reported by Akiyama's group.[62] A series of chiral phosphates were prepared, of which phosphoric acid **53** provided the best results (**eq 19**).[62a] Akiyama and co-workers also developed a chiral Brønsted acid based on the TADDOL skeleton (**Figure 1**, **54**). Phosphoric acid **54** successfully catalyzed the enantioselective Mannich reaction (97% yield, 73% ee) between imine **51** (R^1 = Ph) and the *tert*-butyldimethylsilyl ketene acetal derived from methyl isobutyrate.[63]

Ishihara, Yamamoto, and co-workers introduced the concept of organocatalysis with a chiral Brønsted acid assisted by another Brønsted acid (BBA), contained in the organocatalyst itself or introduced in the reaction medium as an additive.[16] An example of that is catalyst **55**, which has two acidic hydrogens. Mechanistically, the phenolic hydrogen activates the imine, while the hydrogen of the Tf_2CH group is responsible for fixing the HO–N bond, thus stabilizing the chiral transition state.

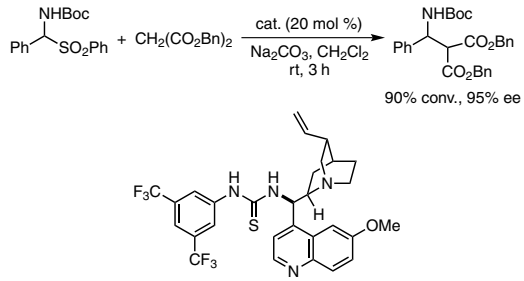
Rueping and co-workers have described the first BBA Mannich reaction that uses a carbonyl compound as nucleophile.[64] In this case, imine activation takes place through formation of an ion pair with the chiral Brønsted acid, whereas activation of the carbonyl compound occurs with a Brønsted acid that cannot form an ion pair with the imine. This concept was applied to the reaction of acetophenone with *N*-(4-chlorophenyl) benzaldimine, catalyzed by BINOL-derived phosphoric acid **56** in



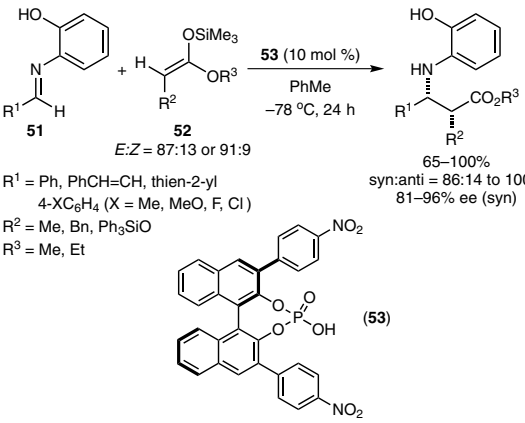
eq 16 *(Ref. 54a)*



eq 17 *(Ref. 57)*



eq 18 *(Ref. 58a)*



eq 19 *(Ref. 62a)*

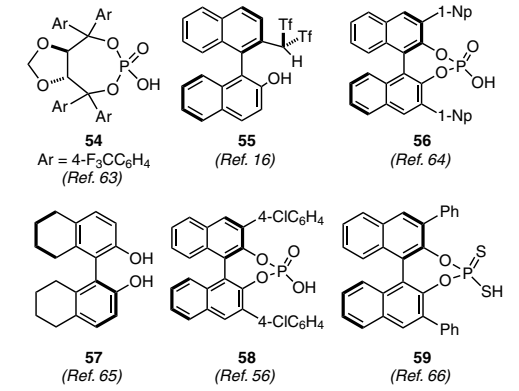


Figure 1. Other Chiral Brønsted Acids Successfully Employed as Catalysts in the Asymmetric Mannich Reaction.

the presence of acetic acid. The resulting Mannich product was obtained with 76% ee. Tillmann and Dixon utilized the same methodology to carry out an enantioselective, Brønsted acid catalyzed Mannich reaction between acetophenone-derived enamines and *N*-Boc imines. Simple (*S*)-H_8-BINOL **57** was identified as the optimal catalyst, affording versatile β-amino aryl ketones in good yields and ee's.[65]

Gong's research group was the first to describe the anti-selective Mannich reaction organocatalyzed by chiral Brønsted acid **58**.[56] High enantioselectivities but modest diastereoselectivities were observed for the Mannich reaction between cyclic ketones, aniline, and aromatic aldehydes.

Recently, Blanchet's group utilized BINOL-derived phosphorodithioic acid **59** as a chiral Brønsted acid in the anti-selective Mannich reaction between cyclohexanone and *N*-(PMP)-4-nitrobenzaldimine, leading to the β-amino ketone in 92% yield, 70:30 anti:syn ratio, and 63% ee.[66]

3. Conclusion

This review has highlighted the main recent advances in the asymmetric Mannich reaction catalyzed by organometallic compounds and organocatalysts, both existing and novel ones. These advances now allow the preparation of numerous types of Mannich adducts highly stereoselectively, greatly enhancing the scope of the traditional Mannich reaction.

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Reginaldo B. dos Santos was born in Matão, Brasil, and obtained his B.Sc. degree in chemistry in 1986 from the Federal University of São Carlos (SP State, Brasil). He then received his M.Sc. and Ph.D. degrees at the same University in 1990 and 1995, working under the supervision of Professor U. Brocksom in the field of organic synthesis. In 1991, he was appointed Assistant Professor in the Department of Chemistry at the Federal University of Espirito Santo (ES State, Brasil), and was promoted to Associate Professor in 1995.

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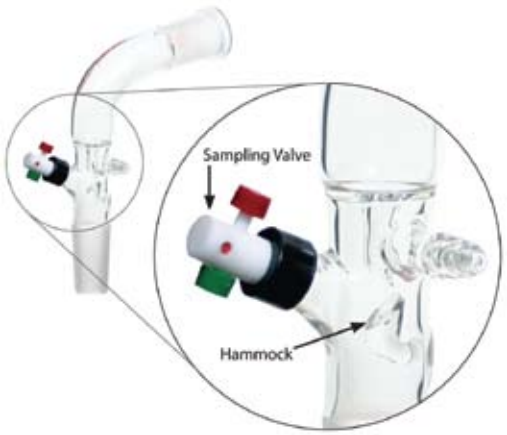

Figure 1. Distillate sampling adapter

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Replacement valve septa	**33310-U**
Septum inserter for valve	**33311**
Hamilton 701SNR syringe, 10 µL, 22s gauge blunt tip needle	**58380-U**

References:

(1) Bruno, T. J.; Ott, L. S.; Smith, B. L.; Lovestead, T. M. Complex fluid analysis with the advanced distillation curve approach. *Anal. Chem.* **2010**, *82*, 777.
(2) Bruno, T. J.; Ott, L. S.; Lovestead, T. M.; Huber, M. L. The composition-explicit distillation curve technique: relating chemical analysis and physical properties of complex fluids. *J. Chromatogr., A* **2010**, *1217*, 2703.
(3) Bruno, T. J.; Ott, L. S.; Lovestead, T. M.; Huber, M. L. Relating complex fluid composition and thermophysical properties with the advanced distillation curve approach. *Chem. Eng. Tech.* **2010**, *33*, 363.

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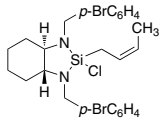
(a) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517. (b) Leighton, J. L. *Aldrichimica Acta* **2010**, *43*, 3.



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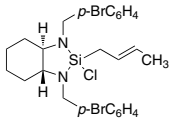

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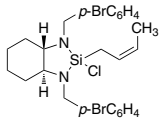

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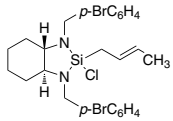

733083

733199	**(*R,R*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(*2Z*)-crotyl-*1H*-1,3,2-benzodiazasilole, 97%**	1 g 5 g
733180	**(*R,R*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(*2E*)-crotyl-*1H*-1,3,2-benzodiazasilole**	250 mg 1 g
733075	**(*S,S*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(*2Z*)-crotyl-*1H*-1,3,2-benzodiazasilole, 97%**	1 g 5 g
733083	**(*S,S*)-1,3-Bis(4-bromobenzyl)-2-chlorooctahydro-2-(*2E*)-crotyl-*1H*-1,3,2-benzodiazasilole**	250 mg 1 g

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Detail from ***The Maas at Dordrecht***. Photograph © Board of Trustees, National Gallery of Art, Washington.

Aelbert Jacobsz Cuyp (1620–1691) of the Golden Age of Dutch Art painted ***The Maas at Dordrecht*** (oil on canvas, 114.9 × 170.2 cm) around 1650. It is possible that Cuyp was commissioned to commemorate an event that may have occurred during the summer of 1646. At that time, an enormous fleet of ships carrying around thirty thousand soldiers was anchored at Dordrecht presumably for symbolic purposes rather than for specific military ones as peace was finally at hand. The Peace of Münster, which ended the Eighty Years' War with Spain, was signed only two years later, in 1648.

One of Cuyp's finest paintings, this work depicts a flurry of maritime activity, while the intricately painted pleyt (riverboat) and adjacent rowboat in the right foreground are clearly the painting's focal point. Not only are the boats authentically depicted, but they also contain numerous figures that have personality and purpose. Most of the ships on the river have their sails raised and flags flying as though they are about to embark. The early morning light floods the scene and creates striking patterns on the clouds, sails, and water, adding a dramatic character to the setting. The weight and massiveness of Cuyp's forms give this work a tangibility that few other marine painters could achieve.

This painting is part of the Andrew W. Mellon Collection at the National Gallery of Art, Washington, DC.

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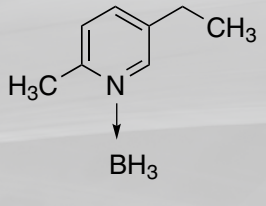

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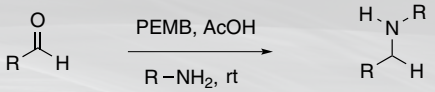

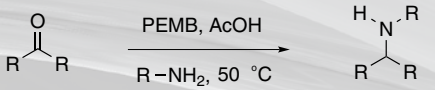

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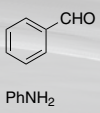
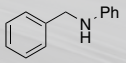
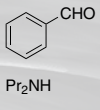
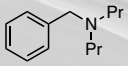
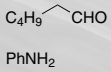
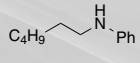
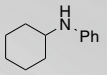
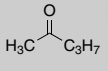
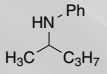
	PEMB, AcOH, MeOH, 25 °C		72 (80)
	PEMB, AcOH, MeOH, 25 °C		0 (96)
	PEMB, MeOH, 25 °C		92 (94)
	PEMB, AcOH, MeOH, 25 °C		92 (93)
	PEMB, AcOH, MeOH, 50 °C		74 (94)

For more examples and experimental detail
Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152.

76684

Halonium-Induced Cyclization Reactions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Mr. Daniel S. Treitler


Ms. Alexandria P. Brucks

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Keywords. halogenation; halolactonization; haloetherification; halolactamization; polyene cyclization.

Abstract. The present review covers synthetically useful electrophilic halocyclization reactions, in particular recent asymmetric variants, and hopes to inspire further investigations of a number of interesting problems that remain in this active research area.

Outline

1. Introduction

The electrophilic addition of halogens to alkenes constitutes one of the oldest known reactions, having been utilized by synthetic chemists for at least 160 years.[1] It is also one of the most valuable, as its many variants afford access to a variety of materials of high utility, whether in and of themselves (such as bioactive natural products), or as valuable synthetic intermediates providing reactive handles to access further functionality and/or complexity. Indeed, haloethers, halohydrins, dihalides, haloamines, and halolactams are but a few of the reaction products that can be formed through such processes; in each case a terminating nucleophile adds in an intra- or intermolecular fashion to the reactive halonium electrophile.

This review seeks to explore those cases where nucleophile addition to halonium ions occurs intramolecularly, a reactivity that can be broadly referred to as electrophilic halocyclization. Such processes specifically utilize amines, alcohols, carboxylic acids, amides, and, perhaps most importantly, carbon nucleophiles (enols, enolates, electron-rich aromatic rings, and alkenes) to generate an array of useful products. Indeed, a cursory scan of the several thousand known halogenated natural product architectures reveals that most possess domains that are the result of at least one electrophilic halocyclization.[2] Our goal in the ensuing sections, which are organized by terminating nucleophile, is to highlight critical discoveries in effecting both racemic as well as asymmetric variants of these reactions (some of which are catalytic). These advances have been driven largely by the genesis of new reagents, improved understanding of chemical reactivity and reaction kinetics, and the application of creative strategies. We also hope to highlight a number of frontiers where room for additional discoveries exist, focusing particularly on carbocyclizations, where even racemic variants have proven difficult to achieve with simple reagents.

2. Halolactonization Reactions

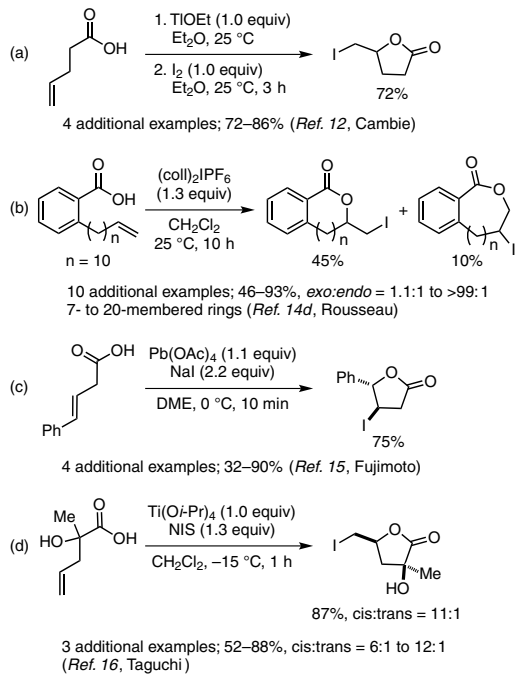
The first halogen-initiated intramolecular cyclizations studied were halolactonizations, specifically bromolactonizations as independently investigated by Fittig and Stobbe in the late 19th century.[3] The iodine-based variant of this process was discovered soon thereafter,[4] and quickly became the halolactonization of choice for synthetic chemists due to the incredible versatility of the C–I bond in leading to additional functionality. Indeed, given the paucity of halogenated natural products known at the time, these endeavors were driven largely by a desire for subsequent manipulation of the halogen handle, rather than the incorporation of the halogen itself. It was not until over 20 years later that chlorolactonization was disclosed,[5] and, as is the case for all classes of halonium-induced cyclizations, it is the chlorine variant that is the least frequently utilized. Fluorine is largely absent from the electrophilic cyclization literature, and will not be discussed in this review.

In comparison to other types of electrophilic halocyclization, halolactonization is the best studied and understood variant, with at least two comprehensive reviews of the process in existence.[6] This review will begin by discussing racemic forms of halolactonization, and then move on to more recent endeavors to utilize adapted variants to generate optically active materials.

2.1. Racemic Halolactonizations

As noted above, iodolactonization was an early chemical discovery; in the early 20th century, it was often used as a titration technique to quantify unsaturated fatty acid isomers based on their respective rates of reaction with a solution of I_2 and KI in

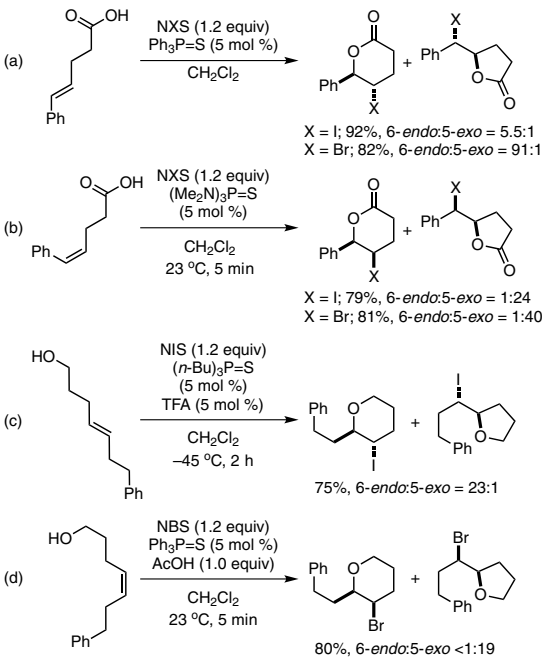
aqueous $NaHCO_3$.[4] An accurate mechanistic understanding of the process was not advanced until 1927, when Reginald Linstead and Cecil May postulated in broad terms (crediting Robert Robinson for his "suggestion") that iodine activation of a double bond precedes attack by a carboxylate nucleophile.[7] Nearly 30 years later, van Tamelen and Shamma further refined that picture by invoking an iodonium ion to explain the relative rates of 5-*exo* and 6-*endo* iodolactonizations.[8] Soon thereafter, Klein reinforced van Tamelen's mechanistic hypothesis by proving that the lactones formed during these reactions have their iodine and ester moieties in a trans orientation.[9]



Scheme 1. Selected Racemic Iodolactonization Reactions.

In terms of the reagents that can effect these processes, for nearly all of the first century of its existence iodolactonization was carried out using the original conditions elucidated by Bougault:[4] I_2 and KI added to a solution of the unsaturated acid substrate in aqueous $NaHCO_3$. In 1953, it was disclosed that ICN in $CHCl_3$ could also initiate iodolactonizations, releasing one equivalent of HCN in the process.[10] Developments of considerably more useful and less toxic conditions came in the 1970s and ensuing decades. For example, in 1972, Barnett showed that if one performed an iodolactonization reaction using I_2 in a biphasic system of Et_2O and aqueous $NaHCO_3$, it was possible to isolate the kinetic cyclization product (one which is not typically the same as the thermodynamic product).[11] This finding implies that in highly polar solvents such as H_2O, the iodide within the product can ring-open the neighboring lactone, reforming the reactive iodonium intermediate. Two years later, in 1974, Cambie and co-workers disclosed that the use of thallium(I) carboxylates as starting materials gave higher yields of the iodolactone products than the analogous sodium salts (**Scheme 1**, Part (a)).[12]

Fundamental alterations to the iodine electrophile followed soon thereafter. Cook et al. reported in 1983 that *N*-iodosuccinimide (NIS) is a highly competent reagent for iodolactonization.[13] Rousseau then demonstrated in the early 1990s that bis(collidine)-iodonium hexafluorophosphate, $(coll)_2IPF_6$, could be used to form macrocyclic iodolactones, albeit only if certain structural motifs such as oxygen atoms, *gem*-dimethyl substituents, alkynes, or aromatic rings were incorporated into the tether between the alkene and carboxyl groups (see Scheme 1, Part (b)).[14] Even more exotic reaction conditions have also proven efficacious in initiating such cyclizations. For example, NaI in the presence of $Pb(OAc)_4$ (see Scheme 1, Part (c)) affords a number of iodolactones,[15] though it should be noted that this system generally affords poor endo vs exo selectivity in those cases where mixtures of products are possible. Additionally, Taguchi and co-workers demonstrated that substrates with a polar group (OH or NHTs) near the carboxylate nucleophile could lead to cyclic products with high cis selectivity by using a Ti(IV) Lewis acid to pre-organize the substrate prior to the addition of NIS or I_2 (see Scheme 1, Part (d)).[16] Finally, in an extensive recent effort, Denmark's group investigated dozens of Lewis base catalysts to determine which ones, in conjunction with NIS, could increase both the yield and selectivity of iodolactonization (**Scheme 2**, Parts (a) and (b)).[17a] This work was predicated on the Denmark group's concept that Lewis base activation of Lewis acids (viewing the iodonium ion as a Lewis acid) can often afford reagents with unique and/or enhanced reactivity.[17b] Significantly, some of these Lewis base activated systems were also effective for accelerating and controlling bromolactonization, iodoetherification, and bromoetherification reactions (see Scheme 2, Parts (a)–(d)). As might be expected, varying the steric and electronic properties of the catalyst had a significant impact on the stereoselectivity of these reactions.



Scheme 2. Lewis Base Catalyzed Halolactonization and Halo-etherification Reactions. *(Ref. 17a,* Denmark*)*

Moving up the periodic table within the halogen family to bromine, the initial reaction conditions (pioneered by Stobbe and Fittig)[3] utilized Br_2 in halogenated organic solvents, rather than the aqueous conditions that were later used for the first iodolactonization reactions. The first mechanistic understanding of the bromolactonization reaction was reported by Arnold's group in 1953.[18] This study was followed by more in-depth investigations by Barnett and McKenna in 1971, who

ultimately came to the same overall mechanistic conclusions as those for iodolactonization.[19] Similarly, many of the advances in reagent design and reaction conditions pioneered for the iodolactonizations described above also proved applicable for the analogous bromonium-induced variants. Kang and co-workers again pioneered the use of the appropriate *N*-halosuccinimide, in this case NBS, as an effective cyclization reagent.[13] Thallium carbonate[20] (**Table 1**, entry 2) and in situ oxidation of halide salts by $Pb(OAc)_4$ also proved competent.[15] Intriguingly, when Rousseau's group explored the use of $(coll)_2BrPF_6$ as a reagent for initiating bromolactonizations, they discovered that the substrate scope could be expanded to include α,β-unsaturated acids, substrates ordinarily unreactive under other halolactonization conditions.[21]

Most recent efforts exploring racemic bromolactonization have been focused on increasing the rate and efficiency of the transformation, especially when initiated by NBS. Indeed, as evidenced by the conditions and yields of entries 3–7 within Table 1, bromolactonization with NBS alone is often a slow and capricious reaction.[20,22,23] Successful additives to rectify this situation include diselenides (entry 8),[24] aryl iodides with nucleophilic ortho substituents (entry 9),[25] Lewis bases (entries 10–12),[17,22] and, surprisingly, simply 3 Å molecular sieves (entry 13).[23]

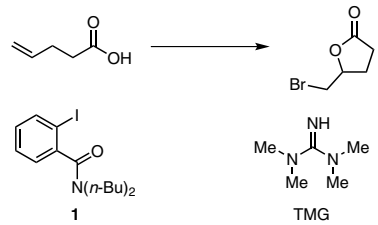
Finally, we turn to chlorolactonizations, the last and least developed of this class of electrophilic halocyclizations. The general paucity of examples of such processes may reflect the relatively lower reactivity of the resultant alkyl halide product in subsequent reactions. The first mention of chlorolactonization in the literature occurred in 1932, when Bloomfield and Farmer disclosed that a mixture of aqueous HOCl and $CaCl_2$ could cyclize select substrates.[5] Interestingly, nearly two decades later, Woodward and Singh illustrated what may well be the first example of a halolactonization in a natural product total synthesis when they used a solution of Cl_2 in $CHCl_3$ to effect a key chlorolactonization step in the preparation of *allo*-patulin.[26] However, due to the unpleasantness of working with chlorine gas, little work on this general reaction was performed in the ensuing decades outside of the publication of a thorough analysis of the stereochemistry of this process by Berti in 1958,[27] along with evidence for the accepted mechanism of olefin activation by electrophilic chlorine followed by intramolecular attack of a carboxyl nucleophile. Eventually, however, improved procedures were identified, including the use of the solid reagent chloramine-T[28] in lieu of Cl_2 (**Scheme 3**, Part (a)) as well as an operationally simple procedure using NaOCl in the presence of any one of several Lewis acids, leading to the formation of 4- or 5-membered-ring chlorolactones (Scheme 3, Part (b)).[29]

2.2. Asymmetric Halolactonizations, Substrate-Controlled

An examination of asymmetric halolactonization reveals that only the iodine- and bromine-induced variants proceed with asymmetry when under substrate control; to the best of our knowledge, no chlorine-based version of such a process has yet been demonstrated. The first attempts to effect substrate control in a halolactonization were published in the 1980s, when efforts to achieve an asymmetric iodolactonization focused on converting the carboxylic acid nucleophile into a chiral amide prior to cyclization. The seminal example appeared in 1981, when Takano and his group appended proline onto a symmetric substrate and cyclized it using I_2 in THF to obtain a desymmetrized product with 16% ee (**Scheme 4,** Part (a)).[30] Several groups later optimized the chiral auxiliary, improving the enantioselectivity for the same substrate and similar materials using C_2-symmetric auxiliaries,[31] sultams,[32] and even axially chiral amides.[33] In some cases, this approach proved capable of delivering the desired desymmetrized products in near optical purity (>98% ee).[32] Additionally, Kurth and co-workers showed in the early 1990s that it was possible to append unsymmetrical substrates with chiral auxiliaries, α-alkylate them with high ee, and then subsequently induce an iodolactonization with up to 99% de; in these events, the influence of the chiral auxiliary as well as the newly installed alkyl group provided mutually reinforcing stereochemical control.[34]

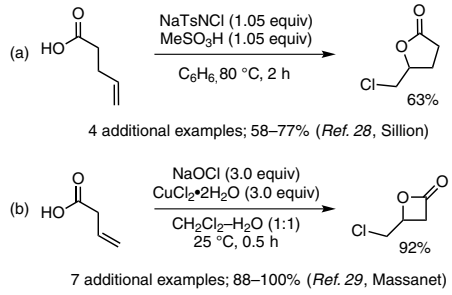
Initial investigations of substrate-controlled asymmetric bromolactonizations pursued similar strategies. Terashima's group provided the seminal example in the late 1970s, using chiral proline-derived carboxylates as nucleophiles (**Scheme 5**, Part (a)).[35] Other auxiliaries that have been successfully demonstrated to date include oxazolidinones[36] and pseudoephedrine-derived amides.[37]

Table 1. Recent Advances in Racemic Bromolactonization



Entry	Conditions[a]	Additive	Time	Yield	Ref.
1	Br_2, Et_2O	aq $NaHCO_3$(xs)	24 h	32%	*20*
2	Br_2, CH_2Cl_2	Tl_2CO_3 (0.8 equiv)	24 h	54%	*20*
3	NBS, THF		24 h	46%	*20*
4	NBS, DMF		24 h	34%	*20*
5	NBS, $CDCl_3$		15 h	15%[b]	*22a*
6	NBS, CH_2Cl_2		24 h	57%	*20*
7	NBS, CH_2Cl_2		54 h	99%	*23*
8	NBS, MeCN[c]	$(PhSe)_2$ (5 mol %)	2 h	55%	*24*
9	NBS, $CDCl_3$	**1** (10 mol %)	0.3 h	100%[b]	*25*
10	NBS, $CDCl_3$	DMF (1.0 equiv)	0.5 h	100%[b]	*22a*
11	NBS, $CDCl_3$	DMA (10 mol %)[d]	0.5 h	89%	*22a*
12	NBS, $CDCl_3$	TMG (1 mol %)	0.25 h	92%	*22a*
13	NBS, CH_2Cl_2	3 Å MS	4.5 h	98%	*23*

[a] Carried out at 25 °C. [b] Percent conversion. [c] At –30 °C. [d] DMA = *N,N*-dimethylacetamide.

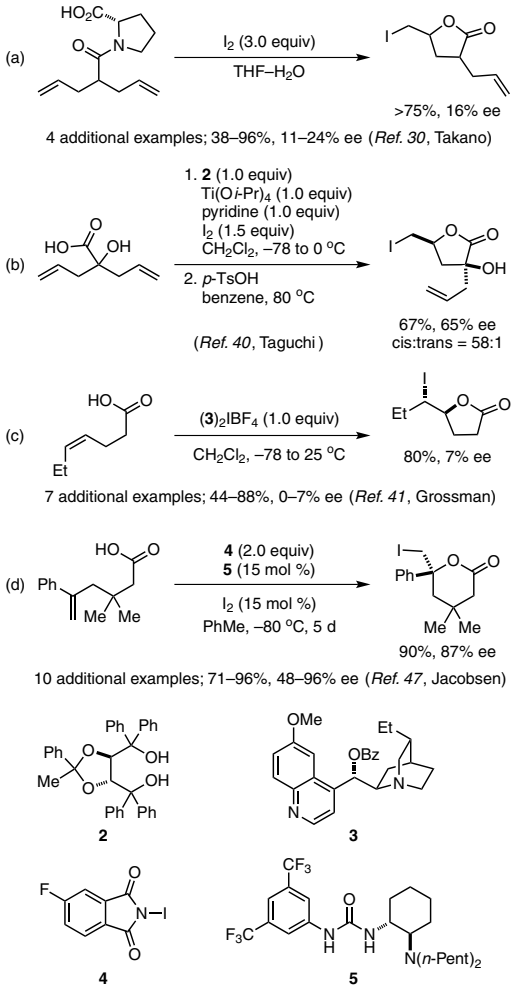


Scheme 3. Selected Chlorolactonization Reactions.

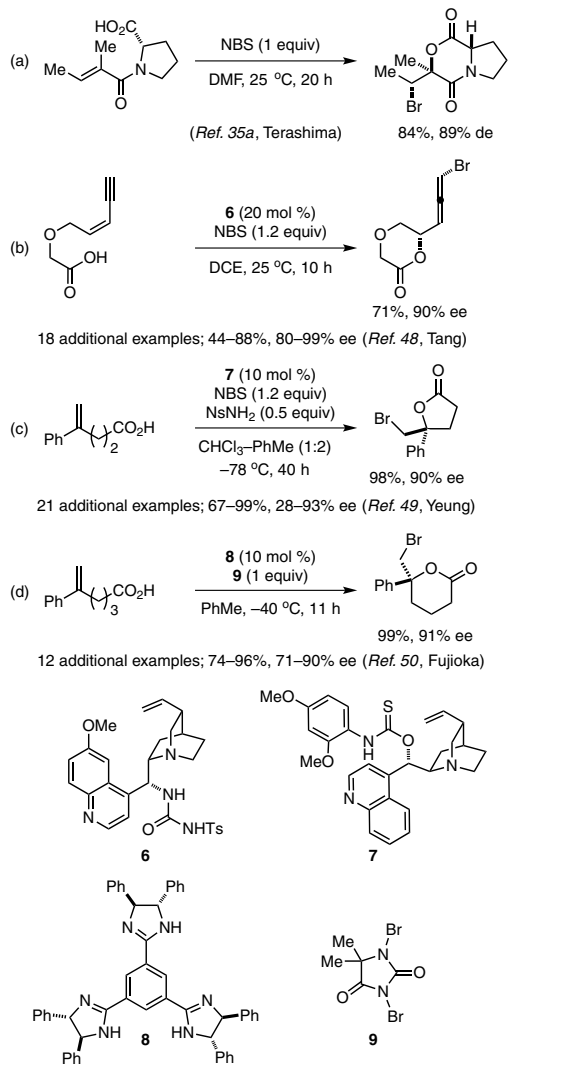
2.3. Asymmetric Halolactonizations, Reagent-Controlled

As with most enantioselective reactions, reagent-controlled approaches for halolactonization (particularly catalytic variants) are more desirable than those based on substrate-control, but have proven slower to develop. A major issue barring the way to any reagent-controlled approach is halonium transfer, a process studied extensively by R. Stan Brown's group[38] and recently revisited by several other teams.[39] The predicament invoked by halonium transfer is that, even if one could deliver a chiral halonium equivalent to only one face of a double bond, this process could be inefficient in terms of enantiocontrol since the resultant halonium ion could, prior to cyclization, rapidly transfer its halogen atom to an unreacted alkene and thereby erase any initial facial selectivity. Nonetheless, some solutions have been identified. The first solution, although not general, was the disclosure of an asymmetric reagent-controlled iodolactonization in 1992 by Taguchi and co-workers, who subjected a symmetrical α-hydroxy acid to I_2 in the presence of a stoichiometric amount of a chiral TADDOL-Ti Lewis acid; these conditions led to the product shown in Part (b) of Scheme 4 in 65% ee.[40] Since this initial discovery, several teams have attempted to identify a more general approach, often by investigating stoichiometric quantities of complexes formed by the reaction of chiral amines with electrophilic iodine. The seminal example utilizing such reagents was disclosed by Grossman and Trupp in 1998 (Scheme 4, Part (c)).[41] However, neither their approach nor adaptations by others (**Table 2**, entries 1–5) have led to iodolactone products possessing more than 50% ee.[42,43] Notably, a similar approach using a chiral amine–bromine complex produced a bromolactone in less than 5% ee,[44] perhaps due to the fact that the relative rate of halonium transfer with respect to nucleophilic capture is highest for bromonium intermediates.[38e,39c]

The first report of a *catalytic* asymmetric iodolactonization relied upon a biphasic system of I_2 in CH_2Cl_2–aqueous $NaHCO_3$ in addition to 30 mol % of a chiral cinchona-derived phase-transfer catalyst; the resultant ee values for the cyclized products were modest, but the concept of catalysis was at least established.[45] Indeed, quite recently, two far more effective approaches for catalytic asymmetric iodolactonization have appeared. The first was Gao's use of a (salen)Co(II) Lewis acid catalyst in conjunction with catalytic NCS and stoichiometric I_2, which resulted in good yields and up to 82% ee of the iodolactone products (see Table 2, entry 6).[46] The second and arguably more powerful



Scheme 4. Examples of Asymmetric Iodolactonization Reactions.



Scheme 5. Examples of Asymmetric Bromolactonization Reactions.

contribution comes from Veitch and Jacobsen, who disclosed that a chiral aminourea catalyst, **5**, in the presence of a rather unique iodinating reagent, **4**, along with a catalytic amount of I_2 is capable of producing a variety of iodolactones in good yields and very high ee's (up to 96%; see Table 2, entry 7 and Scheme 4, Part (d)).[47] This work provides the only example of a highly asymmetric reagent-controlled iodolactonization, indicating that a successful method likely pre-organizes both the nucleophilic carboxylate and the electrophilic alkene prior to reaction; it is not enough to simply make chiral iodonium electrophiles or chiral carboxylate nucleophiles.

In the realm of catalytic asymmetric bromolactonizations, three spectacular approaches have all been published quite recently. In the first of these, Tang's group disclosed that chiral cinchonidine urea **6** was capable of catalyzing the NBS-induced cyclization of carboxylic acids appropriately tethered to enynes with very high ee's.[48] The products were 6- and 7-membered-ring lactones with pendant allenes bearing axial chirality (see Scheme 5, Part (b)). Next, Yeung and co-workers published an organocatalytic approach to 5-membered-ring bromolactones using a similar chiral aminothiocarbamate catalyst, **7**, in the presence of NBS (see Scheme 5, Part(c)).[49] Lastly, Fujioka's group disclosed a C_3-symmetric chiral organocatalyst, **8**, capable of producing similarly enantioenriched bromolactones in the presence of the somewhat exotic brominating reagent 1,3-dibromo-5,5-dimethylhydantoin (**9**) (see Scheme 5, Part (d)).[50]

Finally, there is but a single report of enantioselective chlorolactonization. In a very recent publication, Borhan's group disclosed that commercially available cinchonidine alkaloids catalyzed the asymmetric chlorolactonization of a number of 4-aryl-4-pentenoic acids using 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) as a chlorine source (**eq 1**).[51] The failure of this simple yet elegant approach to also work for iodo- and bromolactonizations underscores the need for unique solutions for each halogen, and highlights reactivity differences that must be overcome not only for successful reaction in a racemic sense, but also if any asymmetry is to be induced in the resultant materials.

3. Haloetherification Reactions

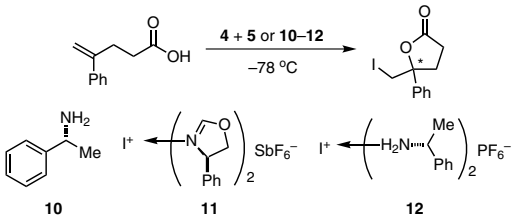
Haloetherification is a highly valuable synthetic method that can produce oxetane, tetrahydrofuran, tetrahydropyran, and even larger ring systems.[52] Although a more recent addition to the electrophilic cyclization arsenal, haloetherification has evolved in a fashion similar to that of halolactonization. Seminal publications were followed by mechanistic and stereochemical investigations to achieve effective racemic reactivity with stoichiometric reagents, which in turn gave way to insights into how to achieve asymmetric variants, including catalytic manifolds.

3.1. Racemic Haloetherifications

The first disclosure of an iodoetherification reaction appeared in a 1967 report by Williams, wherein the treatment of 4-pentenyl alcohol with I_2 in aqueous KI yielded the 5-*exo* tetrahydrofuran product almost exclusively.[53] A more thorough investigation of the reaction was disclosed in 1985, when Yoshida's group cyclized a variety of simple alcohols under several iodoetherification conditions [I_2–$NaHCO_3$, NIS, or $(coll)_2IClO_4$] in order to compare the yields and distribution of the resultant cyclic ether isomers; in most cases, they found that the I_2–$NaHCO_3$ system was superior.[54] In the same year, it was demonstrated that in situ oxidation of a halide salt with $Pb(OAc)_4$ was also useful for iodoetherification (using NaI) as well as bromoetherification (using $ZnBr_2$).[15] Efforts to enhance the rate of racemic iodoetherifications have been the subject of more recent investigations, which have largely focused on using NIS in combination with a catalytic additive. Key results on this front include Morgan's discovery that the addition of 3 mol % $(dppf)PdCl_2$ allows for rapid cyclization of (bishomo)allyl alcohols at room temperature in moderate-to-high yields (**Scheme 6**, Part (a)).[55] Meanwhile, Denmark's Lewis base activation concept proved valuable for enhancing both reaction rate and selectivity for iodoetherification with NIS, as noted earlier and depicted in Part (c) of Scheme 2.[17a] It is of significance that while both of these catalyzed methods are racemic, the authors maintain in each case that the use of either a chiral diphosphine ligand (Morgan) or chiral Lewis base (Denmark) could potentially render these reactions enantioselective.

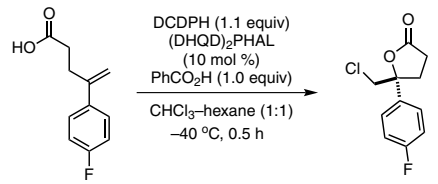
A unique class of iodoetherifications exists in which the pendant nucleophile is not an alcohol. For example, in 2003, Barluenga reacted *ortho*-alkynylbenzaldehydes with Py_2IBF_4 and HBF_4, finding that the oxygen of the pendant aldehyde

Table 2. Advances in Reagent-Controlled Asymmetric Iodolactonization

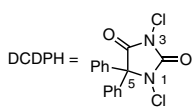


Entry	Conditions	Additive	Time	Yield	ee	*Ref.*
1	NIS, CH_2Cl_2	**10** (4.1 equiv)	0.25 h	~80%	0	*42a*
2	I_2, CH_2Cl_2	**10** (4.1 equiv)	0.25 h	~80%	7%	*42a*
3	ICl, CH_2Cl_2	**10** (4.1 equiv)	0.25 h	~80%	25%	*42a*
4	**11**, CH_2Cl_2		ND	72%	5%	*43*
5	**12**, CH_2Cl_2		ND	70%	7%	*43*
6	I_2, PhMe[a]	NCS (25 mol %) (salen)Co(II) (40 mol %)	20 h	87%	67%	*46*
7	**4**, PhMe[b]	**5** (15 mol %), I_2 (0.1 mol %)	5 d	82%	90%	*47*

[a] At –18 °C. [b] At –80 °C.

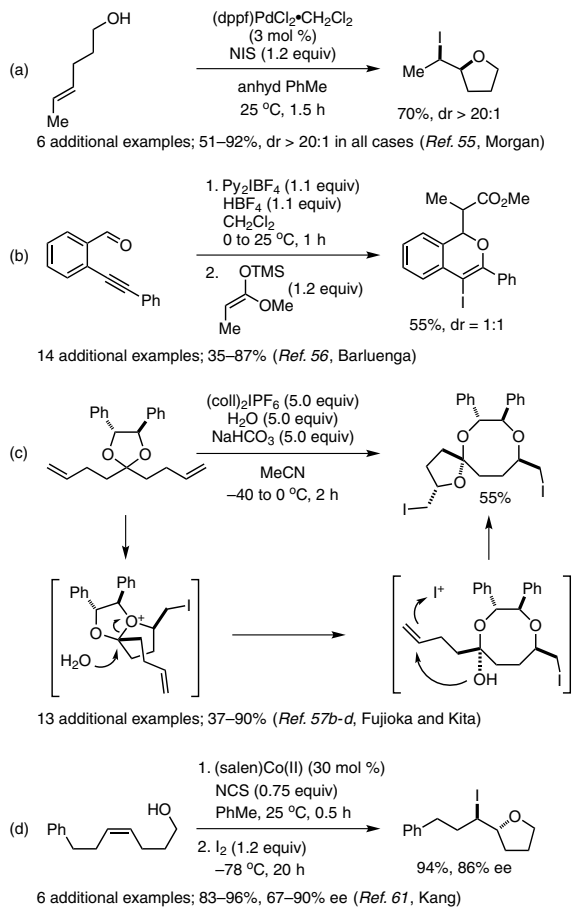


9 additional examples; 55–99%, <5 to 90% ee (*Ref. 51a*, Borhan)

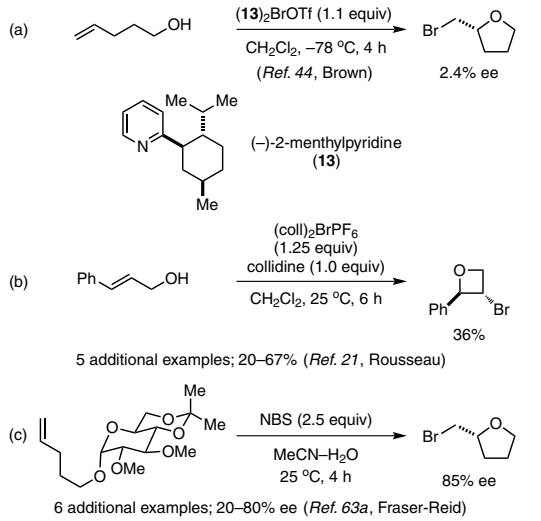


eq 1 *(Ref. 51a)*

can attack the activated alkyne (see Scheme 6, Part (b)).[56] An external nucleophile (alcohol, silyl enol ether, silyl ketene acetal, allylsilane, or electron-rich aromatic ring) is then added to quench the oxonium intermediate and forge a unique heterocyclic framework. Similarly, Fujioka, Kita, and co-workers have published a number of iodoetherifications in which the pendant nucleophile is either an acetal or ketal oxygen.[57] Iodination of an alkene (generally using $(coll)_2IPF_6$) with a pendant cyclic ketal can be used to obtain elaborate bicyclic products with multiple stereocenters. Scheme 6, Part (c) provides a representative example of such a process, including a proposed mechanism leading to an 8-membered ring. Of significance, the chirality of the ketal is transferred efficiently, resulting in high diastereoselection for the process.



Scheme 6. Selected Iodoetherification Reactions.



Scheme 7. Selected Bromoetherification Reactions.

In contrast to iodoetherification, the corresponding bromine variant has been utilized with less frequency. Early reports of the process generally utilized Br_2 in an organic solvent along with base (usually quinoline or KOH).[58] Since then, several additional reagents have been shown to effect this reaction. For example, two natural product total syntheses in 1988 and 1993 featured 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) as the bromoetherification initiator.[59] Similarly, Py_2BrX salts were studied extensively by Brown's group,[60] who even attempted an asymmetric variant, but with little success (**Scheme 7**, Part (a)).[44] Another intriguing discovery was Rousseau's disclosure that cyclization of allylic alcohols could be achieved with $(coll)_2BrPF_6$ to yield the 4-*endo* cyclization products in moderate yields (see Scheme 7, Part (b));[21] these trans oxetanes only form with an aryl group at the 3 position of the allylic alcohol, whereas with alkyl groups, rearrangements occur to form larger, more stable cyclic ethers. The best results to date issue from Denmark's group, who reported that Lewis bases catalyze a number of bromoetherifications in good yields and excellent selectivities (see Scheme 2, Part (d)).[17a] To the best of our knowledge, there are currently no examples of intramolecular chloroetherifications.

3.2. Asymmetric Haloetherifications

The seminal report for effecting an asymmetric haloetherification was Taguchi and co-workers' desymmetrization of a diol using conditions similar to those of their enantioselective iodolactonization (see Scheme 4, Part (b)). In this case, they obtained the desired iodinated tetrahydrofuran product with modest enantioselection (36% ee).[40] Since then, only one catalytic asymmetric iodoetherification method has been disclosed. This work issued from Kang's research group in 2003,[61] and relied upon a catalytic amount of (salen)Co(III)Cl [formed from the reaction of (salen)Co(II) with NCS] in combination with stoichiometric I_2 to effectively cyclize unsaturated alcohols in good yields and with ee values of up to 90% (see Scheme 6, Part (d)). Extensive optimization of the initial result demonstrated that a (salen)-Cr(III)Cl catalyst (in lower loadings) with the addition of K_2CO_3 could boost both yield and enantioselectivity.[62]

In contrast to asymmetric iodoetherifications, no catalytic asymmetric bromoetherifications have been reported to date. There is, however, an early substrate-controlled approach, in which a glucose-derived chiral auxiliary allowed for selected bromoetherifications to proceed in up to 85% ee (**Scheme 7**, Part (c)).[63] A brief mechanistic analysis implicated the importance of the anomeric effect in combination with sterics to produce the good selectivity observed. Overall, however, these results collectively indicate that much room remains for the development of new haloetherification processes, particularly on the asymmetric front.

4. Halolactamization and Haloamination Reactions

Equally as valuable as the addition of X and O across a double bond is the addition of X and N, both from the standpoint of synthetic intermediates as well as bioactive natural products.[64] Such processes, however, are inherently far more challenging to

effect in that attempts to achieve halolactamization using simple unsaturated amides leads to lactones (after hydrolysis of an intermediate iminium ether), an outcome attributed to the higher electronegativity of oxygen relative to nitrogen.[65] As such, most approaches towards halolactamization involve some attempt to enhance the electronegativity of nitrogen in order to improve its nucleophilicity and supersede that of oxygen.

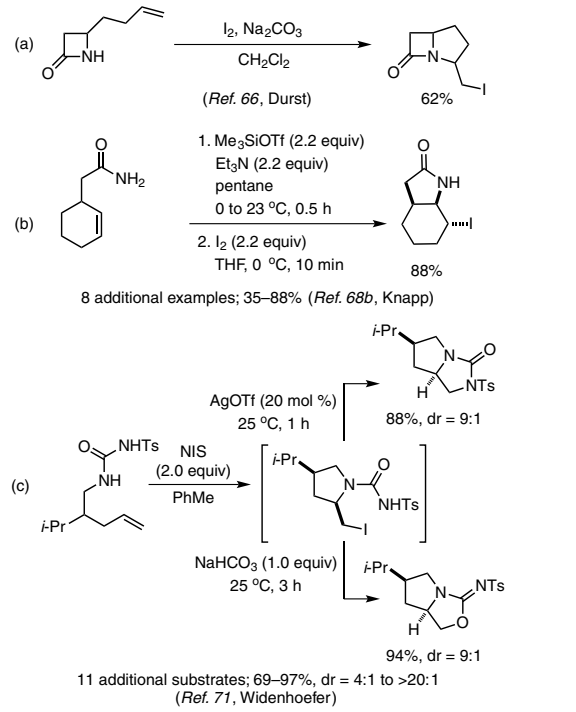
4.1. Racemic Halolactamizations and Haloaminations

The initial demonstration of halolactamization came from Durst, who circumvented the core reactivity problem by reacting 4-homoallyl-β-lactams with I_2 and Na_2CO_3 in CH_2Cl_2 (**Scheme 8**, Part (a));[66] indeed, for this geometrically constrained system, the oxygen atom simply cannot reach the pendant iodonium ion, resulting in a nitrogen-cyclized product. Ganem presented the first general solution in 1982, a result predicated on the fact that *N*-tosylamides cyclized via nitrogen, a consequence attributed to the increased electronegativity of the sulfonylated nitrogen atom.[67] Additional approaches include one developed by Knapp in the 1980s that relied on silylation of both the oxygen and nitrogen of an amide in situ, followed by addition of I_2 (see Scheme 8, Part (b)).[68] The resultant cyclization through nitrogen formed halolactams in moderate-to-good yields. In addition to amide modification, non-amide starting materials, including thioimidates[69] and oxazolines,[70] were shown by a number of groups to be capable of cyclizing to iodolactam products.

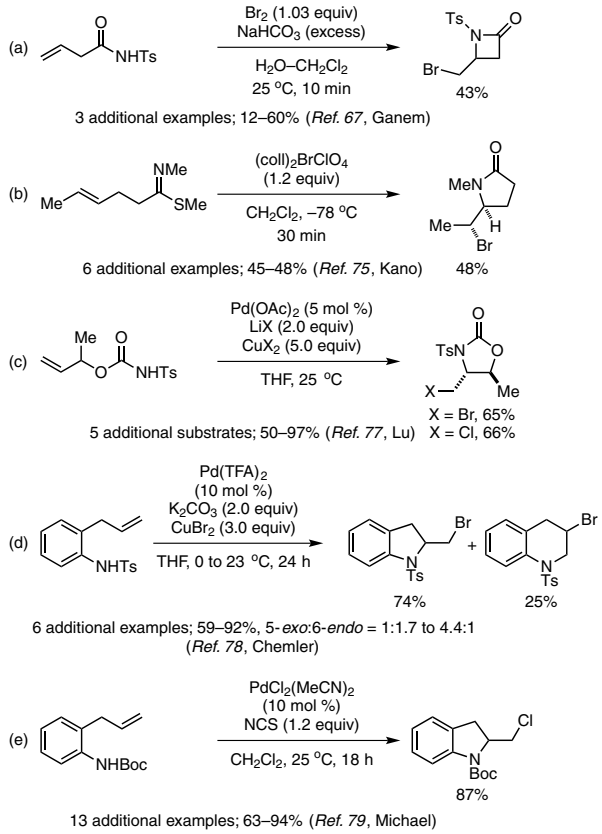
More recently, Li and Widenhoefer enacted double cyclizations by treating *N*-tosylureas with NIS in the presence of $NaHCO_3$ to produce bicyclic isoureas (see Scheme 8, Part (c)).[71] Interestingly, when AgOTf was added in lieu of $NaHCO_3$, bicyclic ureas were formed in good yields, a result presumably derived from the enhanced hardness of the electrophile under these conditions. Finally, nitrogen-terminated iodocyclization has been extended to include amine nucleophiles. In 1999, Kitagawa and Taguchi showed that allylic *N*-tosylamines, upon treatment with I_2 and KO*t*-Bu, form aziridines in good yields.[72] A second approach for cyclizing pendant amines was formulated by Barluenga's group using *ortho*-alkynylanilines in conjunction with Py_2IBF_4–HBF_4 to produce 3-iodoindoles.[73]

The application of many of these concepts has enabled the successful development of both bromo- and chlorolactamizations. The first of these reactions was pioneered by Ganem's group using the same *N*-tosylamides described above for iodolactamization (**Scheme 9**, Part (a)).[67] A few years later, Rajendra and Miller published a similar approach which utilized *O*-acyl hydroxamates rather than *N*-tosylamides,[74] with the advantage here being that cyclization (as achieved with Br_2 and K_2CO_3 in MeCN) generally provided products in higher yields than Ganem's approach. As a final example in terms of substrate variation, Kano and co-workers showed that unsaturated thioimidates were also appropriate for bromolactamization (see Scheme 9, Part (b)).[75]

Several alterations of the electrophilic halogen source have also been explored. Brinkmeyer was the first to use NBS to cyclize both ureas and heteroaromatic-substituted amides in 1989,[76] while Kano's approach (vide supra) utilized $(coll)_2BrClO_4$.[75] More recently, Lu's research group showed that bromolactamization could also be achieved when carbamates and ureas were exposed to stoichiometric $CuBr_2$ and LiBr (see Scheme 9, Part (c)) in the presence of catalytic $Pd(OAc)_2$.[77] The particular value of this discovery is that it could be readily adapted to achieve chlorolactamization simply by using stoichiometric $CuCl_2$ and LiCl. Simultaneously, Chemler and co-workers published a catalyzed intramolecular bromoamination procedure that utilized



Scheme 8. Selected Iodolactamization Reactions.



Scheme 9. Selected Bromo- and Chlorocyclizations Terminated by Nitrogen Nucleophiles.

N-tosyl *ortho*-allylanilines to form a mixture of 5-*exo*- (indoline) and 6-*endo*- (tetrahydroquinoline) cyclization products in the presence of catalytic $Pd(TFA)_2$ and stoichiometric $CuBr_2$ (see Scheme 9, Part (d)).[78] Similarly, palladium catalysis enabled Michael's research group to treat *N*-Boc *ortho*-allylanilines with stoichiometric NCS and effect chloroaminations via a 5-*exo* cyclization (see Scheme 9, Part (e)).[79]

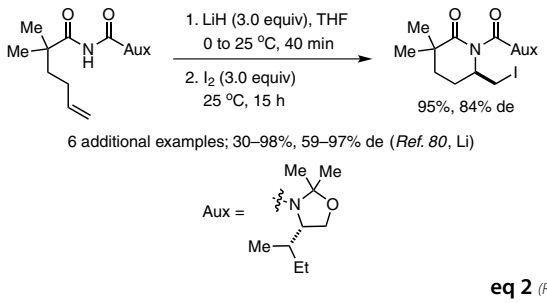
4.2. Asymmetric Halolactamizations and Haloaminations

To date, only a single enantioselective halolactamization procedure is known. In this work, an acyclic imide appended with an oxazolidine chiral auxiliary could, upon deprotonation with LiH followed by I_2 addition, yield cyclic imides in good yields and moderate-to-excellent de's (**eq 2**).[80] As these studies revealed, the effectiveness and selectivity of this reaction process are highly dependent on the identity of the base and probably involve coordination of the lithium counterion to both oxygen atoms of the imide to organize a rigid transition state. Hopefully, this precedent will inspire solutions for related processes as well as true reagent-controlled ones.

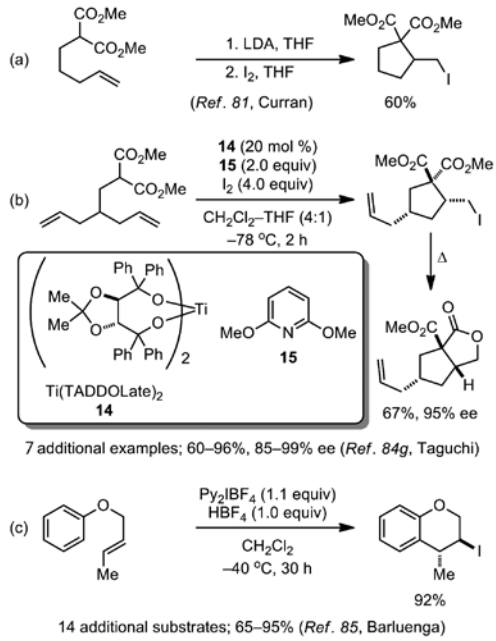
5. Halocarbocyclization Reactions

In addition to the heteroatom nucleophiles discussed so far, a number of halogen-induced cyclizations have been developed in which the halonium intermediate is quenched intramolecularly by a carbon nucleophile. The vast majority of these "halocarbocyclization" reactions are iodination reactions where the nucleophile is a malonate. The seminal example of this process was actually a fortuitous discovery by Curran and Chang in 1989: their attempted α-iodination of dimethyl 4-pentenylmalonate using LDA and I_2 produced instead a cyclic product in 60% yield (**Scheme 10**, Part (a)).[81] Cossy and Thellend followed up on this discovery a year later, expanding the substrate scope for this new cyclization reaction.[82] Stereochemical and mechanistic investigations followed later from Beckwith and Tozer,[83] who determined that the mechanism was likely an ionic one featuring intramolecular attack of the malonate anion onto a pendant iodonium. Further studies from Taguchi's laboratory resulted in enhanced results through the use of titanium Lewis acids—including chiral titanium complexes for enantioselective reactions (see Scheme 10, Part (b))—as well as additives such as nitrogen bases or CuO.[84,72]

Outside of malonates, the majority of the remaining examples of halocarbocyclization utilize electrophilic aromatic substitution onto a halonium ion to form halogen-substituted, fused aromatic ring systems. Only certain reagents, however, have the power to effect this transformation. Among the premier conditions are Barluenga's reagent combination (Py_2IBF_4 with 1 equivalent of HBF_4; Scheme 10, Part (c))[85] as well as systems utilizing NIS or NBS in concert with catalytic $Sm(OTf)_3$. This latter reagent combination enables access to iodinated or brominated tetrahydronaphthalenes, as well as dihydronaphthalenes and chromans.[86]



eq 2 *(Ref. 80)*



Scheme 10. Selected Iodocarbocyclization Reactions.

6. Halonium-Induced Polyene Cyclizations

The preceding sections of this review have dealt with halocyclization processes that are, for the most part, well-studied, and for which a number of successful protocols have been developed; in many instances, catalytic and/or enantioselective processes exist to form the desired products.[87] This review will conclude by discussing halonium-induced polyene cyclizations, a reaction class that might constitute the last major frontier for halonium-induced, intramolecular functionalizations. Indeed, until the recent introduction of three reagents (CDSC, BDSB, and IDSI; see Section 6.2), no earlier system could broadly effect racemic versions of this process, let alone catalytic or enantioselective variants.

6.1. Using Classical Reagents

Iodine-induced polyene cyclizations are reactions that are few and far between in the literature. The inaugural example of the process came in 1977, when Günther, Jäger, and Skell utilized molecular I_2 in CCl_4 to cyclize 4,4-dimethyl-1,6-heptadiene; this cyclization failed completely without the intervening *gem*-dimethyl group.[88] This example remained the only published report until 1988, when Barluenga and co-workers made the critical discovery that Py_2IBF_4–HBF_4 was capable of promoting polyene cyclizations of substrates without such geminal substitution.[85a] Sixteen years later, a second report from the same group illustrated several more examples, including the first terpene-like substrates such as the one shown in **Scheme 11**, Part (a).[85b] Finally, Ishihara's group has presented the first and only enantioselective iodocyclization of polyenes.[89] Their method utilizes NIS and stoichiometric amounts of chiral phosphoramidite nucleophile **16** to afford materials in up to 95% ee (see Scheme 11, Part (b)), though the yields of fully cyclized products are low (below 50%) unless a second and separate acid-mediated step is performed. It is important to note

with all these cases that the substrates include only electron-rich alkenes; no electron-deficient substrates were demonstrated to work under any conditions.

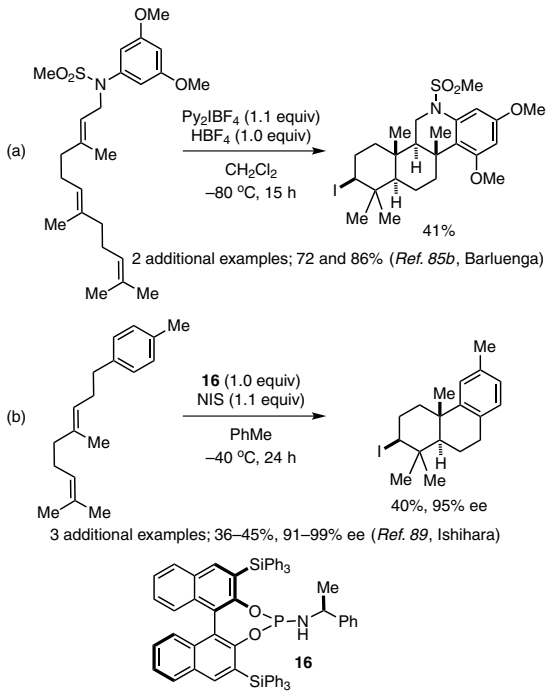
In contrast to iodonium-induced polyene cyclizations, the bromine variant has been studied far more thoroughly, likely as a consequence of the existence of dozens of cyclic brominated terpenoid natural products.[90] The first report of bromonium-induced polyene cyclization came from van Tamelen and Hessler who, in 1966, illustrated that NBS could facilitate cyclization of methyl farnesate to a mixture of bicyclic alkenes in 5% overall yield (**Table 3**, entry 1).[91] Improvements to the NBS-catalyzed cyclization came with the addition of $Cu(OAc)_2$ to provide a monocyclic product from the same starting material in slightly higher yield (entry 2),[92] as well as the addition of catalytic PPh_3 (entry 3) to provide an aryl-terminated product in moderate yield.[89] Polyene cyclizations initiated by Br_2 are scarce and low-yielding, as illustrated by the three examples in entries 4–6, wherein the necessary addition of Lewis acids used to enhance the electrophilicity of bromine and sequester the bromide counterion (so it can serve neither as base nor nucleophile to afford unwanted side-products) still resulted in low yields of the desired materials.[93] A major advancement in the field of bromine-induced polyene cyclization came with the disclosure of TBCO in 1975 by Kato's group.[94] This unique reagent has been used for a number of polyene cyclizations (entries 7, 8, 10),[95] although generally in low-to-moderate yields. TBCO completely fails to cyclize electron-deficient alkenes unless activated further by $AlBr_3$ (compare entries 9 and 10), and even then this combination of reagents affords cyclic products only in very low yields.[94] In fact, this method and the use of Br_2 in the presence of silver or tin Lewis acids are the only two protocols capable of cyclizing substrates containing electron-withdrawing groups situated near the participating alkenes, and both procedures result in very low yields of products.

Finally, to the best of our knowledge, chlorine-induced polyene cyclizations were unknown in the literature prior to the disclosure of the reagents described in the next section. There are few examples of atom-transfer radical cyclizations that result in chlorinated carbocyclic products,[96] but none rely on electrophilic activation of an alkene followed by subsequent cation-π cyclization.

6.2. Using XDSX Reagents

In 2009, our group published a communication disclosing a novel brominating reagent, **B**romo**D**iethyl**S**ulfonium **B**romopentachloroantimonate (or BDSB, **Figure 1**).[97] This air-stable crystalline solid can be prepared in high yield and on a very large scale[98] from Br_2, Et_2S, and $SbCl_5$, and is stable at –20 °C for at least a year. Subsequently, we disclosed the synthesis of CDSC and IDSI (see Figure 1), the analogous chlorine- and iodine-derived compounds, which are similarly air-stable crystalline solids (although IDSI is somewhat less stable, tending to slowly give off ICl, presumably due to its more complicated dimeric structure).[99]

All three reagents proved capable of broadly effecting halonium-initiated polyene cyclization reactions as indicated by the selected examples shown in **Table 4**. Chlorocyclizations (entries 1, 7, 10, and 13) proceeded in much lower yield than the analogous bromo- or iodocyclization reactions, likely due to the much higher reactivity of this halogen; nevertheless, these examples constitute the first such cyclizations achieved without the use of an enzyme. For bromo- and iodocyclizations, BDSB and IDSI proved capable of cyclizing a wide variety of



Scheme 11. Selected Iodonium-Induced Polyene Cyclization Reactions.

geraniol, nerol, and farnesol-derived substrates in moderate-to-excellent yields. Especially notable, these reagents cyclized polyenes with electron-withdrawing groups such as carboxylic acids, esters, and nitrile groups (entries 1–12), which have historically been very difficult or impossible to cyclize utilizing other electrophilic halogenation reagents. In fact, even the very electron-poor alkene of an α,β-unsaturated ester proved capable of participating in an IDSI-induced cyclization (entry 18), a feat never before demonstrated in any halogen-induced polyene cyclization. Although in some cases diastereomeric mixtures of products were formed, for the most part the cyclizations were highly diastereoselective (compare entries 2 and 4), providing the products expected from an all-chair transition state during the cyclization process, in line with the Stork–Eschenmoser hypothesis.[100] Reactions have also been performed on gram-scale (entry 14) with no appreciable decrease in reaction efficiency, as long as they are conducted at suitably dilute concentrations (a general feature of all cation-π reactions).[98]

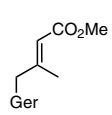
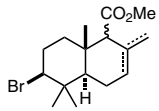
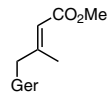
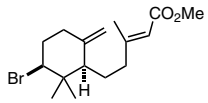
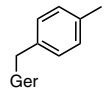
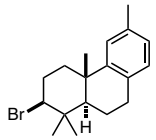
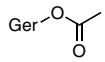
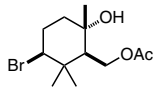
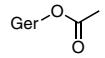
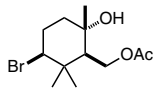
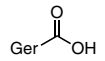
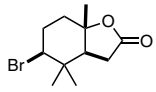
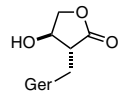
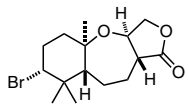
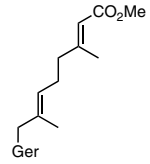
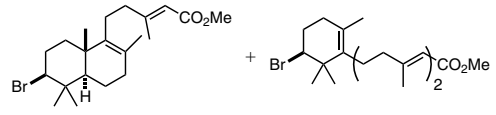
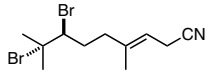
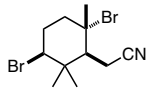
Given these advantages, the true utility of these new reagents lies in the realm of total synthesis. Indeed, BDSB was utilized in the key step in the synthesis of each of the three natural products shown in **Scheme 12**, noting that a previous synthesis of 4-isocymobarbatol used the same cyclization initiated by TBCO, giving the protected natural product in 35% yield.[95i] In addition to the molecules shown in Scheme 12, BDSB and IDSI were used in the formal synthesis of four other natural products; in all cases but one providing the necessary cyclized intermediates in fewer steps and significantly higher yields than those previously reported. In fact, in more than one instance, IDSI behaved as a replacement for electrophilic mercury(II) salts, highly toxic species which have historically proven necessary for achieving complex polyene cyclizations in previously published syntheses. Moreover, Krauss and co-workers have recently utilized BDSB to effect a bromonium-induced transannular cyclization within a 19-membered ring; although the yield for this process was

modest, no other reagent afforded the desired product.[101] Finally, chiral analogues of the XDSX reagents were briefly investigated for these processes, but have not yet been found to produce enantioenriched products, leaving an open challenge for future development. However, these reagents have recently been found to promote a number of other processes outside halonium-induced cyclization of value. For example, BDSB recently effected a highly positionally selective electrophilic aromatic substitution that other reagents did not achieve as part of a drive to prepare a number of complex, resveratrol-derived oligomers.[102]

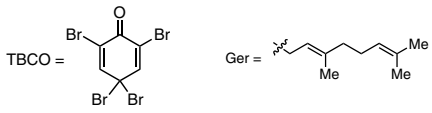
7. Conclusion

For well over a hundred years, organic chemists have utilized electrophilic halocyclization reactions to produce valuable synthetic intermediates as well as complex natural products. During this time, our understanding of these reactions has grown, as have the number of methods developed for undertaking them. The concentrated efforts of, and results from, dozens of research groups throughout the world have culminated in a number of catalytic and/or asymmetric protocols for some halocyclizations. However, as evidenced by the large number of recent high-profile

Table 3. Selected Bromonium-Induced Polyene Cyclizations prior to 2009 and the Introduction of BDSB.

Entry	Starting Material	Conditions	Product	Yield	Ref.
1		NBS, THF–H_2O	 (1:1)	5%	*91*
2		NBS, $Cu(OAc)_2$ *t*-BuOH–HOAc		12%	*92*
3		NBS, Ph_3P, CH_2Cl_2 –78 to –40 °C, 30 h		50%[a]	*89*
4		Br_2, $AgBF_4$ anhyd. $MeNO_2$ 0 °C, 10 min		20%	*93a*
5		Br_2, $SnBr_4$ anhyd. $MeNO_2$ –10 °C		16%	*93a*
6		Br_2, $AgBF_4$, anhyd. $MeNO_2$ –10 °C, 20 min		11%	*93b*
7		TBCO anhyd. $MeNO_2$ 20 °C, 2 h		10%	*95c*
8		TBCO anhyd. $MeNO_2$ –20 °C to 25 °C	 25% 49%		*95f*
9		TBCO CH_2Cl_2, 25 °C		98%	*95b*
10		TBCO, $AlBr_3$ anhyd. CH_2Cl_2 0 °C, 1 h		15%	*94*

[a] Percent conversion.

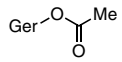
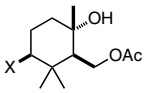
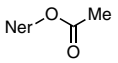
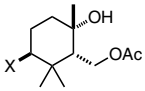
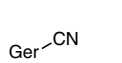
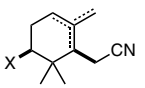
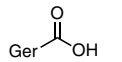
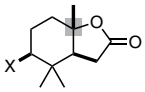
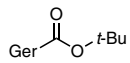
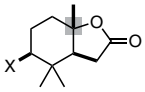
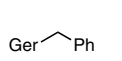
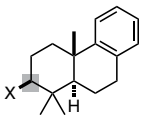
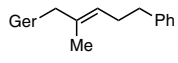
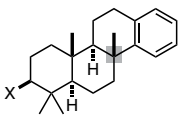
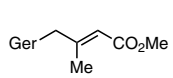
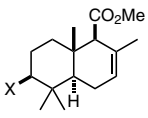


publications dealing with such reactions in various formats, it is clear that there remain many interesting problems to be solved. Our hope is that this review will help to inspire solutions to some of these remaining challenges, furthering the potential of these reactions to reach newer and greater heights of molecular complexity.

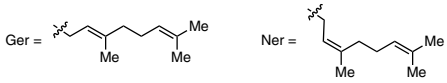
8. Acknowledgements

Our research in the area of halocyclizations has been generously supported by grants from the National Science Foundation (CAREER-0844593, Predoctoral Fellowships to D.S.T. and A.P.B.), the Camille and Henry Dreyfus Foundation (New Faculty Award to S.A.S.), Eli Lilly (New Faculty and Grantee Awards to S.A.S.), and Bristol-Myers Squibb (2011 Unrestricted Grant in Synthetic Organic Chemistry to S.A.S.). S.A.S. is a Fellow of the Alfred P. Sloan Foundation.

Table 4. Selected Halonium-Induced Polyene Cyclizations using CDSC, BDSB, and IDSI. *(Ref. 97,99,* Snyder*)*

Entry	Starting Material	Product	X	Yield
1			Cl	18%[a]
2			Br	84%[b]
3			I	45%
4			Br	71%
5			Br	73%
6			I	85%
7			Cl	38%[c]
8			Br	73%
9			I	79%[d]
10			Cl	20%[c]
11			Br	79%
12			I	88%
13			Cl	46%[e]
14			Br	75%[f]
15			I	93%
16			Br	58%[g]
17			I	60%[g,h]
18			I	77%

[a] Isolated as a 2.2:1 mixture of diastereomers at the chlorinated carbon. [b] Isolated as a 5:1 mixture of diastereomers at the tertiary alcohol carbon. [c] Isolated as a 4:1 mixture of diastereomers at the highlighted carbon. [d] Isolated as a 19:1 mixture of diastereomers at the highlighted carbon. [e] Isolated as a 1:1 mixture of diastereomers at the highlighted carbon. [f] 72% yield on a gram scale (*Ref. 98*). [g] Excess CH_3SO_3H added to reaction mixture to enhance yield of tetracyclic product. [h] Isolated as a 2:1 mixture of diastereomers at the highlighted carbon.



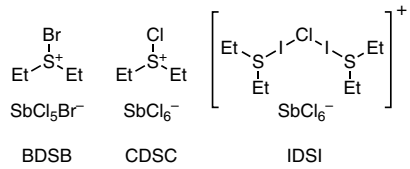


Figure 1. Structure and Appearance of BDSB, CDSC, and IDSI. *(Ref. 97–99,* Snyder*)*

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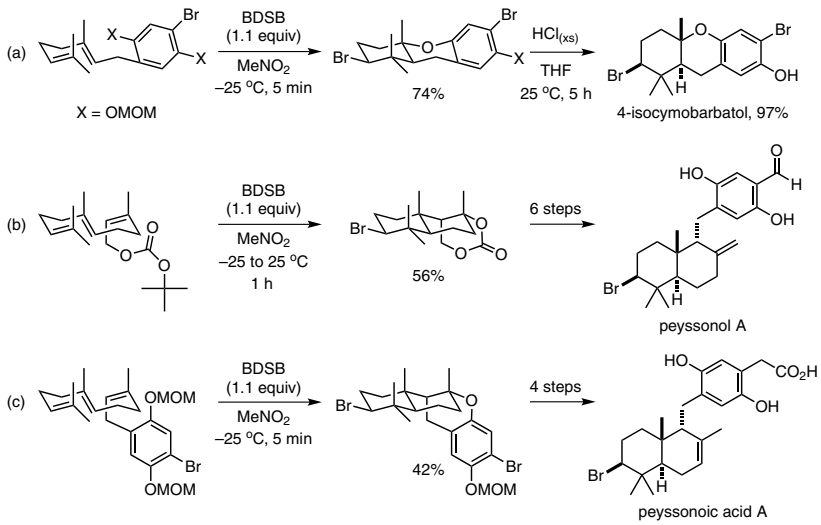

Scheme 12. Natural Products Synthesized using BDSB in the Key Bromocyclization Step. *(Ref. 97,99,* Snyder*)*

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Scott A. Snyder pursued his undergraduate education at Williams College, Williamstown, MA. He obtained his Ph.D. with Professor K. C. Nicolaou at The Scripps Research Institute, during which time he co-authored *Classics in Total Synthesis II*. Scott then trained as an NIH postdoctoral fellow with Professor E. J. Corey at Harvard University. Since August of 2006, he has been an assistant professor of chemistry at Columbia University, where his group is exploring chemical space through the total synthesis of natural products. Recent honors include a Camille and Henry Dreyfus New Faculty Award, an Eli Lilly Grantee Award, an NSF CAREER Award, a Cottrell Scholar Award, a Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry, the DuPont Young Professor Award, and a Columbia University Presidential Teaching Award.

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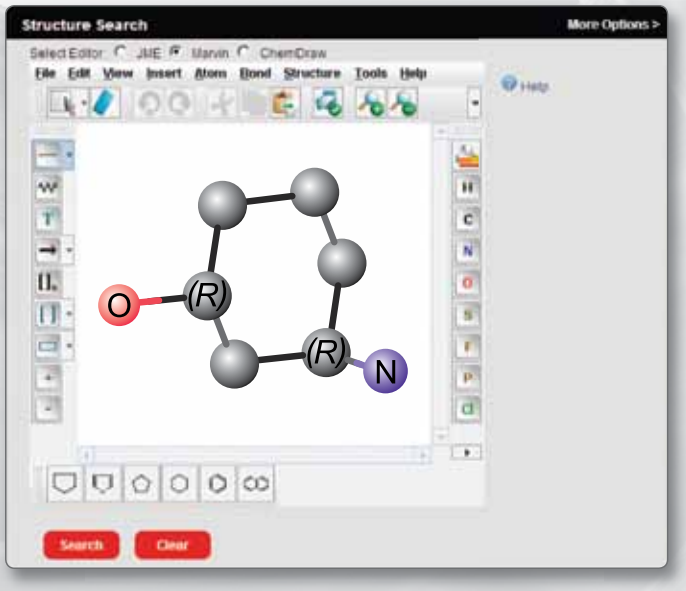

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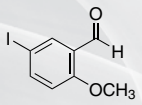

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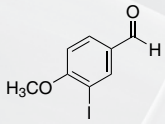

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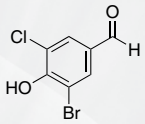

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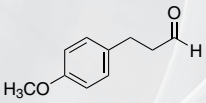

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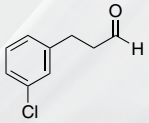

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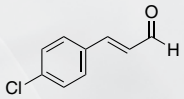

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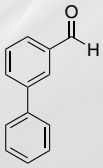

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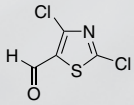

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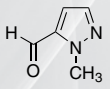

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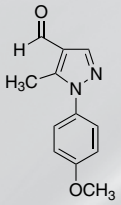

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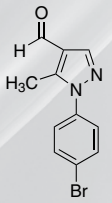

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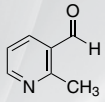

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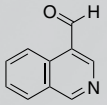

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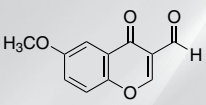

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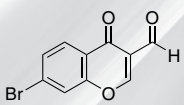

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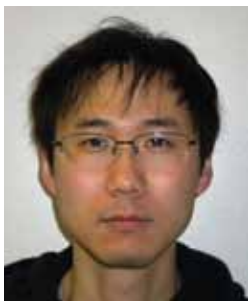
The A^3-Coupling (Aldehyde–Alkyne–Amine) Reaction: A Versatile Method for the Preparation of Propargylamines



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Keywords. metal catalysis; multicomponent coupling; tandem reactions; asymmetric synthesis; propargylamines.

Abstract. This review highlights recent developments in the preparation of propargylamines through the metal-catalyzed, three-component coupling reaction between aldehydes, alkynes, and amines (A^3 Coupling).

Outline

1. Introduction

Propargylamines are versatile intermediates for the preparation of various nitrogen-containing compounds and are key components of biologically active pharmaceuticals and natural products.[1] Traditionally, propargylamines have been prepared through addition of metallated alkynes to C=N electrophiles. Due to the relatively weak acidity of the sp-hybridized C–H bonds of terminal alkynes, various strong bases such as alkylmetals, metallated amides, alkoxides, and hydroxides have been utilized to generate the desired metallated alkyne.[2] However, these metal alkynylides are relatively difficult to handle, and their reactions must be conducted under anhydrous conditions and low temperatures.

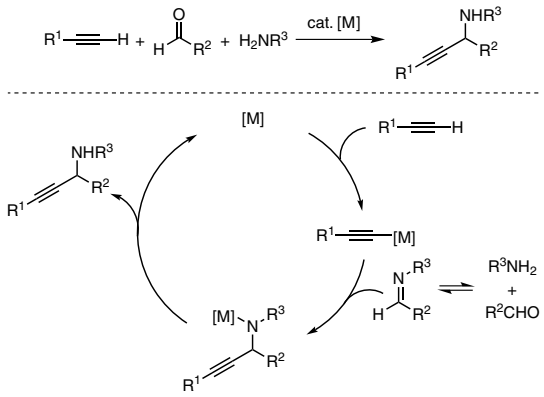
An alternative to stoichiometric metallated alkynes is the use of catalytic quantities of late transition metals. These metals are well known to form π complexes with terminal alkynes, thereby increasing the acidity of the C–H bond. This increased acidity allows weakly basic amines to deprotonate the C–H bond and generate the desired organometallic alkynyl nucleophile.[3] Addition of this metal alkynylide to imines, generated in situ, and subsequent protonation regenerates the metal for another reaction cycle. This multicomponent reaction sequence represents the most direct and efficient method for preparing propargylamines, and is commonly referred to as the A^3-coupling (aldehyde–alkyne–amine) reaction (**Scheme 1**).[4]

The aim of this review is to present and discuss recent significant developments in propargylamine synthesis through the nucleophilic addition of terminal alkynes to imines and their derivatives.

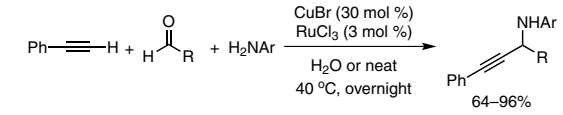
2. Alkynylation of Aldimines Derived from Primary Amines

The direct 1,2 addition of alkynes to imines provides a convenient and rapid access to propargylamines in a single, simple operation. However, unlike activated C=N electrophiles such as nitrones and iminium ions, secondary aldimines are less reactive due to their lower electronegativity[5] and the stronger coordination between the metal catalyst and the propargylamine product as compared to its coordination with the starting aldimine.[4] Although these aldimines can be activated with the appropriate electronegative substituents on the nitrogen atom, such as in *N*-tosyl-, *N*-acyl-, and *N*-phosphinoylimines, the alkynylation of imines is generally difficult and the application of transition-metal catalysis to this process is comparatively restricted. However, the use of co-catalysts, microwave irradiation, suitable ligands, or strong electron-withdrawing aldehydes allows the desired 1,2-addition reaction of alkynes to imines to take place.

Our group reported the first examples of a three-component coupling reaction between a primary amine, an aromatic aldehyde, and phenylacetylene by utilizing $RuCl_3$ and CuBr as co-catalysts under neat or aqueous conditions (**eq 1**).[6a] Independently from our work, Ishii[6b] and Carreira[6c] reported an $[Ir(cod)Cl]_2$-catalyzed addition of trimethylsilylacetylene (TMSC≡CH) to imines in moderate yields under anhydrous conditions and inert atmosphere. Similarly, Kuninobu, Inoue, and Takai reported a $[ReBr(CO)_3(thf)_2]_2$–CuCl catalyst system that was utilized to prepare propargylamines (**Scheme 2**).[7] Although both rhenium

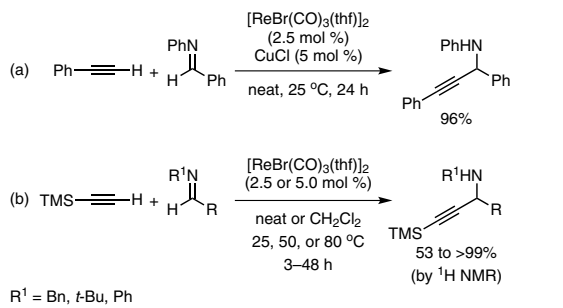


Scheme 1. Generalized Mechanism of the A³-Coupling Reaction. *(Ref. 4)*



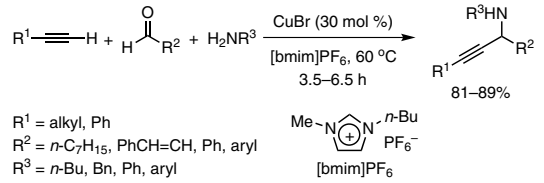
Ar = Ph, 4-XC_6H_4 (X = Me, Cl, Br)
R = *t*-Bu, Ph, 1-Np, 3-XC_6H_4 (X = Cl, Br), 4-XC_6H_4 (X = Me, *t*-Bu, Ph, CF_3, Cl, Br)

eq 1 *(Ref. 6a)*



R^1 = Bn, *t*-Bu, Ph
R = *n*-$C_{10}H_{21}$, Cy, *t*-Bu, (*E*)-PhCH=CH, Ph, 4-XC_6H_4 (X = MeO, CF_3, Br), 2-Fur

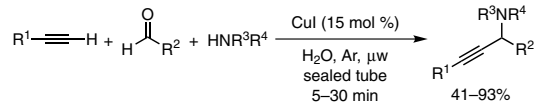
Scheme 2. Rhenium-Catalyzed 1,2 Addition of Alkynes to Imines. *(Ref. 7)*



R^1 = alkyl, Ph
R^2 = *n*-C_7H_{15}, PhCH=CH, Ph, aryl
R^3 = *n*-Bu, Bn, Ph, aryl

[bmim]PF_6

eq 2 *(Ref. 8)*



R^1 = *n*-C_5H_{11}, TBSOCH$_2$, Ph, TMS
R^2 = *n*-Pr, Cy, Ph, 1-Np, 2-XC_6H_4 (X = F, Cl)
4-XC_6H_4 (X = Me, MeO, Cl, Br, NO_2), 2-Fur
R^3,R^4 = Et,Et; *i*-Pr,*i*-Pr; Cy,Cy; Ph,Ph; Me,Bn; Ph,H; *t*-Bu,H
R^3,R^4NH = pyrrolidine, piperidine, morpholine

eq 3 *(Ref. 9)*

and copper were found to be critical for the alkynylation reaction when PhC≡CH was employed, $[ReBr(CO)_3(thf)_2]_2$ alone catalyzed the 1,2-addition reaction when trimethylsilylacetylene was substituted for phenylacetylene.

While the use of co-catalysts can greatly aid in the 1,2 addition of alkynes to imines, single-catalyst systems have been successful under certain conditions. For example, utilizing ionic liquids as solvents, the A³ coupling of primary amines occurs under mild conditions with copper(I) salts (**eq 2**).[8] While ionic liquids are useful as green solvent media, the imidazole-based ionic liquid can also play a second role as a carbene ligand to the copper catalyst under basic conditions.

Several groups (Tu,[9] Zhu,[10] and van der Eycken[11]) have reported highly efficient and widely applicable CuX (X = Cl, Br, I) catalyzed A³-coupling reactions involving primary and secondary amines under microwave irradiation in water, toluene, or solvent-free conditions. The vast majority of these reactions were completed in 25 minutes or less, and yields ranged from moderate to excellent. One example is featured in **eq 3**; in this case, it was necessary to carry out the reaction in a sealed tube to avoid low conversions and formation of byproducts.[9]

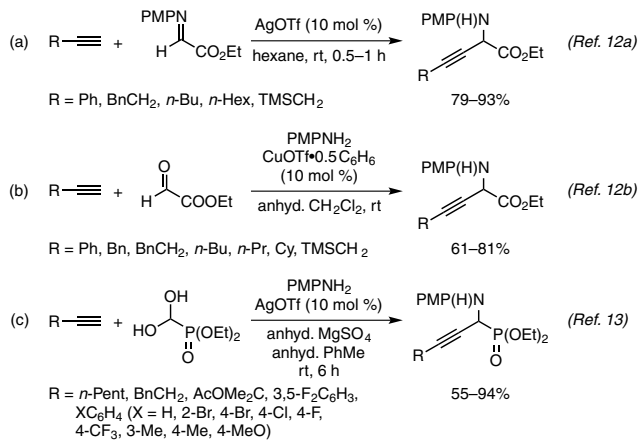
Finally, the reactivity of the aldimine in the 1,2-addition reaction can be improved by increasing its electrophilicity through the incorporation of a strong electron-withdrawing functional group into the aldehyde. Chan[12] and Zhao[13] have disclosed that the use of ester- or phosphonate-bearing aldehydes allows the A³-coupling reaction to occur under mild conditions (**Scheme 3**).[12,13]

3. Alkynylation of Aldimines Derived from Secondary Amines

The A³ coupling is relatively easier and can be performed under milder conditions with secondary than with primary amines. This is attributed mainly to the fact that iminium ions, derived from secondary amines, are much more electrophilic than their (neutral) imine counterparts that are derived from primary amines. Thus, various mid- and late-transition metals have been shown to catalyze the A³-coupling reaction of secondary amines.

3.1. Copper Catalysts

Copper(I) complexes are by far the most extensively utilized catalysts for the A³-coupling reaction with secondary amines. Although copper in the +1 oxidation state represents the vast



Scheme 3. A³-Coupling Reactions of Aldehydes Bearing Electron-Withdrawing Substituents.

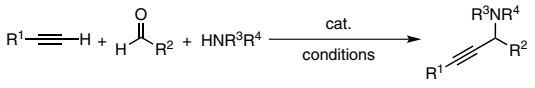
majority of examples of this multicomponent coupling reaction, a few reports have disclosed the use of Cu(II) as catalyst. In terms of Cu(I), various simple and inexpensive copper halides (CuCl,[14] CuBr,[15] and CuI[16]) have been reported as catalysts. Recent advances in this field have included the development of recovery and reuse strategies through immobilization of the copper catalyst or through the use of recyclable solvents. Park and Alper employed Cu(I) complexes in ionic liquids to catalyze the alkynylation reactions with good yields and over 5 recovery and reuse cycles (**Table 1**, entry 1).[17] Polyethylene glycol (PEG) can also be utilized as a cheap alternative to traditional organic solvents in the A^3-coupling reaction and allows the use of CuI as catalyst over 5 cycles without loss of activity (entry 2).[18] In 2007, Li and Wang described an efficient and reusable heterogeneous Cu(I) organic–inorganic composite material (SiO_2-CHDA-Cu^I) for the A^3-coupling reaction under solvent-free conditions (entry 3).[19] The immobilized copper catalyst was easily recycled without leaching of copper, as determined by Inductively Coupled Plasma (ICP) analysis. Likhar and co-workers reported that an imine-functionalized copper complex immobilized on silica (SiO_2-Py-CuI) is an effective catalyst for the A^3-coupling reaction in MeCN at 90 °C (entry 4).[20] This catalyst system was quantitatively recovered from the reaction medium by simple filtration, and was reused several times without loss of catalytic activity. In 2008, Lei Wang and co-workers prepared a silica-supported complex of Cu(I) and an N-heterocyclic carbene (NHC) (SiO_2-NHC-Cu^I) and used it to achieve high yields in the A^3-coupling reaction (entry 5).[21] Examples of heterogeneous supports other than silica (entry 6)[22] for immobilizing the copper metal include: (i) molecular sieves (entry 7),[23] (ii) magnetite (entry 8),[24] and (iii) zeolites (entry 9).[25] In all cases, the scope of the A^3-coupling reaction was relatively good with respect to dialkyl and alkyl aryl secondary amines. However, diarylamines were found to be poor substrates. With respect to the aldehyde, both aromatic and aliphatic aldehydes were effective partners. However, the reaction did not proceed when strong electron-withdrawing substituents were present at the para position of the aromatic aldehydes. For the alkyne component, both aliphatic and aromatic terminal alkynes successfully underwent the A^3-coupling reaction.

3.2. Silver and Gold Catalysts

Since the first report by Li and co-workers on the use of AgI as catalyst for the A^3-coupling reaction,[26] similar uses of silver in the form of nanoparticles have been disclosed.[27] The advantage of silver nanoclusters is a low catalyst loading and the ease with which the catalyst can be recycled.

Li's group also reported the first example of a $AuBr_3$-catalyzed alkynylation of iminium ions.[28] In the same report, AuCl, AuI, and $AuCl_3$ were also shown to be viable catalysts for the A^3-coupling reaction. In 2006, Li and co-workers disclosed that gold catalyzes the A^3-coupling reaction of α-oxyaldehydes, providing the products with modest diastereoselectivities (**eq 4**).[29] They also found that gold was key in achieving success as other coinage metals were ineffective in the alkynylation reaction. Wong, Che, and co-workers have reported a Au(III)salen complex as a catalyst for the alkynylation of iminium ions generated from enantiopure cyclic amino acid derivatives (**eq 5**).[30] The multicomponent coupling reaction was highly diastereoselective (up to 99:1) and was effective in alkynylating iminium ions containing delicate endoperoxide moieties (**eq 6**).[30] The same group prepared the gold complex [Au(C^N)Cl_2] (N^CH = 2-phenylpyridine) and illustrated its use as an efficient catalyst for the A^3-coupling reaction.[31] Once again, high diastereoselectivity was demonstrated with chiral cyclic amino acid derivatives. In

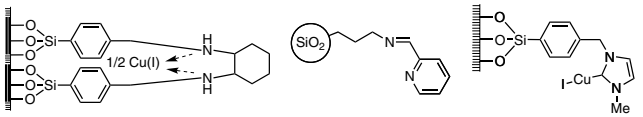
Table 1. Reuse and Recovery Systems Employed in the A^3 Coupling of Secondary Amines



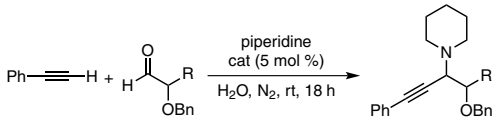
R^1 = aryl, alkyl; R^2 = aryl, alkyl, H; R^3,R^4 = alkyl, alkyl; alkyl, aryl

Entry	Catalyst	Conditions	Yield	Cycles[a]	Ref.
1	CuCN (2 mol %)	[bmim]PF_6, 120 °C, 2 h	54–98%	5	*17*
2	CuI (10 mol %)	PEG-400, 100 °C, 12 h	85–96%	5	*18*
3	silica-CHDA-Cu(I)	neat, 80 °C, 12 h	82–99%	15	*19*
4	SiO_2-Py-CuI (5 mol %)	MeCN, 90 °C, N_2	54–93%	5	*20*
5	SiO_2-NHC-Cu(I) (2 mol %)	neat, rt or 70 °C, 24 h	43–96%	10	*21*
6	●–$(CH_2)_3SO_3CuCl$ (0.05 mol %)	H_2O, reflux, 8–24 h	52–98%	4	*22*
7	Cu(II)–4 Å MS	PhMe, reflux, 15 h	40–99%	3	*23*
8	$Cu(OH)_x$–Fe_3O_4 (0.1 mol %)	neat, 120 °C, 3 h	39 to >99%	10	*24*
9	CuI–USY zeolite (~8 mol % Cu(I))	neat, 80 °C, 15 h	55–90%	5	*25*

[a] Number of times the recycled catalyst was used without loss of activity.



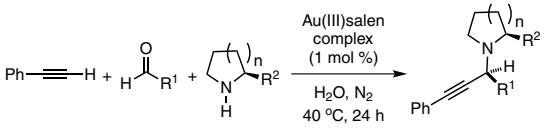
silica-CHDA-Cu *(Ref. 19)* | SiO_2–Py *(Ref. 20)* | SiO_2-NHC-Cu(I) *(Ref. 21)*

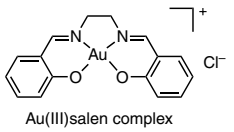


R	Cat	Yield	dr
Me	AuI	69%	50:50
Cy	AuI	70%	65:35
n-Pent	AuI	93%	73:27
n-Pent[a]	$AuBr_3$	94%	68:32
n-Pent[a]	AuCl	89%	64:36
n-Pent	AuCl	89%	72:28

[a] At 60 °C.

eq 4 *(Ref. 29)*



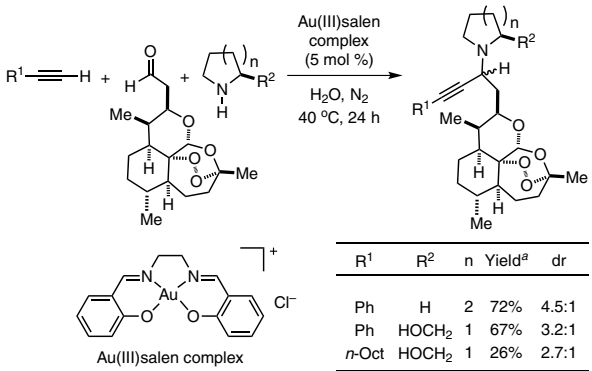


Au(III)salen complex

R^1	n	R^2	Yield	dr
Ph	2	H	94%	----
Cy	2	H	99%	----
Cy	1	H	97%	----
Cy[a]	2	H	90%	----
Ph[b]	1	EtO_2C	67%	84:16
Ph	1	$MeOCH_2$	74%	95:5
Ph	1	$HOCH_2$	82%	99:1
Cy	1	$HOCH_2$	89%	99:1
Ph	1	$HO(Ph)_2C$	83%	99:1

[a] TMSC≡CH used instead of PhC≡CH. [b] Isolated yield based on 59% conversion.

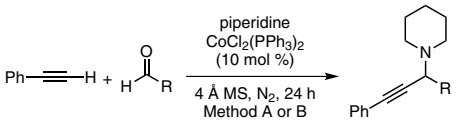
eq 5 *(Ref. 30)*



R¹	R²	n	Yield[a]	dr
Ph	H	2	72%	4.5:1
Ph	$HOCH_2$	1	67%	3.2:1
n-Oct	$HOCH_2$	1	26%	2.7:1

[a] Isolated yields of separable mixtures of diastereomers, each of which displayed cytotoxicity against the HepG2 cell line.

eq 6 *(Ref. 30)*



R	Yield[a] A	B
Ph	91%	90%
4-EtC_6H_4	90%	93%
4-FC_6H_4	96%	96%
Et_2CH	91%	90%
Cy	84%	85%
i-Pr[b]	98%	92%
Ph[b]	98%	86%
Ph[c]	70%	----
Ph[d,e]	70%	----
Ph[f]	65%	56%

[a] Method A: PhMe, 70 °C; Method B: CH_2Cl_2, rt. [b] Bn_2NH used instead of piperidine. [c] Morpholine employed instead of piperidine. [d] At 100 °C. [e] 1-Decylacetylene used instead of PhC≡CH. [f] TMSC≡CH employed insead of PhC≡CH.

eq 7 *(Ref. 43)*

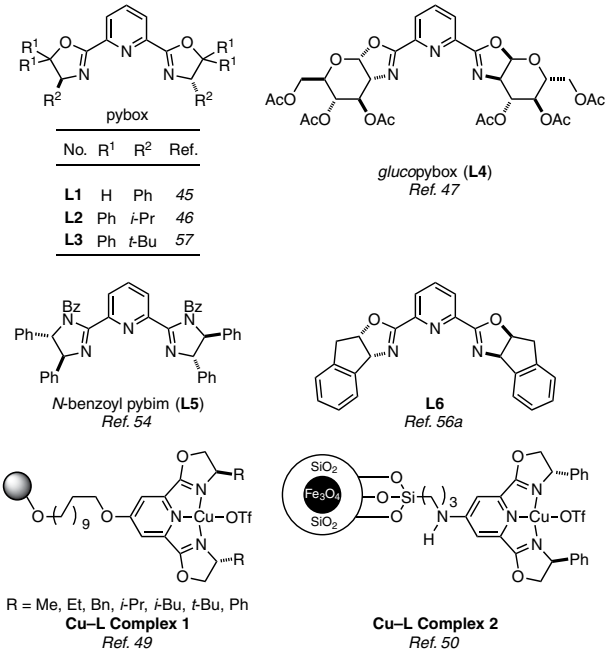


Figure 1. Common Chiral Ligands Employed in Asymmetric A³-Coupling Reactions.

addition, the [Au(C^N)Cl_2] complex effectively catalyzed the alkynylation reaction for 10 successive reaction cycles.

The use of gold nanoparticles as catalysts for the A³ coupling is one example of the growing interest in metal nanocluster catalysis. Kidwai and co-workers reported the first example of gold nanoclusters (16–20 nm)—derived from the reduction of $AuCl_3$ with hydrazine—as an effective catalyst for the A³-coupling reaction.[32] Similarly, Contel's group reported that reaction of gold complexes with water-soluble phosphines resulted in the formation of water-soluble nanoparticles (10–15 nm) that effectively catalyzed the A³-coupling reaction.[33]

Recently, various groups have reported the preparation of immobilized, heterogeneous gold catalysts for the A³ coupling. Kantam and co-workers reported the preparation of Layered Double Hydroxide-supported gold (LDH–$AuCl_4$), and showed its utility in the A³ coupling of secondary amines.[34] Gold nanoclusters immobilized on nanocrystalline CeO_2 and ZrO_2 were successfully employed by Corma's group in the A³-coupling reaction.[35] These heterogeneous catalysts are air-stable and easily recovered and reused. Meanwhile, Ying and co-workers reported a PbS–Au nanocomposite as an efficient heterogeneous catalyst for the multicomponent coupling reaction between aldehydes, alkynes, and amines.[36] Due to the sticky nature of the PdS–Au nanocomposite powder, Ying found it necessary to incorporate a carbon support in order to simplify the handling and recycling of the catalyst.

3.3. Other Metal Catalysts

Recently, metals not belonging to group 11; e.g., Fe, Co, Ni, In, and Zn; have been employed as active catalysts for the A³ coupling of secondary amines. Metal complexes of iron are readily available, inexpensive, and environmentally friendly. These features are highly desirable in a catalyst, and the incorporation of iron catalysis in organic synthetic processes would thus be advantageous.[37] In 2009, Li[38] and Wang[39] independently reported $FeCl_3$ as an active catalyst for the A³ coupling at elevated temperatures (120 °C in toluene or 70 °C, neat). More recently, Moores, Song, Li, and co-workers found that magnetite (Fe_3O_4) nanoparticles could be used as an environmentally benign and economical catalyst for the A³-coupling reaction.[40] The strong magnetic properties of Fe_3O_4 facilitated the separation of the iron catalyst from the reaction medium, and over 12 cycles of the A³-coupling reaction were performed without loss of catalytic activity.

Other first-row transition metals—Ni,[41] Zn,[42] and Co[43]—have also shown catalytic activity in this type of reaction. In particular, cobalt complexes, especially $CoCl_2(PPh_3)_2$, are effective catalysts for the A³ coupling of aliphatic and aromatic aldehydes under mild reaction conditions (**eq 7**).[43] With respect to main group metals, $InCl_3$ has been employed as a catalyst for the A³-coupling reaction,[44] in which indium(III) acetylide is proposed as the active nucleophilic reagent for the alkynylation reaction.

4. Asymmetric A³-Coupling Reactions

Optically active propargylamines are useful building blocks for the preparation of enantiopure nitrogen-containing compounds, and enantioselective A³-coupling reactions have played a key role in the synthesis of these valuable intermediates. Since Li and co-workers' initial report in 2002 of a copper-catalyzed addition of alkynes to *N*-arylimines using pybox ligand **L1** (**Figure 1** and **Table 2**, entry 1),[45] subsequent reports of enantioselective addition of terminal alkynes to C=N electrophiles have been dominated by copper catalysis. Similarly to Li's initial report, Bisai and Singh have disclosed an asymmetric A³-coupling

reaction utilizing Cu(I)-*i*Pr-pybox-diPh (**L2**), and obtained similar yields and levels of enantioselectivity (entry 2).[46] A carbohydrate-based pybox ligand (**L4**) was developed by Irmak and Boysen and applied in the asymmetric alkynylations of aryl imines (entry 3).[47] Although the chemical yields and enantioselectivities of the propargylamine products were for the most part modest, the glucose-based pybox shows great promise as an alternative to conventional pybox ligands.

In the initial report on the asymmetric A^3 coupling, it was noted that the reaction could be performed in water, albeit with slightly diminished yields and enantioselectivities. Liu and collaborators were able to improve the reactivity and enantioselectivity of the reaction in water by utilizing stearic acid as a surfactant (entry 4).[48] The asymmetric addition of phenylacetylene to *N*-benzylideneaniline (PhCH=NPh) in water, with stearic acid as additive, was completed within 24 h in 86% yield and 85% ee (48 h, 77% yield and 80% ee, without surfactant). In addition, the Cu(I)–pybox catalyst was reused several times by simply reloading the aqueous solution with fresh batches of the imine and alkyne. With respect to the recovery and reuse of copper–pybox complexes in the asymmetric A^3-coupling reaction, Portnoy and co-workers prepared various copper-chiral pybox complexes on polystyrene resins as heterogeneous catalysts (entry 5).[49] In general, the enantiomeric excesses of the chiral propargylamine products did not exceed 83% and were lower than those obtained with the homogeneous catalytic system. However, these researchers showed that the heterogeneous catalyst system could be reused in at least three consecutive runs. A magnetically recoverable Fe_3O_4 nanoparticle-supported copper-pybox complex has been employed by our group to catalyze the enantioselective alkynylation of imines (entry 6),[50] and was reused six times without significant loss in activity or enantioselectivity.

In addition to pybox ligands, chiral diamines,[51] diimines,[52] and N-tosylated β-aminoimines[53] have been employed as ligands for the copper-catalyzed addition of terminal alkynes to imines. However, the chemical yields and enantiopurities of the resulting propargylamines were inferior to those obtained with the pybox-based catalyst systems. A notable exception was reported by Nakamura's group, who developed chiral bis(imidazoline)–copper [pybim (**L5**)–Cu] systems, and showed them to have exceptional activity and enantioselectivity with aliphatic alkynes and aldehydes that were difficult to couple by using the copper–pybox systems (entry 7).[54] Rueping and co-workers carried out a silver-catalyzed enantioselective alkynylation reaction in which the imines were activated by hydrogen bonding with a chiral phosphonic acid.[55a] Arndtsen's group applied the same concept by employing copper as catalyst and *N*-Boc-proline as chiral ligand (entry 8).[55b] It was noted that the enantioselectivity of the alkynylation reaction could be readily tuned through the use of achiral phosphine ligands.

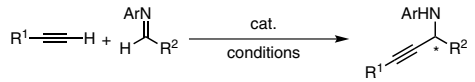
The asymmetric alkynylation of activated imines bearing electron-withdrawing substituents, e.g., α-imino esters, is effectively catalyzed by Cu(I) salts and pybox ligands **L1** or **L6**, providing facile access to unnatural amino acid derivatives (entry 9).[56] Although the preformed imine was utilized initially, it was possible to perform the enantioselective A^3-coupling reaction with in situ generated imines, albeit with lower enantioselectivities.[56c] Similarly, Dodda and Zhao reported the preparation of chiral α-aminopropargylphosphonates from the 1,2-alkynylation of α-iminophosphonates catalyzed by copper–pybox system (**L3**, entry 10).[57] Although good yields and moderate enantioselectivities were observed, the catalyst loading for this system could be lowered to 2 mol % and still achieve the desired results.

Knochel and co-workers have published a series of reports on the catalytic use of CuBr, (*R*)- or (*S*)-quinap (**L7**), and 4 Å molecular sieves in anhydrous toluene to afford tertiary propargylamines in good yields and enantioselectivities (**eq 8**).[58] A drawback of Knochel's protocol is the use of the rather expensive quinap as a chiral ligand. However, Carreira and co-workers have demonstrated that the chiral P,N-ligand pinap (**L8**) is a viable alternative to quinap, furnishing the desired propargylamines and achieving a greater level of enantiomeric excess.[59]

5. A^3 Coupling in Tandem Reactions

Multicomponent tandem reactions are attractive transformations that provide facile access to molecularly complex compounds. The incorporation of the A^3-coupling reaction into such sequences is of great interest, since the A^3-coupling product is amenable to further manipulation as a result of the reactivity of the triple bond

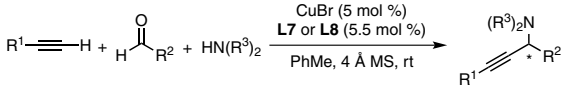
Table 2. Copper-Catalyzed Asymmetric 1,2 Addition of Alkynes to Imines



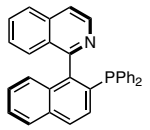
R^1 = aryl, alkyl, TMS; R^2 = aryl, EtO_2C, $(EtO)_2P{=}O$

Entry	Catalyst	Conditions	Yield	ee	Ref.
1	CuOTf–**L1** (10 mol %)	PhMe[a] 22 °C, 4 d or 35 °C, 2 d	63–93%	88–96%	*45*
2	$CuPF_6$– **L2** (10 mol %)	$CHCl_3$, 0 °C 12–48 h	61–99%	77–99%	*46*
3	CuOTf•0.5C_6H_6 (5 mol %), **L4** (8 mol %)	CH_2Cl_2, rt 48 h	21–92%	0–99%	*47*
4	CuOTf–**L1** (10 mol %)	H_2O, stearic acid, rt 24–48 h	60–89%	35–97%	*48*
5	**Cu–L Complex 1** (10 mol %)	CH_2Cl_2 or THF, 40 °C 24 h	trace–90%	<5 to 83%	*49*
6	**Cu–L Complex 2** (10 mol %)	CH_2Cl_2, 35 °C, Ar 1.5–2 d	80–94%	84–92%	*50*
7	CuOTf•PhMe–**L5** (10 mol %)	CH_2Cl_2, rt 12–120 h	28–93%	81–98%	*54*
8	$CuPF_6(MeCN)_2$ (2.5 mol %) phosphine ligand (5 mol %) Boc-proline (10 mol %)	CH_2Cl_2, 0 °C 72 h	65–92%	89–99%	*55b*
9	CuOTf•0.5C_6H_6 (10 mol %), **L6** (10 mol %)	CH_2Cl_2, 0 °C 36–48 h	55–92%	48–91%	*56a*
10	CuOTf–**L3** (2.0 mol %)	$CHCl_3$ (anhyd.), rt 10 h	56–92%	60–81%	*57*

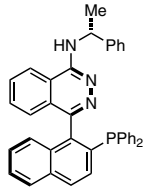
[a] In DCE, an ee of 99.5% was observed.



R^1 = alkyl, aryl, TMS; R^2 = alkyl, aryl; R^3 = alkyl

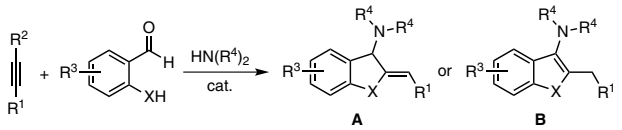


(*R*)-quinap (**L7**)
43–99%, 32–96% ee
Ref. 58a



pinap (**L8**)
72–82%, 94–99% ee (*S*)
Ref. 59

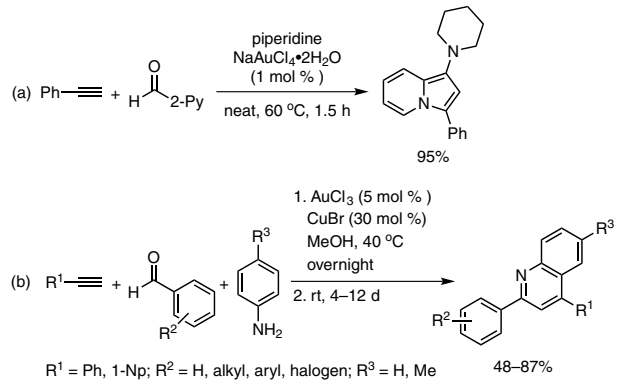
eq 8



R^1 = H, alkyl, aryl, heteroaryl; R^2 = H, TMS
R^3 = H, alkyl, alkoxy, aryl, halogen, nitro; R^4 = alkyl, cycloalkyl

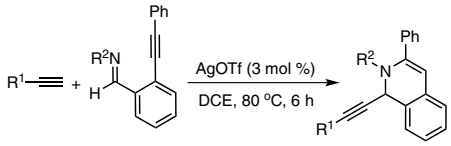
X	Catalyst	Conditions	Yield	Ref.
O	CuI (5 mol %)	130 °C, μw, neat, 0.5 h	**A**, 44–88%	*60b*
O	$Cu(OTf)_2$ (5 mol %) CuCl (5 mol %)	DMAP, MeCN, reflux, 6 h	**B**, 22–99%	*61*
O	CuI (20 mol %)	K_2CO_3, $(n\text{-Bu})_4NBr$, PhMe 110 °C, 2–3 h	**B**, 33–86%	*62*
NTs	$Cu(OTf)_2$ (5 mol %) CuCl (5 mol %)	DMAP, MeCN, 80 °C 12–16 h	**A**, 32–98%	*63*

eq 9



R^1 = Ph, 1-Np; R^2 = H, alkyl, aryl, halogen; R^3 = H, Me

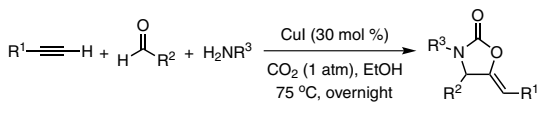
Scheme 4. Cascade A³-Coupling–Cycloisomerization Reactions. *(Ref. 64,65)*



R^1	R^2	Yield
Ph	Ph	93%
n-Bu	Ph	90%
EtO_2C	Ph	86%
Ph	*n*-Bu	42%
Ph	Bn	70%
Ph	allyl	70%
Ph[a]	Ph	58%

[a] *n*-Bu instead of Ph in the intramolecular acetylene group.

eq 10 *(Ref. 66a)*



R^1 = Ph, 4-MeC_6H_4, 4-MeONp
R^2 = *n*-Pent, Ph, 4-XC_6H_4 (X = Me, Me_2N, CN, Br)
R^3 = *n*-Bu, allyl, $Bn(CH_2)_2$

eq 11 *(Ref. 68)*

in propargylamines and the possibility that the metal catalyst employed for the A³ coupling could also catalyze subsequent transformations.

The ability of group 11 metals to coordinate and activate alkynes for nucleophilic addition provides the means by which propargylamines formed in the A³-coupling reaction can be further functionalized. In 2005, our group reported a novel method for generating polysubstituted 1,2-dihydroquinoline derivatives with high regioselectivity by using a silver catalyst in a one-pot domino process of hydroamination, alkyne–imine addition, intramolecular hydroarylation, and hydroarylation.[60a] Our group subsequently reported the transformation of salicylaldehydes into dihydrobenzofurans bearing exocyclic alkenes by a tandem A³-coupling–intramolecular cyclization under microwave conditions (**eq 9**).[60b] One limitation of this methodology is the need for a heteroatom directing group on the alkyne to facilitate the cyclization reaction. Sakai and co-workers have demonstrated that the propargylamines generated from the A³-coupling reaction of alkynylsilanes undergo the intramolecular cyclization to furnish modest-to-excellent yields of benzofurans in the presence of a mixed copper salt system under basic conditions.[61] Yanzhong Li and co-workers obtained similar results for benzofurans prepared by utilizing CuI as catalyst in refluxing toluene under basic conditions.[62] Finally, Gevorgyan's group reported a cascade reaction involving 2-aminobenzaldehydes, secondary amines, and alkynes to generate 3-aminoindoles.[63] They also demonstrated the preparation of optically active indolines through an asymmetric A³-coupling reaction. However, they noted that the one-pot A³-coupling–cyclization sequence diminished the enantioselectivities and that the reaction needed to be performed stepwise in order to provide the desired chiral indoline with modest enantiomeric excess.

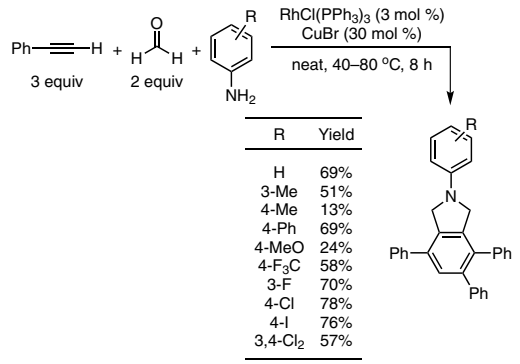
Intramolecular cyclization of the aromatic ring of the aldehyde or the amine can be incorporated with the A³-coupling reaction to provide interesting fused-ring systems. Yan and Liu reported the Au(III)-catalyzed coupling of pyridine-2-carboxaldehyde with secondary amines and alkynes to form aminoindolizines (**Scheme 4**, Part (a)).[64] In addition, they demonstrated the mildness of their method by incorporating chiral amino acid derivatives successfully without loss of enantiomeric purity. Wang's group employed a mixed Au(III)–Cu(II) catalyst system in MeOH to carry out a sequential reaction to prepare quinolines (**Scheme 4**, Part (b)).[65] Although the synthesis required several days for full conversion, it was possible to decrease the reaction time significantly to 10 minutes by raising the reaction temperature; this, however, resulted in slightly reduced yields.

The preparation of dihydroisoquinolines by addition of nucleophiles, such as nitromethane and terminal alkynes, to *ortho*-alkynylarylaldimines was reported by Asao and co-workers in 2005 (**eq 10**).[66] This sequential reaction proceeds through initial silver-catalyzed *intra*molecular addition of imine to the alkyne to generate an active iminium salt, which is then trapped by the external alkynyl nucleophile. Yao's group reported a similar protocol starting from in situ generated *ortho*-alkynylarylaldimines.[67] While their catalytic system was comprised of CuOTf and pybox, no enantioselectivity was observed.

Our group has successfully carried out a four-component coupling by incorporating carbon dioxide into the A³-coupling reaction to furnish oxazolidinones bearing exocyclic alkenes in modest-to-good yields (**eq 11**).[68] Although the tandem reaction was limited to electron-rich aliphatic amines (due to the inability of propargyl aryl amines to form complexes with CO_2) that are traditionally poor substrates for the A³-coupling reaction, this problem was alleviated by the substoichiometric use of CuI and

the conversion of the aliphatic amines into carbamic acids by CO_2.

The incorporation of the A^3-coupling product into a tandem reaction can be achieved through the use of mixtures of catalytic species that are chemically compatible. Our group introduced a double A^3 coupling[69a] and a tandem A^3-coupling–[2 + 2 + 2] cycloaddition[69b] to prepare isoindoline frameworks (**eq 12**). While use of the commercially available Wilkinson's catalyst and CuBr provides the desired heterocycle in modest-to-good yields, some limitations of this approach include its inability to incorporate aliphatic amines and alkynes.



R	Yield
H	69%
3-Me	51%
4-Me	13%
4-Ph	69%
4-MeO	24%
4-F_3C	58%
3-F	70%
4-Cl	78%
4-I	76%
3,4-Cl_2	57%

eq 12 *(Ref. 69b)*

6. Conclusions and Outlook

The catalytic, direct 1,2 addition of alkynes to imines and iminium ions, generated from the condensation of amines and aldehydes, represents the most convenient method to access propargylamines. Although numerous examples of the A^3-coupling reaction have been reported thus far, there still exist many challenges and opportunities for this multicomponent coupling reaction. Expanding its scope to include difficult substrates such as aliphatic primary amines and ammonia, development of highly enantioselective A^3-coupling reactions with broad substrate specificity, and incorporating the A^3-coupling reaction into tandem processes are all challenges that are expected to be overcome in the near future.

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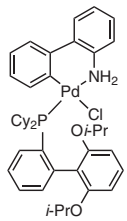

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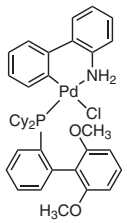

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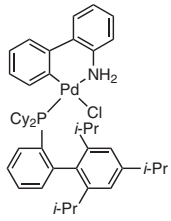

741825

753246	Chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g
753009	Chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g
741825	Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-[2-(2′-amino-1,1′-biphenyl)]palladium(II)	250 mg 1 g 5 g

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Seashore with Fishermen (oil on canvas, 101.9 × 127.6 cm) was painted around 1781/1782 by the British portrait and landscape painter, Thomas Gainsborough (1727–1788). While better-known as a portraitist for the more lucrative portraits of royalty and nobility that he painted most of his life to support his family, he never lost his fondness for landscape painting.

Gainsborough painted this landscape in his later years, when he reportedly declared that he was tired of painting portraits. Depicting fishermen struggling against strong winds and waves to launch their boat into the water, he imparts a measure of spontaneity and sensibility to the scene. His personal style is reflected in the way he merges the figures with the scene behind them, and in his handling of paint for which he was much admired.

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

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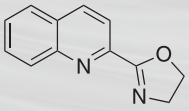

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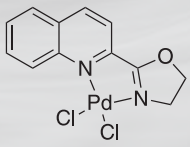

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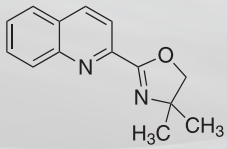

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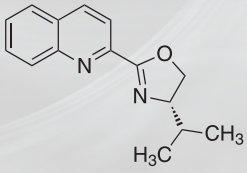

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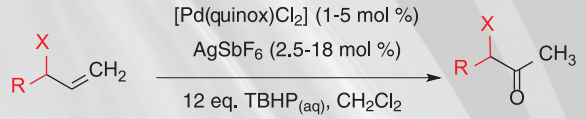
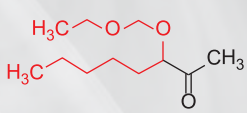
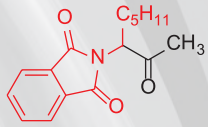
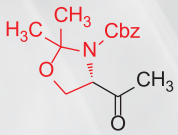




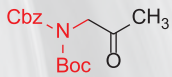
81%, 4 h



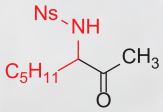
82%, 20 min



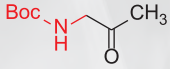
69%, 16 h



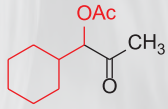
95%, 2.5 h



88%, 4 h



74%, 2.5 h



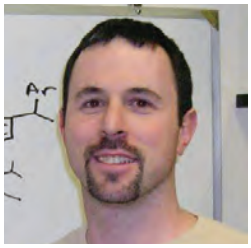
89%, 17 h

Scheme 1: Pd-quinox catalyzed Wacker oxidation of allylic functionalized terminal alkenes.

References: (1) Michel, B. W.; Camelio, A. M.; Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 6076. (2) Michel, B. W.; McCombs, J. R.; Winkler, A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 7312. (3) Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317.

Peroxide-Mediated Wacker Oxidations for Organic Synthesis

Dr. Brian W. Michel



Prof. Matthew S. Sigman

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Keywords. Wacker-type oxidation; quinox; homogeneous catalysis; TBHP; catalyst control.

Abstract. Peroxide-mediated Wacker-type oxidations are reviewed. The initial development of rhodium-catalyzed systems, which activate molecular oxygen, has led to the use of hydro- and alkylperoxides as oxidants in the catalytic conversion of terminal olefins into methyl ketones via a common mechanistic hypothesis. Additionally, ligand-modulated systems have been developed. In particular, the use of *tert*-butylhydroperoxide (TBHP), along with palladium and the uniquely suited ligand, quinox, constitutes a highly selective system for the oxidation of classically challenging substrates.

Outline

1. Introduction

The Wacker oxidation is a powerful synthetic transformation, which converts a terminal olefin into a methyl ketone via palladium catalysis, traditionally employing molecular oxygen as the terminal oxidant and a copper co-catalyst.[1–3] Good functional-group tolerance, ease of reaction, and the orthogonal reactivity of the substrate and product have led to the widespread application of this transformation in the industrial preparation of commodity chemicals, such as acetaldehyde, and in target-directed synthesis.[4] The most common system used is that initially reported by Clement and further advanced by Tsuji, employing a DMF–H_2O solvent system.[2,3] In the Tsuji–Wacker oxidation, water is the source of the oxygen atom, which is incorporated into the product, and molecular oxygen is the terminal oxidant (**Scheme 1**).[2,3]

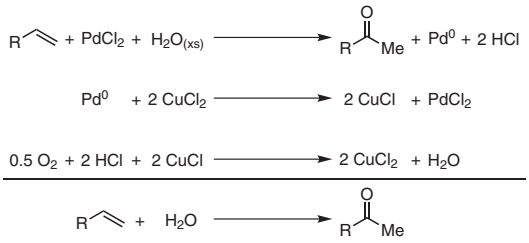
An alternative approach, which is less commonly employed for synthetic applications, utilizes an electrophilic metalloperoxide species, formed by metal activation of molecular oxygen or exogenous hydro- or alkylperoxides. These peroxymetallic reagents and/or catalysts are proposed to coordinate an olefin, which subsequently inserts in a peroxymetallation step (**Scheme 2**).[5] Early work in this field follows closely related metal-catalyzed, peroxide-mediated epoxidation reactions.[6,7] An advantage of this mechanistic manifold for effecting the transformation of terminal alkenes into methyl ketones seems to lie in the "preloaded" catalyst and the selective syn-metallation step. This is contrary to the Tsuji–Wacker oxypalladation step, which may occur in an anti fashion, but can be particularly dependent on the reaction conditions.[8–16] Overall, some of the peroxymetallation reactions display good synthetic potential as they predominantly lead to a single oxidation product via catalyst control, whereas the Tsuji–Wacker reaction is subject to substrate control (vide infra).

More recently, peroxide-mediated, ligand-modulated, palladium-catalyzed systems have been reported. These systems, which utilize commercially available peroxides, allow for the efficient and selective oxidation of substrates, which would otherwise give mixtures of products when oxidized using Tsuji–Wacker conditions. The Wacker oxidation has been extensively reviewed,[4,17–20] including instances which produce aldehydes;[21] however, peroxide-mediated Wacker-type oxidations have not recently been surveyed and are the focus of this review article.

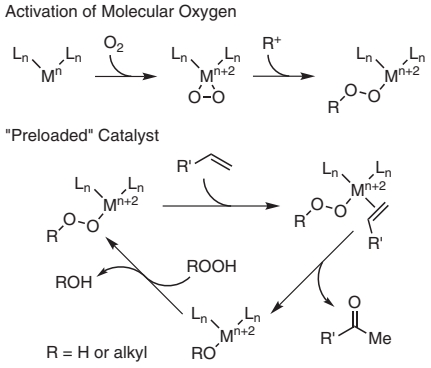
2. Peroxide-Mediated Wacker-Type Oxidations

In peroxide-mediated Wacker-type oxidations, the source of the oxygen atom incorporated into the ketone product differs from that of the classical Wacker oxidation. In the Wacker oxidation, the oxygen atom arises from a molecule of water or hydroxide ion (see Scheme 1). Palladium is reduced to the zero oxidation state and is ultimately reoxidized to Pd(II) by molecular oxygen in an oxidase-type catalyst system (i.e., molecular oxygen is the terminal oxidant, but not the source of the oxygen atom incorporated into the product).[1] In peroxide-mediated oxidations, an oxygen atom is incorporated into the ketone product from the terminal oxidant, either molecular oxygen or a peroxide (analogously to an oxygenase system).[17,22–26] This key mechanistic difference between these two types of alkene oxidation has been probed by isotopic labeling studies and will be discussed in the relevant sections.

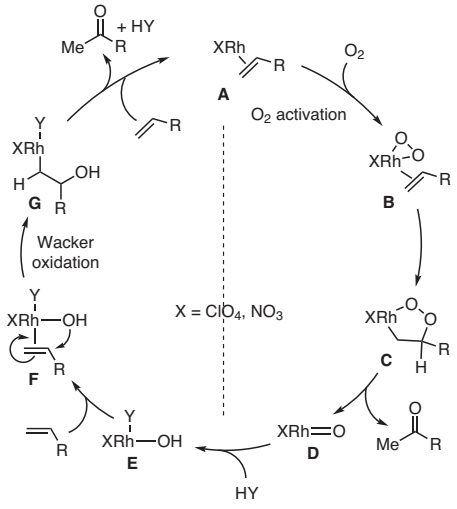
A number of transition metals; including iridium,[27] ruthenium,[28,29] platinum,[30] rhodium,[5,6,20,22,24,26,29,31–46] and palladium;[23,25,26,47–61] either activate molecular oxygen or use exogenous peroxide to convert terminal olefins into methyl ketones. Significantly, the seminal systems involve rhodium, while palladium systems appear to have the greatest synthetic potential. In the next section, rhodium systems which utilize molecular oxygen will be discussed. This will be followed by a discussion of the use of palladium in conjunction with



Scheme 1. Oxidase-Type Catalysis of the Wacker Oxidation.



Scheme 2. General Representation of the Activation of Molecular Oxygen That Leads to Intermediates Similar to Those Proposed When Exogenous Hydro- or Alkylperoxides Are Used.



Scheme 3. Mimoun's Proposed Catalytic Cycle for the Rhodium-Catalyzed Oxidation of Olefins. *(Ref. 5)*

molecular oxygen or hydrogen peroxide; similar reactive intermediates should be shared by these systems. Finally, systems, which employ *tert*-butylhydroperoxide (TBHP) and palladium, will be discussed, including their use in the oxidation of olefins that are challenging substrates in the Tsuji–Wacker oxidation.

2.1. Rhodium–Dioxygen

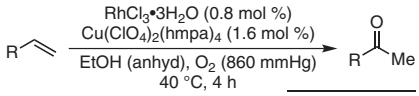
Isolated, or in situ generated, rhodium–dioxygen species are capable of oxidizing terminal olefins to methyl ketones. In 1972, Dudley and Read reported the seminal work on rhodium co-oxygenation of terminal olefins and Ph_3P to methyl ketones and Ph_3PO.[31] Mimoun and co-workers significantly advanced the studies of related systems and developed a working mechanistic hypothesis.[5,22,24] To this effect, a rhodium-catalyzed system has been developed, utilizing $RhCl_3$ and $Cu(ClO_4)_2(hmpa)_4$ in alcoholic solvents under an O_2 atmosphere. It is proposed that Rh(III) oxidizes two equivalents of the alcohol (2 EtOH → 2 MeC(O)H) to give a Rh(I) species, which can then activate molecular oxygen to give a peroxorhodium(III) complex. Two moles of terminal olefin are then oxidized for each mole of O_2 consumed. While this is the same stoichiometry observed in the classical Wacker oxidation, the oxygen atoms in the ketone product are proposed to arise from molecular oxygen via two distinct, but interdependent pathways (**Scheme 3**).

It is proposed that, in the first stage of the catalytic cycle, molecular oxygen is activated by the olefin–rhodium complex **A** to the peroxorhodium(III) complex **B**, which upon insertion of the double bond gives metallocycle **C**. Decomposition of **C** provides the first equivalent of ketone product and the rhodium oxo species **D**. Subsequent protonation gives **E**, and coordination of another equivalent of olefin to the rhodium delivers **F**. A classical Wacker-like sequence is proposed to follow with syn-oxyrhodation to give **G**; this is followed by β-hydride migration to give the second equivalent of ketone. Coordination of another alkene regenerates the Rh(I) species **A**.

Mimoun and co-workers reported good methyl ketone selectivity for various simple alkyl olefin substrates. However, the conversion decreased with increasing hydrophobicity of the substrate (**eq 1**).[5] While some benzaldehyde product is detected from the oxidative cleavage of styrene, the main oxidation product is acetophenone.

2.2. Palladium–O_2 and Palladium–H_2O_2

Igersheim and Mimoun found that palladium–dioxygen complexes could convert terminal olefins into methyl ketones in the presence of a strong acid via formation of a palladium hydroperoxide (Pd–OOH) intermediate (**Scheme 4**).[23] This species is proposed to



R	Conv.[a]
n-Bu	48%
n-Hex	42%
n-decyl	32%
Ph	24%

[a] Selectivity for the methyl ketone ranged from ≥97% to ≥98%.

eq 1 *(Ref. 5)*

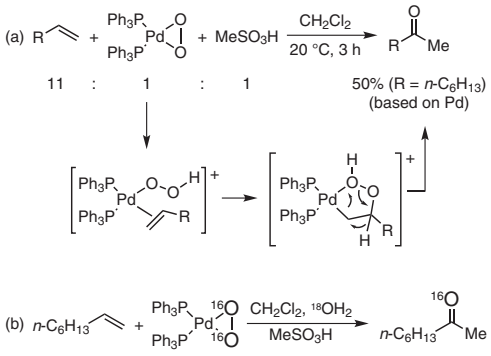
coordinate an olefin, followed by peroxymetallation, peroxide bond cleavage, and hydrogen-atom shift to provide the methyl ketone product. Isotopic labeling studies indicate that the oxygen atom incorporated in the ketone product arises from molecular oxygen, and not from adventitious water (see Scheme 4, Part (b)). The reaction is stoichiometric in palladium, proceeding with concomitant oxidation of the phosphine ligands.

Molecular oxygen can insert into a palladium hydride species generated upon β-hydride elimination from primary or secondary alkoxides. Takehira and co-workers reported the oxidation of cyclopentene to cyclopentanone with co-oxidation of ethanol to acetaldehyde (**Scheme 5**, Part (a)).[52] Yields of cyclopentanone were dramatically improved when the same group utilized $CuCl_2$ as co-catalyst in the reaction (see Scheme 5, Part (b)).[53,54] The authors suggest that a heterobimetallic Pd–Cu(I) species is formed and that the role of copper is as a transient oxygen carrier that facilitates the generation of a Pd–OOH species (see Scheme 5, Parts (c) and (d)). This is particularly interesting, considering the growing support for the role of copper in other Pd–Cu–O_2 systems as more than a facilitator of the reoxidation of Pd(0) to Pd(II).[16,62-64] In addition to oxidizable alcohols as viable solvents, THF and methyl ethyl ketone are competent solvents for the reported transformation. As suggested by Takehira and co-workers, and later supported by the findings of Cornell and Sigman,[59] this is likely due to the ability of these molecules to form alkyl peroxides (see Scheme 5, Part (e)), which can then act in a similar fashion to hydrogen peroxide. Brégeault et al. reported a related system that utilizes $BiCl_3$ and LiCl, and proposed the involvement of heterobimetallic complexes.[48] However, olefin isomerization and other internal ketone isomers were observed as significant byproducts in this system.

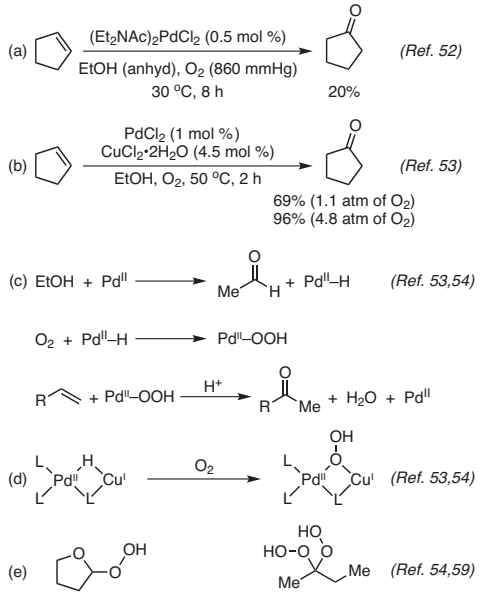
Uemura and co-workers reported the catalytic oxidation of terminal olefins to methyl ketones in a process coupled to the oxidation of isopropanol, generating H_2O_2 and a proposed Pd–OOH intermediate (**Scheme 6**).[51] As discussed previously, it is proposed that a Pd–H is generated upon oxidation of a sacrificial alcohol. Molecular oxygen can then insert into the Pd–H bond to give a Pd–OOH species, which can either coordinate an olefin and undergo peroxypalladation or react with another molecule of alcohol to give H_2O_2 and return the palladium to the alcohol oxidation pathway. Evidence for the generation of the Pd–OOH species is provided by an observed enhancement in the rate of O_2 consumption when the reaction is performed in the presence of alkene as compared to identical conditions in the absence of alkene. The authors suggest that this is a result of a more rapid consumption of the putative Pd–OOH intermediate when the alkene is present.

Roussel and Mimoun have reported a hydrogen peroxide mediated system using very low loadings of palladium (0.07 mol %) to achieve good conversions of simple olefins into the corresponding methyl ketones with good-to-high selectivities (**eq 2**).[25] The byproducts were identified as 3- and 4-octanone, although they generally constituted a small percentage of the product mixture. Unfortunately, this reaction lacks synthetic applications presumably because of the undesirable characteristic, from a safety standpoint, of catalytic H_2O_2 decomposition by palladium. Additionally, overoxidation was observed as a result of these conditions in the oxidation of 4-vinylcyclohexene to acetophenone (**eq 3**).[51]

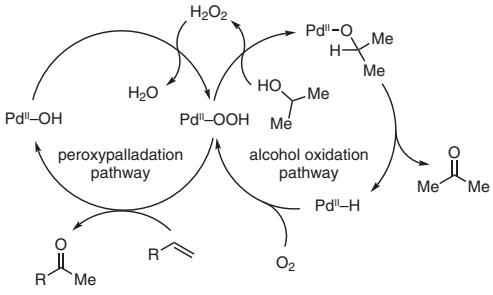
Choudary and co-workers reported a montmorillonite *N*-(silylpropyl)-ethylenediamine–palladium complex that converts terminal olefins into methyl ketones with short reaction times and very low catalyst loading (0.02 mol %) in the presence of H_2O_2 (**eq 4**).[50] The catalyst retained full catalytic activity through four reaction cycles.



Scheme 4. (a) The reaction of $(Ph_3P)_2PdO_2$ with a Strong Acid and a Terminal Olefin. The Proposed Mechanism Proceeds Through a Pd–OOH species. (b) Isotopic Labeling Indicates the Source of the Oxygen Atom Incorporated in the Product. *(Ref. 23)*



Scheme 5. (a) and (b) Cyclopentene Is Converted into Cyclopentanone. (c) The Reaction Is Proposed to Occur via Alcohol Oxidation to Provide a Pd–H species, into Which Molecular Oxygen Can Insert. (d) The Authors Suggest an Operative Pd–Cu Heterobimetallic Species. (e) THF and MEK Are Known to Form Peroxides, Which May Act in a Similar Fashion to H_2O_2.

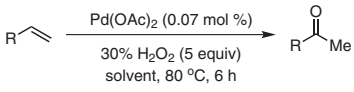


Scheme 6. Proposed, Linked Catalytic Cycles for Alcohol Oxidation and Peroxide-Mediated Wacker-Type Reactions Sharing a Pd–OOH Intermediate. *(Ref. 51)*

2.3. Palladium–TBHP

Mimoun et al. synthesized and isolated a series of tetrameric palladium *tert*-butylperoxide carboxylates, $[RCO_2PdOO\textit{t}\text{-}Bu]_4$, which precipitated out of a solution of $Pd(O_2CR)_2$ in 80% *tert*-butylhydroperoxide (TBHP).[47] In particular, the active oxidant palladium *tert*-butylperoxide trifluoroacetate (PPT) was prepared. This complex stoichiometrically oxidizes 1-hexene to 2-hexanone in less than 10 minutes (based on palladium, **Scheme 7**, Part (a)). Support for TBHP as the source of the oxygen atom in the ketone product came from the preparation of the stable peroxymercuration adduct **1**. Upon transmetallation with Na_2PdCl_4, adduct **1** provides an unstable, presumed pseudo-palladacyclic intermediate **2**, which decomposes to provide acetophenone (see Scheme 7, Part(b)).

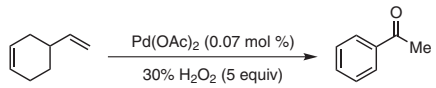
In an unanticipated result, Cornell and Sigman discovered a ligand-modulated, peroxide-mediated Wacker-type oxidation, where TBHP was used in conjunction with an N-heterocyclic carbene ligand (**eq 5**).[59] While investigating a copper-free, direct O_2-coupled Wacker oxidation, it was found that styrene (a classically challenging substrate for the Tsuji–Wacker oxidation)[21,65] could be oxidized to acetophenone in THF. However, when the reaction progress was monitored by in situ FTIR spectroscopy, an extended induction period was observed. It was hypothesized that this was the result of a palladium-catalyzed oxidation of THF, as indicated by the observed formation of γ-butyrolactone. Instead of utilizing molecular oxygen, TBHP was an efficient stoichiometric oxidant for the transformation of styrenes into acetophenone derivatives. Unfortunately, the synthetic utility of this system is limited to styrenyl substrates due to the propensity of the catalyst to isomerize alkenes and oxidize the resultant internal alkenes.[66]



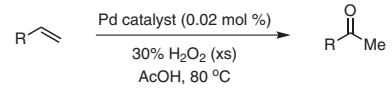
R	Solvent	Conv.[a]	Ketone[b]
n-C_6H_{13}	*t*-BuOH	89%	82%
n-C_6H_{13}	AcOH	96%	95%
n-C_8H_{17}	*t*-BuOH	90%	80%
n-C_8H_{17}	AcOH	95%	92%
n-$C_{10}H_{21}$	*t*-BuOH	89%	75%
n-$C_{10}H_{21}$	AcOH	92%	90%
$AcOCH_2$	*t*-BuOH	8%	83%
$AcOCH_2$	AcOH	100%	85%

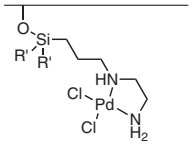
[a] Determined by GC with *ortho*-dichlorobenzene as internal standard. [b] % selectivity for the methyl ketone product as compared to other products. Determined by GC.

eq 2 *(Ref. 25)*



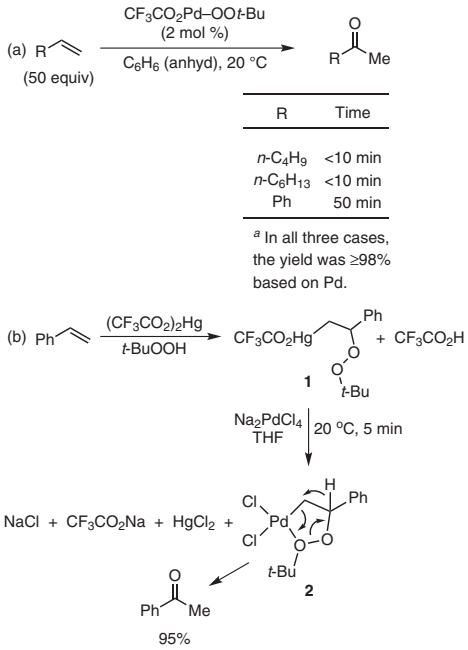
eq 3 *(Ref. 51)*





R	Time	Yield
n-C_4H_9	45 min	96%
n-C_6H_{13}	60 min	92%
n-C_8H_{17}	60 min	92%
n-$C_{10}H_{21}$	60 min	90%
$AcOCH_2$	55 min	94%
Ph	30 min	98%

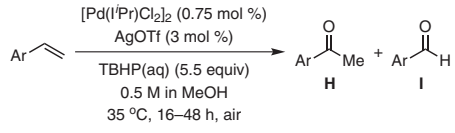
eq 4 *(Ref. 50)*

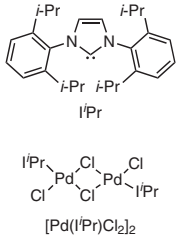


R	Time
n-C_4H_9	<10 min
n-C_6H_{13}	<10 min
Ph	50 min

[a] In all three cases, the yield was ≥98% based on Pd.

Scheme 7. (a) Stoichiometric Oxidation of Terminal Olefins to Methyl Ketones by PPT (CF_3CO_2Pd–OO*t*-Bu). (b) Transmetallation of Peroxymercuration Adduct with Palladium to Provide Acetophenone. *(Ref. 47)*





Ar	Conv.	Yield	**H:I**
Ph	>99%	75%	>130:1
2-MeC_6H_4	>99%	79%	36:1
3-MeC_6H_4	>99%	83%	22:1
4-MeC_6H_4	>99%	86%	22:1
2,4,6-$Me_3C_6H_2$	95%	71%	>150:1
3-ClC_6H_4	>98%	80%	>150:1
3-$O_2NC_6H_4$[a]	90%	79%	>150:1
Ph[b,c]	NA	42%[d]	42:35
Ph[e]	97%	NA	2.3:1[f]

[a] $[Pd(I^iPr)Cl_2]_2$ (2.25 mol %), AgOTf (12 mol %). [b] [alkene] = 0.3 M, $[Pd(I^iPr)Cl_2]_2$ (1.25 mol %), AgOTf (4 mol %), 35–50 °C. [c] (*E*)-PhCH=CHPh used as starting material. [d] 2 equiv of PhCH=O produced via oxidative cleavage. [e] (*E*)-PhCH=CHMe employed as starting material. [f] **H** is a 53:47 mixture of regioisomeric ketones.

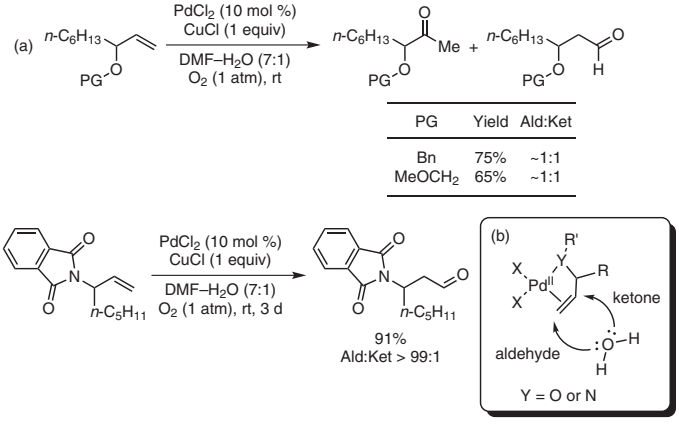
eq 5 *(Ref. 59)*

Our group has further explored copper-free Wacker oxidations that utilize the bidentate amine ligand sparteine,[16,66] as well as ligand-modulated, TBHP-mediated Wacker-type oxidations.[57,58,60,61] As a result of these investigations, a highly selective oxidation system has been developed and will be discussed below.

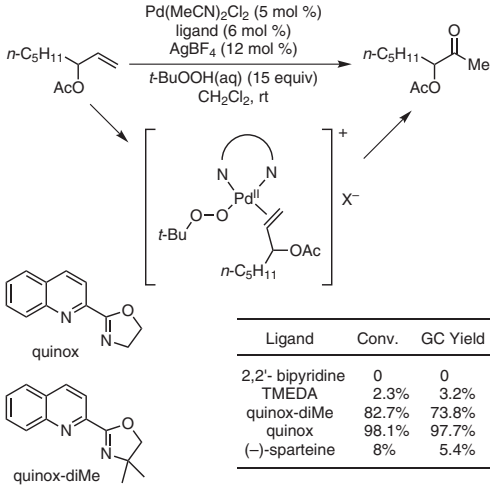
Alkene substrates with adjacent heteroatoms can undergo anti-Markovnikov oxidation yielding aldehyde products (**Scheme 8**).[21,67–70] This phenomenon has been reviewed[21] and has also been exploited as a means to selectively prepare aldehydes.[68–70] Since this outcome is thought to originate from a secondary coordination of the Lewis basic heteroatom to the electrophilic palladium, it was hypothesized that the proposed syn-peroxypalladation mechanism in combination with a bidentate amine ligand would leave only a single electrophilic alkene binding site (**eq 6**).[57]

It was found that the quinox ligand scaffold was uniquely suited for effective catalysis in this system (see eq 6). Through empirical optimizations, a highly active catalyst system was developed, which oxidized terminal olefins selectively to their methyl ketone products (**eq 7**, **8**).[57,58,61] The quinox ligand is readily prepared from simple starting materials (**Scheme 9**)[57,58] and is also commercially available. Substrates, such as protected allylic alcohols[57] and amines,[58] as well as unprotected homoallylic alcohols[61] are selectively oxidized with catalyst control using the Pd(quinox)–TBHP system. These findings are in direct contrast to the observed results in the Tsuji–Wacker oxidation of these substrate classes (see Scheme 8 and **eq 9**).[21]

Kinetic evidence and ligand modification studies support the hypothesis that a defined coordination sphere and syn-peroxypalladation are responsible for the excellent observed selectivity.[60] The reaction shows [TBHP] saturation kinetics that is supportive of a mechanism in which palladium is "preloaded" with the peroxide. A hypothesis that the defined coordination sphere results from the electronic disparity between the ligand modules was supported by systematic modification of the quinox ligand electronics. The reaction rate was observed to increase

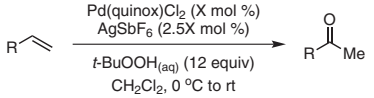


Scheme 8. (a) Substrates with Proximal Heteroatoms Can Give Aldehyde Products under Tsuji–Wacker Conditions. (b) anti-Markovnikov Oxypalladation Leads to Aldehyde Product. *(Ref. 67,68)*



Ligand	Conv.	GC Yield
2,2'- bipyridine	0	0
TMEDA	2.3%	3.2%
quinox-diMe	82.7%	73.8%
quinox	98.1%	97.7%
(–)-sparteine	8%	5.4%

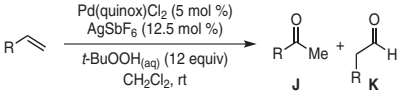
eq 6 *(Ref. 57)*



Entry	R	X	Time	Yield[a]
1	n-C_8H_{17}	2	0.3 h	86%
2	$HO(CH_2)_9$	2	0.6 h	98%
3	$MeO_2C(CH_2)_8$	2	0.6 h	87%
4	$Me_2C(OCH_2CHO)(CH_2)_4$	2	0.5 h	95%
5	$Cl(CH_2)_9$	2	1.3 h	89%
6	4-MeC_6H_4	5	0.8 h	88%
7	3-$O_2NC_6H_4$	5	17 h	60%
8	4-$BocNHC_6H_4$	5	1 h	83%
9	n-$C_5H_{11}CH(OAc)$[b]	5	20 h	89%
10	n-$C_5H_{11}CH(OAc)$[c]	5	20 h	99%
11	n-$C_5H_{11}CH(OTBS)$[d]	2	4.5 h	77%
12	n-$C_5H_{11}CH(OCH_2OEt)$	5	4 h	81%
13	$CyCH(OAc)$[b]	5	17 h	89%
14	$PhCH(OTBS)CH_2$	2	0.6 h	92%
15	$PhCH(OTBS)CH_2$[e]	2	0.6 h	99%
16	n-$C_5H_{11}CH(OAc)CH_2$[b]	3	3 h	94%
17	$(n\text{-}C_5H_{11})_2C(OH)CH_2$	3	5 h	81%
18	$Ph_2C(OH)CH_2$	3	24 h	---[f]
19	n-$Bu(Me)C(OH)CH_2$	5	5 h	84%
20	$Ph(Me)C(OH)CH_2$[g]	10	8 h	79%
21	$[H_2C(CH_2)_3CH_2]C(OH)CH_2$	5	6.5 h	71%
22	(R,R)-n-$C_5H_{11}C(OH)CH(Me)$[b,h]	5	24 h	57%

[a] All yields represent average isolated yields of at least two reactions performed on a >0.5-mmol scale unless otherwise noted. [b] Substrate added at room temperature. [c] Alkene, 98% ee; ketone, 98% ee. [d] 15 mol % $AgSbF_6$ used. [e] Alkene, 92% ee; ketone, 92% ee. [f] Complex mixture, mostly recovered starting material. [g] Single experiment. [h] An average of 35% starting material was recovered.

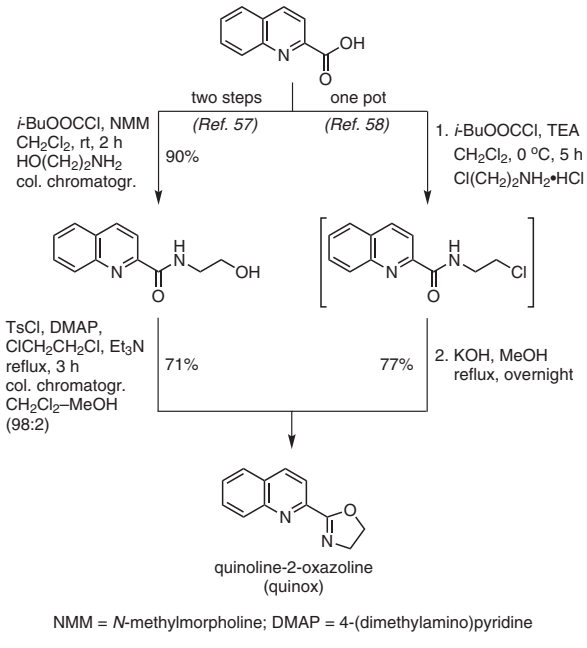
eq 7 *(Ref. 57,61)*



Entry	R	Time	Yield[a,b]
1	Phth-NCH(n-C_5H_{11})[c,d]	19 h	91%
2	Phth-NCH_2[c]	18 h	79%
3	Phth-NCH(n-C_5H_{11})CH_2[c,e]	0.3 h	82%
4	CbzNHCH_2[e]	0.8 h	81%
5	BocNHCH_2[e]	2.5 h	74%
6	Boc(Cbz)NCH_2	2.5 h	95%
7	Boc_2NCH_2	2.5 h	93%
8	CbzNHCH(n-C_5H_{11})[f]	12 h	74%
9	Boc(Cbz)NCH(n-C_5H_{11})	14 h	76%
10	TAcNHCH(n-C_7H_{15})[g]	23 h	67%
11	TsNHCHPh	2 h	90%
12	NsNHCH(n-C_5H_{11})	4 h	88%
13	(R)-$Me_2C(OCH_2CHNCbz)$[h]	16 h	69%

[a] All yields represent average isolated yields of at least two reactions performed on a >0.5-mmol scale unless otherwise noted. [b] Except where noted, **J:K** > 95:5. The **J:K** ratio was determined by GC, ^{1}H NMR integrations, and/or yields of isolated products. [c] $AgSbF_6$ (18 mol %) used. [d] **J:K** 96:4. [e] Substrate added at 0 °C. [f] **J:K** 90:10. [g] TAc = trichloroacetyl, $Cl_3CC(=O)$. An average of 12% starting material was recovered. [h] Alkene, >99% ee; ketone, >99% ee.

eq 8 *(Ref. 58)*



NMM = *N*-methylmorpholine; DMAP = 4-(dimethylamino)pyridine

Scheme 9. Synthesis of Quinox Using Ethanolamine or 2-Chloroethylamine Hydrochloride. *(Ref. 57,58)*

with addition of electron-withdrawing groups to the quinoline ring (**Figure 1**, Part (a)). Additionally, in a series of 4-trifluoromethylquinoline-2-pyridyl ligands, it was observed that more electron-releasing groups on the pyridine ring (i.e., the more donating ligand module) also increased the rate of reaction (see Figure 1, Part (b)).

3. Summary and Outlook

The development of Wacker-type oxidations in which rhodium activates molecular oxygen has led to a number of catalytic systems that utilize O_2 insertion into palladium hydrides. Similarly, hydrogen peroxide has been employed as a stoichiometric oxidant in palladium-catalyzed systems. The catalytic decomposition of hydrogen peroxide to generate molecular oxygen by palladium and the lack of synthetic evaluation of these systems may be the reason why they have not seen broad synthetic applications. The Pd(quinox)–TBHP Wacker-type oxidation has proven to be highly selective for the oxidation of substrates that are not selectively oxidized under Tsuji–Wacker conditions. Future work in this field should aim to achieve the very low catalyst loadings reported in the Pd–H_2O_2 systems with the catalyst-controlled selectivity observed in ligand-modulated catalysis.

4. Acknowledgement

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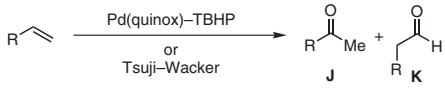
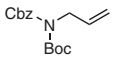
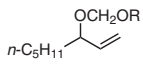
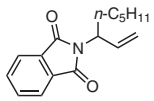


	Tsuji–Wacker			Pd(quinox)–TBHP[a]		
Alkene	**Yield**	**J:K**	**Ref.**	**Yield**	**J:K**	**Ref.**
	85%[b]	57:43	*58*	95%	>95:5	*58*
	56%[b,c]	60:40	*58*	69%	>95:5	*58*
	65%[d,e]	~50:50	*67*	81%[e]	>95:5	*57*
	91%[b]	<1:99	*68*	91%	>96:4	*58*

[a] For reaction conditions, see equations 7 and 8. [b] $PdCl_2$ (20 mol %), CuCl (1 equiv), DMF–H_2O (7:1), O_2, rt, 3 d. [c] 32% of starting material was recovered. [d] $PdCl_2$ (10 mol %), CuCl (1 equiv), DMF–H_2O (7:1), O_2, 60 °C, 24 h. [e] R = Me (Tsuji–Wacker); R = Et (Pd(quinox)–TBHP).

eq 9 *(Ref. 57,58)*

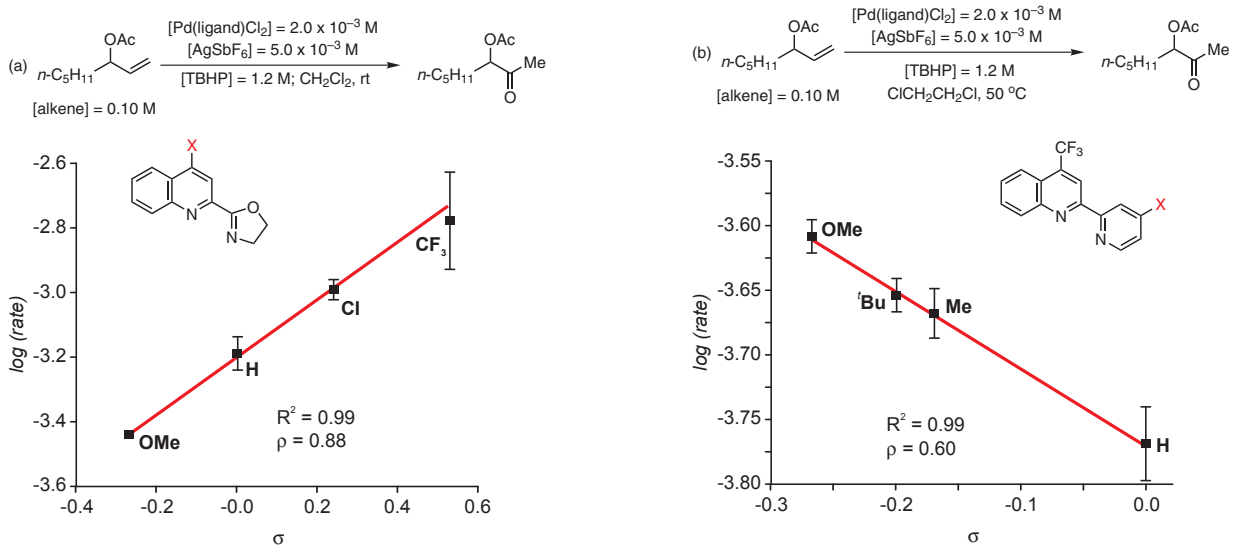


Figure 1. Hammett Correlation of the log(rate) vs σ_p Values for a Series of (a) 4-Substituted Quinox Ligands, and (b) Quinolinylpyridyl Ligands. *(Ref. 60)*

5. References

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Brian W. Michel was born in Kirkland, WA. He obtained a B.S. degree in chemistry in 2006 from Western Washington University, working on the enantioselective synthesis of heliannuols C and E under Professor James Vyvyan. In 2006, he joined the Department of Chemistry at the University of Utah. Brian completed the requirements for his Ph.D. degree with Professor Matthew Sigman, developing and understanding catalytic oxidation reactions. In 2011, he moved to the University of California, Berkeley, where he is currently working in Professor Christopher Chang's laboratory on developing probes for the study of small cellular signaling molecules.

Matthew S. Sigman received a B.S. degree in chemistry in 1992 from Sonoma State University and his Ph.D. degree in 1996 with Professor Bruce Eaton at Washington State University. He then completed an NIH postdoctoral stint with Professor Eric Jacobsen at Harvard University. In 1999, he joined the faculty of the University of Utah, where his research program has focused on the development of new synthetic methods.

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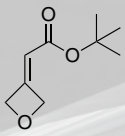

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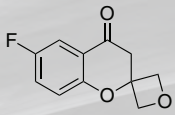

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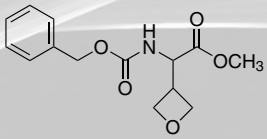

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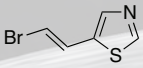

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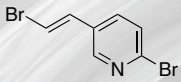

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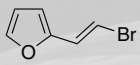

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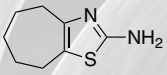

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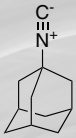

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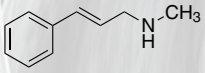

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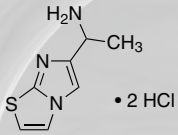

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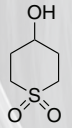

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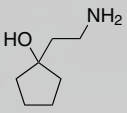

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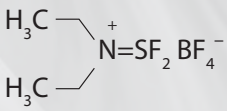

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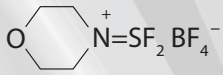

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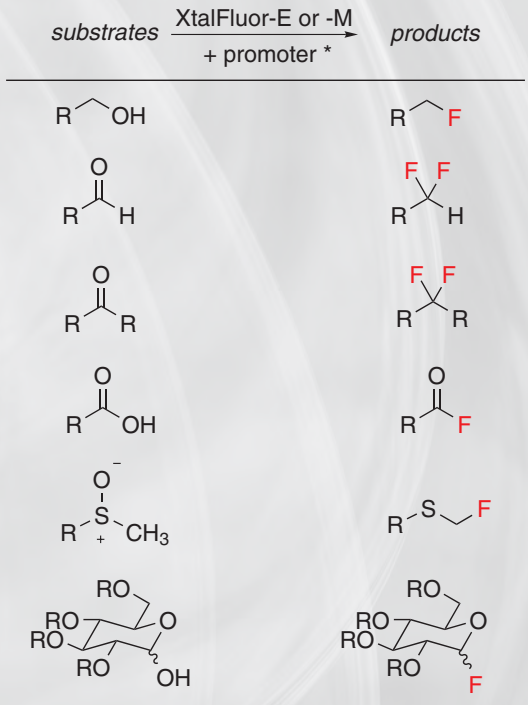

* *Promoters:* DBU, $Et_3N{\cdot}3HF$, or $Et_3N{\cdot}2HF$

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Organofluorine Chemistry: Deoxyfluorination Reagents for C–F Bond Synthesis

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Keywords. fluoroalkanes; C–F bond; organofluorine chemistry; fluorination reagents; deoxyfluorination.

Abstract. The influence of the C–F bond on the conformation of organic molecules is outlined. Strategies for incorporating the C–F bond into molecular frameworks by deoxyfluorination reactions are summarized with a particular focus on recent and emerging fluorination reagents. The syntheses of individual stereoisomers of straight-chain alkanes carrying up to six consecutive C–F bonds is presented to illustrate the power of the deoxyfluorination approach in controlling the introduction of the C–F bond at a stereogenic center.

Outline

1. Introduction

Since the 1950s, organofluorine compounds have significantly impacted many aspects of the chemical industry. Because of its extreme chemical properties, fluorine continues to be incorporated in a large number of new performance molecules[1] such as commercially significant pharmaceutical and agrochemical products.[2] Beyond bioactives, fluorinated organics are important entities in such industrially relevant materials as liquid crystal cocktails and organic dyes for the next generation of displays and solar cell devices.[3] As a consequence, innovation in organofluorine chemistry remains an important theme in contemporary organic synthesis, contributing to new molecular products and having a positive impact on society. The majority of commercially significant organofluorine compounds contain F-aryl and/or F_3C-aryl moieties; however, the demand for improved properties is challenging chemists to prepare compounds that possess a C–F bond at a stereogenic center,[4] as the C–F bond introduces very particular properties into organic molecules.[5]

This review summarizes the impact of the C–F bond when selectively introduced into an organic molecule. It also highlights recent developments in reagents and methods for the incorporation of fluorine into organic compounds by deoxyfluorination reactions, and presents informative examples from the recent literature to illustrate these transformations. The synthesis of alkanes carrying three, four, five, or six consecutive (vicinal) C–F bonds is also used to highlight deoxyfluorination methodologies.

2. The Polar C–F Bond in Organic Molecules

Some general properties of fluorine in organic molecules have been reviewed and are summarized here.[5,6] The high electronegativity of fluorine, the highest value (ε = 3.98) on the Pauling scale, compacts the nucleus and fluorine is sterically compressed. When covalently bound to carbon, fluorine is the smallest atom next to hydrogen (van der Waals radii of H = 1.2 Å, F = 1.47 Å, O = 1.52 Å, and N = 1.55 Å). Often, fluorine can replace hydrogen, e.g., in a drug candidate to modify its pharmacokinetic properties, because the substitution does not perturb the overall steric profile of the molecule, and fluorine tunes the electronic properties of the molecule.[7] Due to its high electronegativity, carbon-bound fluorine is a very weak hydrogen-bond acceptor relative to oxygen and nitrogen. Thus, the introduction of fluorine provides an electronic torque through a molecule, which is not accompanied by an increase in intermolecular hydrogen-bonding interactions.[8] The C–F bond is highly polar and this renders it the strongest (105 kcal mol^{-1}) and shortest (except for C–H) in organic chemistry, as the polarity imparts a significant electrostatic character ($C^{\delta+}$–$F^{\delta-}$) to this otherwise covalent bond.

The polar nature of the C–F bond introduces a dipole, and the dipole orients itself relative to other polar functional groups and charged atoms within a molecule, favoring certain conformations and disfavoring others (**Figure 1**). For example, α-fluoroamides **A** generally adopt a C–F/C=O antiperiplanar conformation,[9] an interaction which has been used to influence the structure of oligopeptides of β-amino acids[10] and to explore the preferred enantiomeric conformations of amides binding to biological receptors.[11]

A preferred conformation is also found in β-fluoroammonium systems, where protonated β-fluoroamines have a strong preference for a gauche conformation between the vicinal C–F and $C–N^+$ bonds, which aligns the C–F and N^+–H dipoles antiparallel to each other.[12] For this reason 3-fluoropiperidinium rings **B** adopt an axial rather than an equatorial conformation of the C–F bond.[13] This effect is also observed in analogous 4- and 5-membered rings such as **C** and **D**, which adopt puckered conformations dictated by this

interaction.[14,15] This observation extends to acyclic systems, where β-fluoroethylammonium **E** and even β-fluoroethylpyridinium **F** have highly preferred gauche rather than anti conformations, due to intramolecular charge–dipole interactions.[16] This interaction is largely electrostatic and can be several kcal mol^{-1} in magnitude. This effect has recently been applied proactively to influence the conformation of intermediates in organocatalysts[17] and of nitrogen rings in DNA-binding drug molecules.[15]

In neutral acyclic alkanes such as 1,2-difluoroethane (**G**), vicinal C–F bonds prefer to lie gauche to each other (**Figure 2**).[18] The high polarity of fluorine lowers the energy of the σ* antibonding orbital associated with the C–F bond, allowing electron-rich orbitals to donate (hyperconjugate) into this orbital in a stabilizing interaction. A vicinal C–F bond is the least able hyperconjugative donor, and is therefore the least preferred to align in an anti conformation, and generally adopts a gauche orientation, relative to a vicinal C–F bond. This accounts for the counterintuitive observation that **G** has a gauche conformer that is lower in energy than the anti conformer. The magnitude of the fluorine gauche effect in **G** is relatively small (< 1.0 kcal mol^{-1}), as it appears to be entirely stereoelectronic (σ–σ*) in nature.[19]

In systems where fluorine atoms are attached to alternate carbon atoms along an acyclic chain, the 1,3-C–F bonds will generally avoid a parallel orientation, due to dipolar repulsion.[20] Thus, acyclic chains where fluorines are arranged in runs of adjacent carbons with an all-syn stereochemistry adopt helical conformations.[21,22] This arises because dipolar repulsion between the 1,3-C–F bonds twists the C–C bonds away from an anti-zigzag conformation such as the one indicated in stereoisomer **J**. The helical arrangement is also reinforced by weaker hyperconjugative interactions leading to 1,2-gauche C–F preferences. However, if a configuration of C–F bonds is constructed such that there is no 1,3 repulsion, e.g., as in stereoisomer **J**, then the chain is able to adopt an extended anti-zigzag conformation.[23]

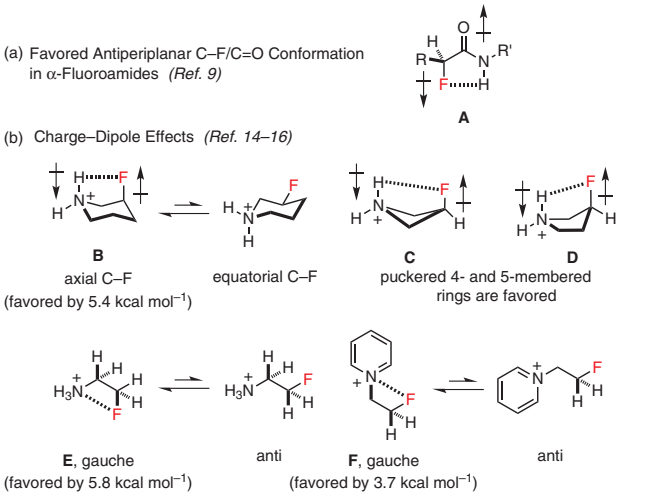


Figure 1. Intramolecular Interactions between the C–F and Other Dipoles Lead to Preferred Conformations.

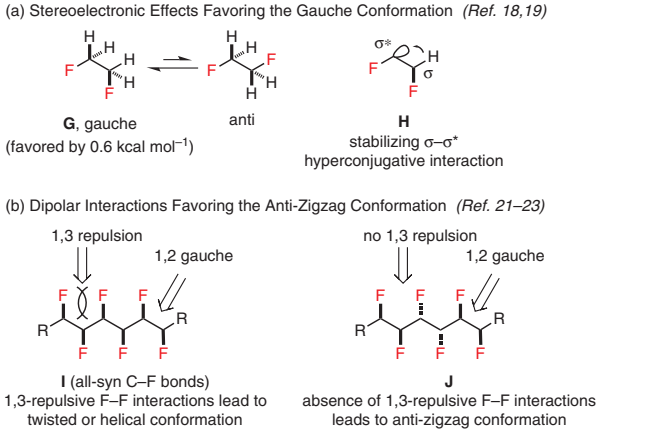


Figure 2. Stereoelectronic and Dipolar Effects in Vicinal Di- and Poly-fluoroalkanes.

3. Deoxyfluorination Reagents

Synthesis strategies are required in order to incorporate the C–F bond and exploit its polar nature in molecular design. This review highlights some of these strategies and emerging reagents that have been employed for stereospecific C–O to C–F (deoxyfluorination) reactions (**Figure 3**).[24–34]

Activated C–O bonds (epoxides, triflates, etc.) can be cleaved by fluoride ion (e.g., fluoride salts or TBAF) or by HF reagents such as pyridinium poly(hydrogen fluoride) (PPHF, Py•(HF)$_X$, or Olah's reagent)[24] or Et$_3$N•3HF. The user friendly formulations of HF remain important in terms of their simplicity of use and effectiveness. Dehydroxyfluorination reagents for the conversion of alcohols continue to evolve. DAST was introduced[25] by DuPont as the first bench-stable dehydroxyfluorination reagent and a useful alternative to a combination of SF_4 and HF. However, DAST is unstable to heat and Deoxo-Fluor® has emerged[26] as a more heat-stable alternative. Related reagents such as MOST[27] have also found a place as DAST alternatives.

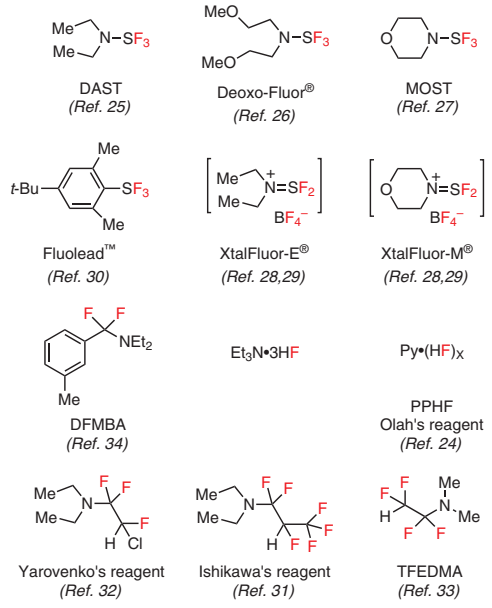


Figure 3. Most Popular Deoxyfluorination Reagents.

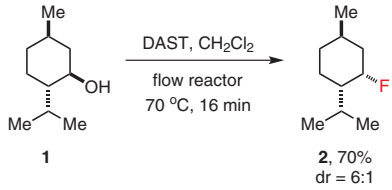
Recently, XtalFluor-E®, XtalFluor-M®,[28,29] and Fluolead™ [30] have been introduced as a new generation of deoxyfluorinating reagents. They are attractive as bench-stable solids, and the scope of these reagents is unfolding as they are being evaluated by the chemistry community. This class of reagents tends not to be stereoselective in their deoxyfluorination reactions, as they are more prone to S_N1 than S_N2 reactions. However, modified protocols are emerging that significantly improve the stereoselectivity of such reactions.

Although Ishikawa's[31] and Yarovenko's[32] reagents were among the first generation $R_2N\text{-}CF_2R$ deoxyfluorination reagents, new variants of this class continue to emerge such as TFEDMA[33] and DFMBA.[34]

3.1. DAST and Deoxo-Fluor®

Diethylaminosulfur trifluoride (DAST), reported by Middleton in 1975,[25] is currently the most commonly used dehydroxyfluorination reagent for the conversion of alcohols into fluorinated compounds. The reagent was introduced as a user friendly derivative of the reactive gas SF_4. When SF_4 was introduced by DuPont, it offered a valuable method for deoxyfluorinations (R–OH to R–F, $R_2C{=}O$ to R_2CF_2, and RCO_2H to RCF_3).[35] However, SF_4 is toxic, needs to be contained, and is not so straightforward to handle particularly in organic chemistry research laboratories. DAST has thus assumed a prominent position in fluorination reactions; however, it suffers from poor thermal stability, and is potentially hazardous to scale up. Deoxo-Fluor® introduced by Lal in 1999,[26] is emerging as a significant competitor to DAST for dehydroxyfluorination reactions, with the advantage that it is more thermally stable than DAST. The ether side chains apparently coordinate to the sulfur, rendering the reagent less prone to decomposition by molecular disproportionation, which DAST undergoes upon heating.

One strategy for controlling DAST-mediated reactions is to develop automated reactor methods. This has recently been achieved by Seeberger's group,[36] who have reported flow-reactor methodology for the conversion of benzyl and secondary alcohols with DAST into their respective fluorides. Contact times are short, and a range of substrates were explored to exemplify the methodology. Both electron-rich and electron-deficient benzyl alcohols were converted in good yields, as was menthol (**1**), which efficiently generated the corresponding fluoride, **2**, with good configurational inversion, and in a short reaction time (**eq 1**).



1 **2**, 70%, dr = 6:1

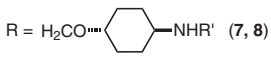
eq 1 *(Ref. 36)*

Although secondary aliphatic alcohols generally display good stereochemical control (inversion) in DAST reactions, this is not the case for secondary benzylic alcohols which are very prone to S_N1 reaction modes and thus show very poor stereospecificity. To address this issue, Bio, Waters, and co-workers have recently introduced a valuable modification, which involves addition of a TMS-amine to the DAST or Deoxo-Fluor® reaction (**eq 2**).[37] For example, the addition of 4-TMS-morpholine (**3**) or Et_2NTMS (**4**) to DAST or Deoxo-Fluor® dehydroxyfluorinations of **7** and **8**, intermediates in process development, improved the enantiomeric purity of products **11** and **12** from 50% to 96% ee. The method was recently extended to alcohols (*R*)-phenethanol (**5**) and ethyl (*S*)-mandelate (**6**), which are particularly prone to an S_N1 reaction course.[38] Without TMS-amine additives, the enantiomeric purity of products **9** and **10** is very low (7–23% ee's); however with the TMS-amine, the conversions become highly stereospecific, increasing ee's to 95–99%, a modification that should find wide application.

5–8 **9–12**

SM	R	R^1	Reagent	Additive	Conditions	ee
5	Me	H	DAST	----	CH_2Cl_2, rt, 15 h	7%
5	Me	H	Deoxo-Fluor®	----	CH_2Cl_2, rt, 15 h	13%
5	Me	H	DAST	**3**[a,b]	CH_2Cl_2, rt, 15 h	95%
5	Me	H	Deoxo-Fluor®	**3**[a,b]	CH_2Cl_2, rt, 15 h	84%
6	CO_2Et	H	DAST	----	CH_2Cl_2, rt, 24 h	8%
6	CO_2Et	H	Deoxo-Fluor®	----	CH_2Cl_2, rt, 24 h	23%
6	CO_2Et	H	DAST	**3**[a,c]	CH_2Cl_2, rt, 24 h	99%
6	CO_2Et	H	Deoxo-Fluor®	**3**[a,c]	CH_2Cl_2, rt, 24 h	99%
7	*d*	F	DAST	----	CH_2Cl_2, –70 °C	56%
8	*d*	F	Deoxo-Fluor®	----	CH_2Cl_2, –70 °C	50%
7	*d*	F	DAST	Et_2NTMS (**4**)	CH_2Cl_2, –70 °C	99%
8	*d*	F	Deoxo-Fluor®	**3**[a]	PhMe, 0 °C	96%

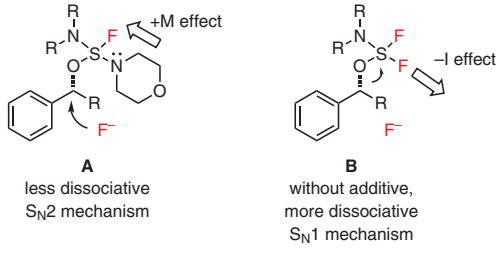
[a] 4-TMS-morpholine (**3**). [b] 3 equiv. [c] 1 equiv. [d] **7**, R' = Cbz; **8**, R' = Boc.



(**7, 8**)

eq 2 *(Ref. 37,38)*

It is suggested[38] that intermediate **A** is less prone to S_N1 dissociation, due to the mesomeric donor (+M) nature of the additional nitrogen lone pair derived from the amine. By comparison, the inductive (–I)

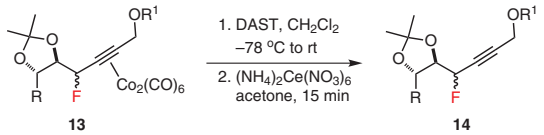


A
less dissociative
S_N2 mechanism

B
without additive,
more dissociative
S_N1 mechanism

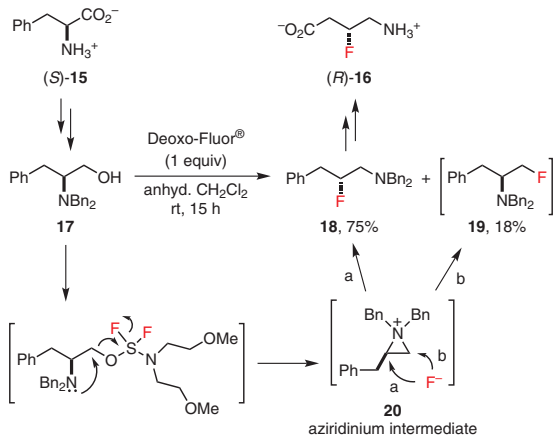
M = mesomeric (donor) effect of nitrogen lone pair
I = inductive effect of the two fluorine atoms

Figure 4. TMS-Amine Additives Lead to a Less Dissociative Reaction Intermediate **A**. *(Ref. 38)*

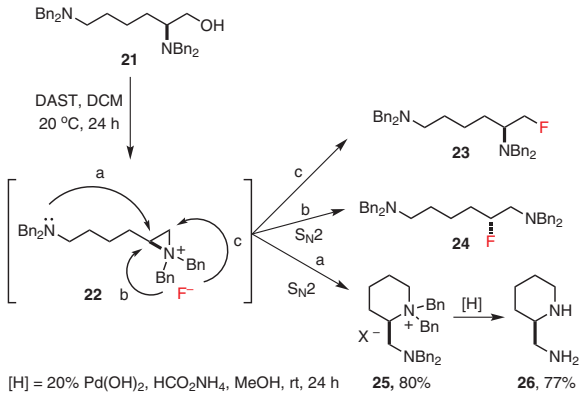


R	R^1	13 anti:syn	14 Yield	14 anti:syn
H	Bn	1:2.3	88%	13:1
$BnOCH_2$	Bn	1.5:1	81%	5.4:1
$BnOCH_2$	PMB	2:1	90%	5:1

eq 3 *(Ref. 39)*



Scheme 1. Synthesis of (*R*)-3-F-GABA from (*S*)-Phenylalanine. Fluorination of *N,N*-Dibenzyl-β-amino Alcohol with Deoxo-Fluor® and DAST Involves a Rearrangement. *(Ref. 41b)*



Scheme 2. Reaction Pathways on Treatment of (*S*)-**21** with DAST. *(Ref. 42)*

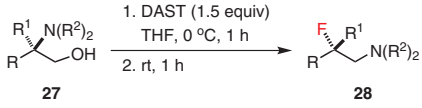
effect of the two fluorines in intermediate **B** renders the benzylic group a better leaving group and the S_N1 process is promoted (**Figure 4**).

In 2010, Zhang and co-workers reported the DAST-mediated dehydroxyfluorination of diastereoisomeric internal propargylic alcohols, as part of a program for preparing monofluorinated sugars.[39] While the reaction gave poor yields (7–34%) of propargyl fluorides, the corresponding alkyne–cobalt carbonyl complexes (**13**), generated via the Nicholas reaction,[40] were much more amenable to fluorination. The easy removal of the cobalt carbonyl group from the initial products with CAN offers a practical method for DAST-mediated propargyl fluorination (**eq 3**).

Reactions of β-amino alcohols with DAST and Deoxo-Fluor® generate rearranged products, often in a highly stereoselective manner. This reaction has proven advantageous in the synthesis of enantiomers of 3-fluoro-γ-aminobutyric acid (3-F-GABA) such as (*R*)-**16** from (*S*)-phenylalanine (**15**) (**Scheme 1**).[41] Such selectively fluorinated GABA analogues prefer conformations where the C–F bond is gauche to the $C–NH_3^+$ bond, due to a stabilizing charge–dipole interaction (see Figure 1), and they have been useful for studying the binding of GABA to receptors and enzymes, as conformationally biased GABA analogues.[41] The key step in the synthesis of **16** involves dehydroxyfluorination of *N,N*-dibenzylated-β-amino alcohol **17** with DAST or Deoxo-Fluor®. This generates rearranged β-fluoroamine **18** as the major product, alongside that of the direct fluorination, **19**, in a 4:1 ratio. Rearrangement of **17** proceeds via an aziridinium intermediate, **20**, which partitions to either **18** or **19** depending on the regiochemistry of the ring opening by fluoride ion.

Similarly, treatment of (*S*)-2,6-bis(dibenzylamino)hexanol (**21**) with DAST generates aziridinium intermediate **22**, which undergoes ring opening by three different pathways to generate products **23**, **24**, and **25**.[42] Optimization of the reaction conditions resulted in an efficient intramolecular and stereospecific cyclization (80%) to give tetrabenzylpiperidinium salt **25**. This product was hydrogenated, providing a convenient synthesis of cyclic diamine **26** (**Scheme 2**).

Duthion et al. have also reported a highly enantio- and completely regioselective rearrangement of optically active β-amino alcohols to tertiary β-fluoroamines induced by DAST (**eq 4**).[43] In contrast to the product distribution observed with β-amino alcohol **21** (see Scheme 2), reaction of β-amino alcohols **27** with DAST provided only tertiary β-fluoroamines **28**, without a trace of any primary regioisomers. This methodology was successfully applied to the DAST-induced enantioselective rearrangement of *N,N*-diallylamino alcohol **29** to provide tertiary β-fluoroamine **30** as a precursor for the preparation of LY503430, a potential therapeutic agent for Parkinson's disease (**eq 5**).[43]



No	R	R^1	R^2	Yield	ee
a	Ph	H	allyl	95%	----
b	CO_2Me	Me	Bn	84%	91%
c	Me	Bn	Bn	90%	>99%
d	Ph[a]	allyl	Bn	95%	77%

[a] 2.2 equiv of DAST was used.

eq 4 *(Ref. 43)*

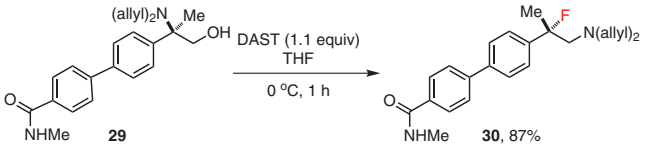
DAST and Deoxo-Fluor® have been explored in dehydroxyfluorination reactions of α,β-epoxy alcohols to generate fluorinated α,β-epoxides.[44] For such secondary alcohols, the success of the fluorination is very dependent on the substrate diastereoisomer. For example, Aoyagi et al. have reported the dehydroxyfluorination of the natural product triptolide, **31**, and its analogues (e.g., **33**)—triepoxides isolated from the Chinese medicinal plant *T. wilfordii*.[45] Reaction of triptolide **31** with DAST gave the corresponding 14β-fluorinated product **32** as a single stereoisomer in 77% yield, whereas fluorination of 14-*epi*-triptolide **33** under similar conditions gave the corresponding fluorinated product **34** in very poor yield (12%) along with three other byproducts (**Scheme 3**).[45] It appears that, in general, *anti*-α,β-epoxy secondary alcohols are converted much more smoothly than their syn diastereoisomers.

Our group has made similar observations whereby Sharpless-oxidation-derived *anti*-α,β-epoxy alcohols react with DAST or Deoxo-Fluor® to give the corresponding inverted fluorides, generally in good yields and high stereospecificity.[44] In contrast, the *syn*-α,β-epoxy alcohols are poor substrates and give significant levels of rearranged decomposition products. Stereoelectronics appears to favor a smoother conversion of the anti diastereoisomers, although the origin of the effect is not clear.

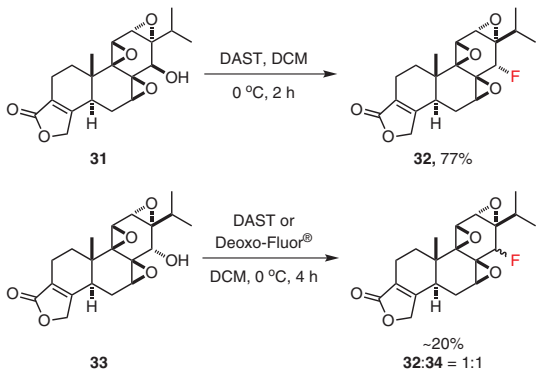
3.2. XtalFluor-E® and XtalFluor-M®

In 2009, Couturier and co-workers[28,29] reported the preparation and utilization of the crystalline reagents diethylamino- and morpholinodifluorosulfinium tetrafluoroborate salts, XtalFluor-E® and XtalFluor-M®, respectively. The salts are generated via fluoride ion transfer to BF_3•THF in a solution of dialkyl(trimethylsilyl)amine and SF_4 in CH_2Cl_2 (**Scheme 4**). A one-pot preparation appears to offer a practical method of synthesis. These reagents are relatively safe and cost-efficient to prepare, as there is no requirement to carry out the risky distillation of DAST. XtalFluor-E® and XtalFluor-M® can efficiently transform alcohols into their corresponding fluorides, but the reactions require the addition of either an HF•amine reagent or DBU for efficient transformation.

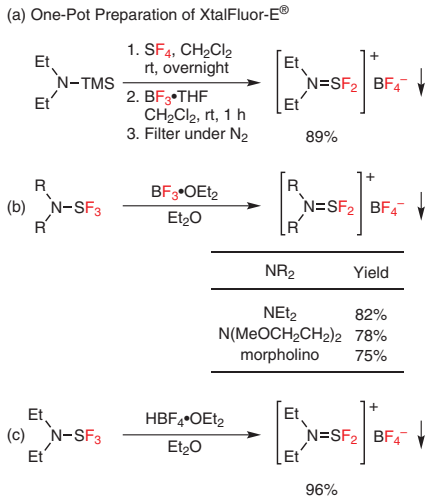
Amine•HFs, such as Et_3N•3HF, provide the fluoride ion for reaction with intermediate **35**. Without the amine•HF, DBU deprotonates intermediate **35** to promote fluoride ion release, such that this fluoride can act as a nucleophile in a subsequent step to complete the reaction (**Scheme 5**).[28] These reagents fluorinate a wide range of alcohols including primary, secondary, tertiary, and allylic alcohols (**Table 1**).[28] The XtalFluor reagents display good stereochemical integrity and reduce the levels of elimination side products often observed with DAST and Deoxo-Fluor®.



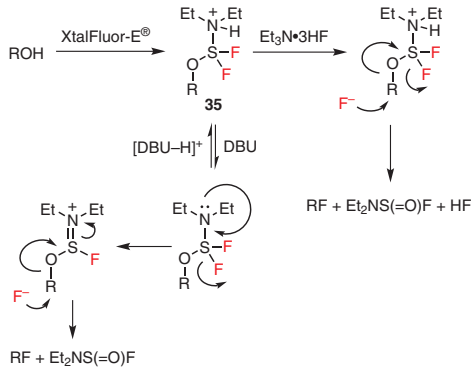
eq 5 *(Ref. 43)*



Scheme 3. Dehydroxyfluorination of Triptolide Alcohol Diastereoisomers Show Different Efficiencies. *(Ref. 45)*



Scheme 4. Preparation of XtalFluor-E® and XtalFluor-M®. *(Ref. 28,29)*



Scheme 5. Effects of DBU or Amine•HF on Alcohol Fluorination Reactions with XtalFluor-E®. *(Ref. 28)*

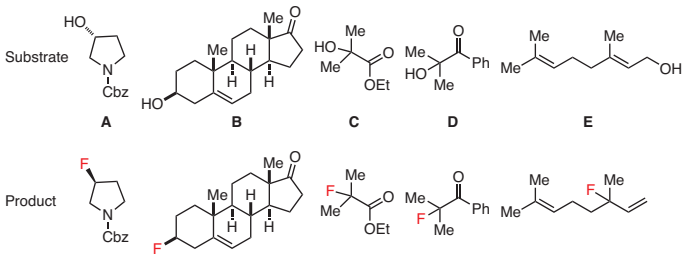
3.3. Fluolead™

In the early 1960s, shortly after the introduction of SF_4, phenylsulfur trifluoride ($PhSF_3$) was prepared and found to act as a modest deoxyfluorination reagent.[46] It converted aryl aldehydes into the corresponding difluorides; however, it was not sufficiently reactive to carry out deoxyfluorinations on alkyl aldehydes, ketones, and carboxylic acids. Umemoto and co-workers[30] have recently introduced a second-generation $PhSF_3$ reagent, 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride, which is being marketed as Fluolead™, as a safe, shelf-stable, and easy-to-handle deoxyfluorinating agent. Fluolead™ is chemically more stable than $PhSF_3$, and more thermally stable than DAST because the C–S bond in Fluolead™ is stronger (714 ± 1.2 kJ mol^{-1}) than the N–S bond (464 ± 21 kJ mol^{-1}) in DAST. The reagent is prepared from the disulfide, formed after $ZnCl_2$-catalyzed reaction of 3,5-dimethyl-*tert*-butylbenzene **36** and S_2Cl_2 (**Scheme 6**). Reaction of the disulfide intermediate with chlorine and KF generates Fluolead™ in high yield.

The number of reactions reported with Fluolead™ is still relatively small; some examples are summarized in **Table 2**.[30] The stereoselective inversion of secondary alcohol **37** into fluorocycloalkane **38** has been demonstrated, and the anomeric fluoroglycoside **40** is readily prepared from hemiacetal **39**. However, fluorination of *syn*-1,2-cyclopentanediol (**41**) gave 1-(arylsulfinyloxy)-2-fluorocyclopentane **42** as a mixture of two diastereoisomers (95:5) rather than the vicinal difluoride. Unprotected 3-hydroxypyrrolidine (**43**) gave sulfinylated pyrrolidine **44** as the fluorinated product.

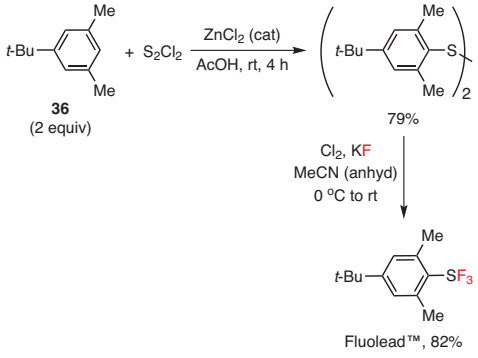
Recently, Haufe and co-workers reported the stereoselective synthesis of (*3R*)-3-fluoro-1-tosylpiperidine (**46**) from hydroxymethylpyrrolidine **45** using a combination of Fluolead™ and Olah's reagent (**Scheme 7**).[47] The reaction is very efficient (95% yield) and proceeds via aziridinium intermediate **47**, with only a minor amount of non-ring-expanded primary fluoride **48** in the product mixture.

Table 1. Reaction of Alcohols with XtalFluor-E® and XtalFluor-M®. *(Ref. 28)*



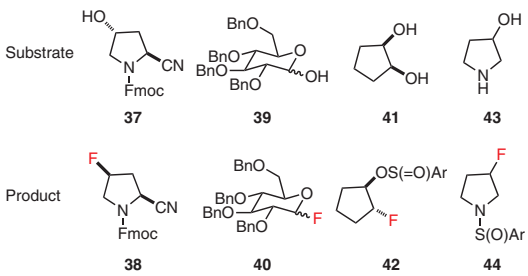
Entry	ROH	XtalFluor[a]	Additive[b]	Conditions[c]	Yield	ee
1	**A**	-M®	Et_3N•3HF	Et_3N, –78 °C to rt, 3 h	80%	97.0%
2	**A**	-E®	Et_3N•3HF	Et_3N, –78 °C to rt, 6 h	74%	98.0%
3	**A**	-E®	Et_3N•3HF	rt, 16 h	60%	95.6%
4	**A**	-E®	DBU	–78 °C to rt, 24 h	86%	98.2%
5	**B**	-M®	Et_3N•3HF	Et_3N, –78 °C to rt, 2 h	47%	----
6	**B**	-E®	Et_3N•3HF	Et_3N, –78 °C to rt, 5 h	45%	----
7	**B**	-E®	Et_3N•3HF[d]	rt, 16 h	77%	----
8	**C**	-M®	Et_3N•3HF	Et_3N, –78 °C to rt, 24 h	72%	----
9	**C**	-E®	Et_3N•3HF	Et_3N, –78 °C to rt, 24 h	64%	----
10	**D**	-E®	Et_3N•3HF	–78 °C to rt, 8 h	72%	----
11	**D**	-M®	Et_3N•3HF	Et_3N, –78 °C to rt, 24 h	83%	----
12	**D**	-E®	Et_3N•3HF	Et_3N, –78 °C to rt, 8 h	77%	----
13	**D**	-E®	DBU	rt, 24 h	93%	----
14	**E**	-M®	Et_3N•3HF	Et_3N, 0 °C to rt, 0.75 h	88%	----
15	**E**	-E®	Et_3N•3HF	Et_3N, –78 °C to rt, 1 h	90%	----

[a] 1.5 equiv of Xtalfluor reagent employed. [b] 2.0 equiv of Et_3N•3HF and 1.5 equiv of DBU used. [c] 1 equiv of Et_3N utilized. [d] 4.0 equiv of Et_3N•3HF used.



Scheme 6. Synthesis of Fluolead™. *(Ref. 30)*

Table 2. Fluorinations with Fluolead™ (4-*t*-Bu-2,6-$Me_2C_6H_2SF_3$). *(Ref. 30)*



Entry	ROH	Additive (equiv)	Conditions	Yield[a]
1	**37**	----	CH_2Cl_2, 0 °C to rt, 60 h	85%
2	**39**	----	CH_2Cl_2, rt, 2 h	84%
3	$(CH_2OH)_2$	Et_3N (2)	CH_2Cl_2, rt, 15 h	91%[b]
4	**41**	----	1. CH_2Cl_2, –60 to 0 °C, 2 h 2. reflux, 17 h	95%
5	$MeNH(CH_2)_2OH$	Et_3N•3HF (0.5)	1. $(CH_2Cl)_2$, 75 °C, 5 min 2. Et_3N (3.6 equiv), rt, 1 h	65%[c]
6	**43**	PPHF (0.8)	1. CH_2Cl_2, rt, 4 h 2. Et_3N (22 equiv), rt, 2 h	85%[d]

[a] Ar = 4-*t*-Bu-2,6-$Me_2C_6H_2$. [b] $FCH_2CH_2OS(=O)Ar$. [c] $MeN[S(O)Ar]CH_2CH_2F$. [d] dr = 1:1.

3.4. Ishikawa's, Yarovenko's, and TFDMA Reagents

In 1959, Yarovenko and Raksha reported the addition adduct of Et_2NH and chlorotrifluoroethene (see Figure 3 and **Scheme 8**).[32] This proved to be a good dehydroxyfluorination reagent particularly for the conversion of alcohols into alkyl fluorides.[48] A related reagent, the

adduct of Et_2NH and hexafluoropropene, generally prepared in an ether solution, was reported by Ishikawa's group in 1979.[31] The resultant perfluoropropene–diethylamine adduct (PPDA), or Ishikawa's reagent, is an equilibrium mixture of fluoroalkylamine and (*E*)-fluoroenamine (3:1). The reagent is used as a dehydroxyfluorination reagent directly without distillation. Ishikawa's reagent is more stable and has found wider applications than Yarovenko's;[49] it can be stored for a long time without significant decomposition.

More recently, researchers at DuPont have introduced a related reagent, 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA), the adduct between tetrafluoroethylene and Me_2NH.[33] It is a more volatile reagent than its predecessors and, as a consequence, is discharged from a cylinder. Nevertheless, it displays comparable dehydroxyfluorination reactivity,[50] and reagent-derived side products are readily removed due to their volatility.

These reagents fluorinate a range of primary and secondary alcohols, generating alkyl fluorides and the corresponding reagent-originated amides [$Et_2N(CO)R$] as co-products. However, the reactions of this group of reagents can suffer from formation of ester and amide side products, and dialkyl ethers are a particular problem with PPDA. In an interesting reaction, treatment of allylic alcohol **49** with PPDA led to the formation of α,α-F,CF_3 amide **51** (**Scheme 9**).[51] The reaction appears to proceed via a [3,3]-sigmatropic rearrangement of intermediate **50**. When propargylic alcohol **52** was treated with PPDA, a similar rearrangement took place via intermediate **53**, generating amide **54** with high *Z*-allene stereoselectivity.[51]

3.5. *N,N*-Diethyl-α,α-difluoro(*meta*-methylbenzyl)amine (DFMBA)

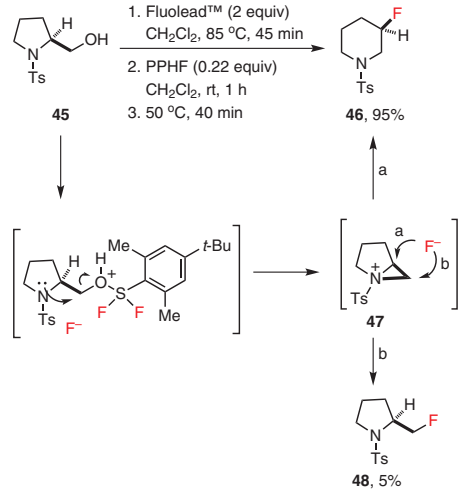
In 2004, *N*,*N*-diethyl-α,α-difluoro(*meta*-methylbenzyl)amine (DFMBA) was introduced as a deoxyfluorination reagent, and shown to have high thermal stability.[34] Hara and co-workers have used DFMBA for the deoxyfluorination of sugars.[34] The reagent is prepared by deoxychlorination of *N*,*N*-diethyl-3-methylbenzamide with oxalyl chloride, followed by halogen exchange with Et_3N•3HF (**Scheme 10**).[52] DFMBA mediates smooth dehydroxyfluorination of primary, secondary, tertiary, and benzyl alcohols, usually in heptane or dodecane.[52–54] The reactions require heating, since they can be quite sluggish at ambient temperature. Microwave irradiation has been employed to accelerate these reactions, and a range of transformations have been carried out by this method (see Scheme 10).[53]

The sluggish nature of the transformations arises from the stability of the complexed intermediate prior to nucleophilic fluorination. DFMBA has been employed in the selective monofluorination of 1,2- and 1,3-diols in heptane or diglyme under heating or by microwave irradiation to generate fluoro esters (**Scheme 11**).[52,54]

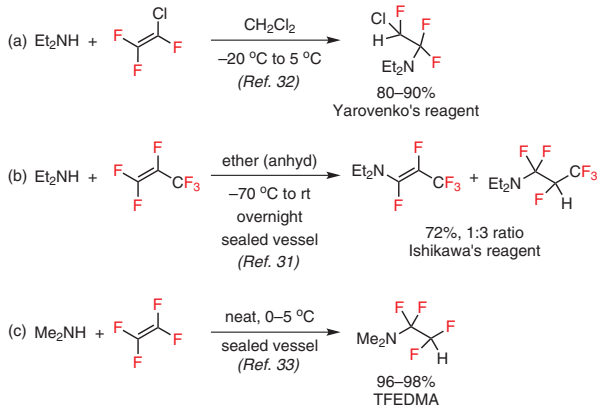
Interestingly, Hara and co-workers reported the conversion of epoxides into vicinal difluorides with DFMBA in the presence of Et_3N•3HF (**eq 6**), a reaction that is generally difficult with most deoxyfluorination reagents.[55] This is a particularly striking transformation given that a range of functional groups are tolerated.

4. Synthesis of Vicinal Polyfluorinated Alkane Stereoisomers

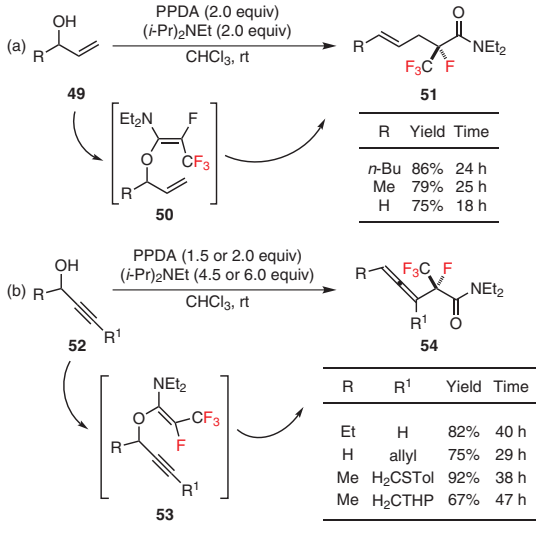
Our group has utilized a variety of deoxyfluorination reactions to prepare single stereoisomers of alkane chains with runs of fluoromethylene groups.[22] Some of these syntheses are summarized below for alkyl chains carrying three, four, five, or six vicinal fluorine atoms as single stereoisomers. A key reagent for these protocols is Et_3N•3HF. Reagents in which HF is complexed with amines,



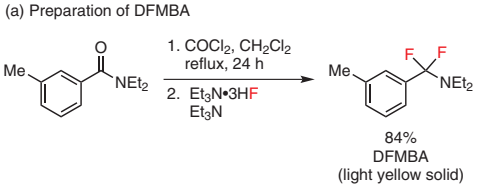
Scheme 7. Fluolead™ Mediated Ring Expansion of **45**. *(Ref. 47)*



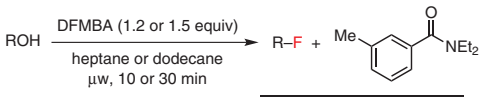
Scheme 8. Reagents Derived from 1:1 Adducts of Fluoroalkenes and Dialkylamines.



Scheme 9. Reactions of PPDA with Allylic and Propargylic Alcohols. *(Ref. 51)*



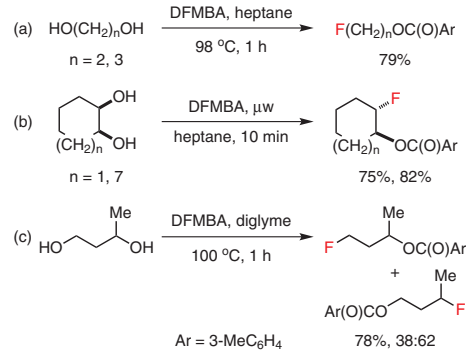
(b) Deoxyfluorination of Alcohols with DFMBA



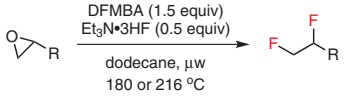
R	Yield
CH_2=CH$(CH_2)_9$	86%
$BnOCH_2CH_2$	72%
n-$C_{10}H_{21}CHFCH_2$	87%
n-$C_{10}H_{21}CH(CH_2F)$	63%
n-$C_{10}H_{21}CHMe$	72%
$(n\text{-}C_6H_{13})_2CH$	50%
n-$BuO(O)C(CH_2)_4$	80%
4-$BrC_6H_4CH_2$[a]	95%

[a] 50 °C, 2 h.

Scheme 10. Preparation and Reactions of DFMBA. *(Ref. 52,53)*



Scheme 11. Reactions of Diols with DFMBA. *(Ref. 54)*



R	Yield
n-$C_{10}H_{21}$	75%
$BnOCH_2$	68%
$AcO(CH_2)_9$	71%
n-$C_8H_{17}CH$=$CH(CH_2)_2$	67%
$EtO_2C(CH_2)_8$	78%
4-*i*-BuC_6H_4[a]	61%

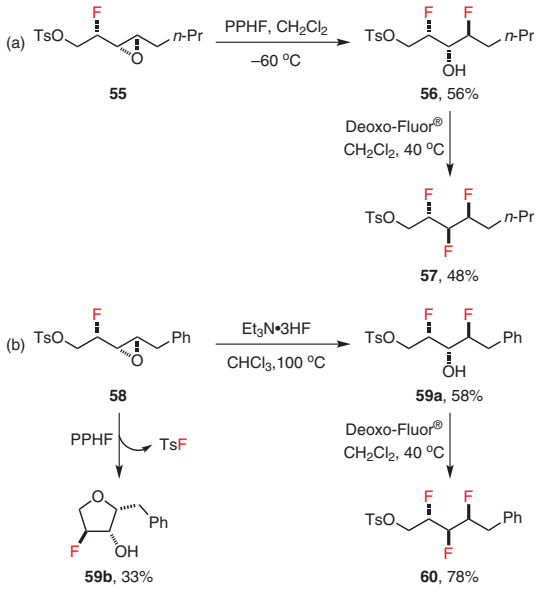
[a] 100 °C, 20 h.

eq 6 *(Ref. 55)*

particularly, pyridinium poly(hydrogen fluoride) (PPHF, Olah's reagent)[24] and Et_3N•3HF have been widely used as fluoride sources for C–F bond synthesis. They have advantages over tetra(*n*-butyl)-ammonium fluoride (TBAF) and other fluoride ion reagents (e.g., CsF) in that they are less basic and thus less prone to promoting elimination reactions. One route to alkane stereoisomers containing three contiguous fluorines starts with fluoro-α,β-epoxides **55** or **58** and leads to intermediates **56** and **59a** (**Scheme 12**).[44] These fluoro-α,β-epoxides ring-open away from the electronegative fluorine with inversion of configuration. A Deoxo-Fluor® mediated dehydroxyfluorination reaction was then used to install the third fluorine atom in each case to give trifluoroalkanes **57** and **60**.

Generally, epoxide ring-opening reactions with PPHF take place at lower temperatures than those with Et_3N•3HF due to the more acidic nature of PPHF. However, this difference in acidity can result in different reaction pathways. For example, when fluoro-α,β-epoxide **58** was treated with PPHF, an intramolecular cyclization to generate a tetrahydrofuran, **59b**, was observed.[44] This presumably occurs after protonation of the epoxide with PPHF, formation of an intermediate phenonium cation, and fluoride-promoted removal of the tosyl group. In contrast, the reaction with Et_3N•3HF follows a more classical S_N2 mechanism to give fluorohydrin **60**.

A key reaction in the synthesis of the vicinal tetrafluorohexane diastereoisomers **68** and **69** was the Grubbs metathesis reaction of allylic fluoro ether **62**, itself generated by epoxide ring-opening of **61** using Et_3N•3HF (**Scheme 13**).[21,56] Dihydroxylation of the resultant C_2-symmetric olefin **63** gave a 4.3:1 mixture of syn diols **64** and **65**. These were separated by chromatography and taken through the subsequent steps as separate isomers. Sharpless's cyclic sulfate methodology[57] was used to install the third fluorine by reaction of **66** with TBAF, and then the final fluorine was installed in a Deoxo-Fluor® reaction, after



Scheme 12. Preparation of Vicinal Trifluoro Motifs and Divergent Reactions of PPHF and Et_3N•3HF. *(Ref. 44)*

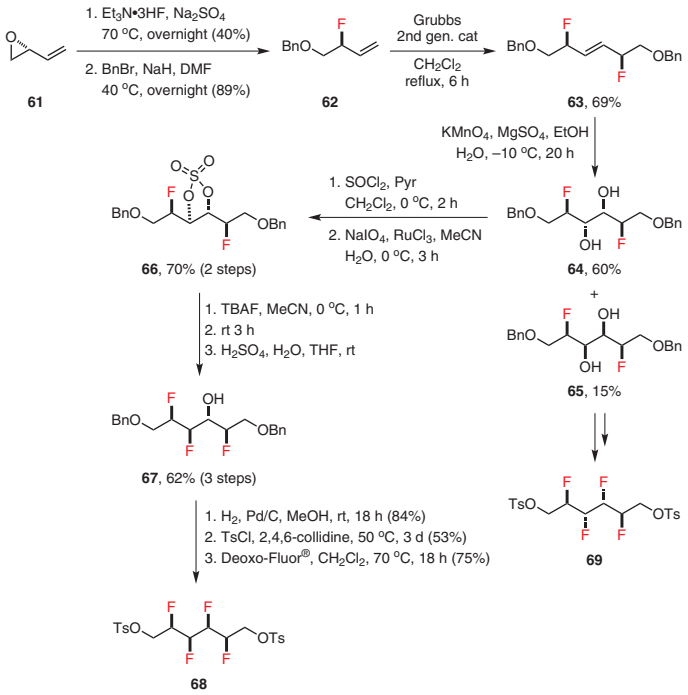
conversion of the peripheral benzyl ethers of **67** into the ditosyl ester **68**. Solution NMR and X-ray structure analysis revealed that **68** and **69** have different carbon-chain conformations. The all-syn isomer **68** has a twisted structure, whereas **69** adopts a more classical extended anti-zigzag carbon-chain conformation. The twisted conformation of **68** can be attributed to the molecule avoiding 1,3-C–F bond repulsion, a situation that is relaxed in the extended structure of **69**.

Bis(allylic) alcohol **70** was a starting point for our group's synthesis of both vicinal pentafluoroheptane stereoisomers **76** and **79**, in which all five fluorines were introduced by deoxyfluorination reactions (**Scheme 14**).[58] Sequential Sharpless epoxidations of the opposite enantiomeric sense generated the optically inactive *meso*-bis(epoxide) alcohol **71**. A Deoxo-Fluor® reaction of this secondary alcohol resulted in an efficient conversion to fluoride **72**, as a single diastereoisomer, with inversion of configuration. A sequence of a double epoxide ring-opening with $Et_3N•3HF$ generated diol **73**; this was followed by double dehydroxyfluorination to form pentafluoride **74**. This stereoisomer was converted via its diol **75** to di(tosylate) **76**.

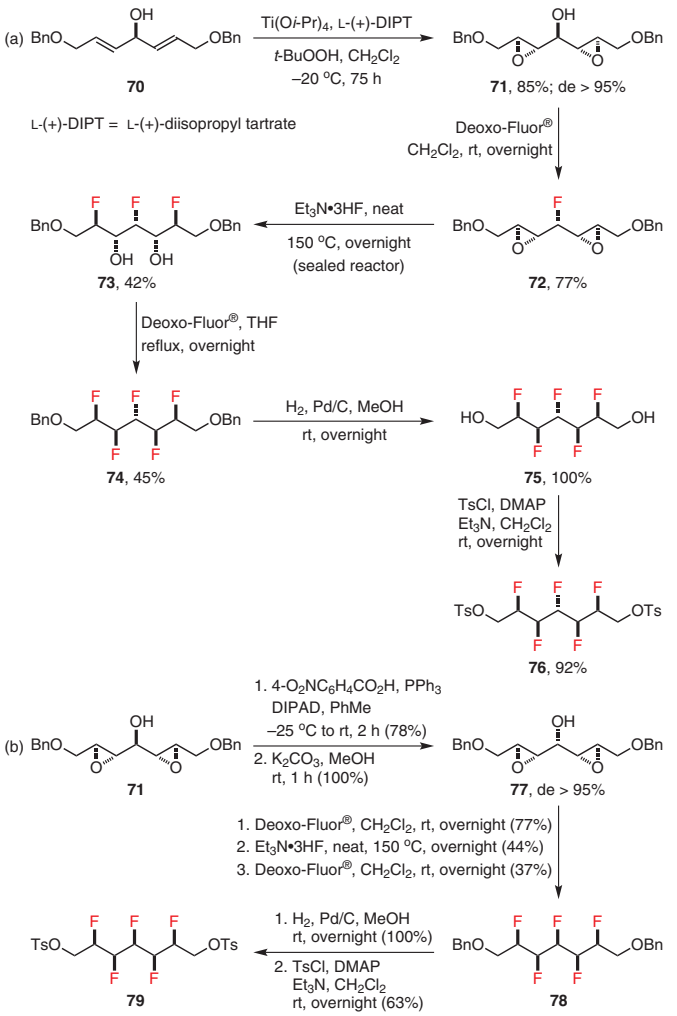
Generation of the all-syn stereoisomer required a configurational inversion of the central alcohol carbon in bis(epoxide) **71**. This was achieved by a Mitsunobu inversion to generate all-syn alcohol **77**. Di(epoxy) alcohol **77** underwent double epoxide ring-opening and double deoxyfluorination with Deoxo-Fluor® to give the all-syn pentafluoroheptane stereoisomer **78**. Hydrogenation to the diol was followed by conversion to di(tosylate) **79**.

The synthesis of the most advanced representatives of this fluoroalkane series, vicinal hexafluorohexanes, has also been reported by our group (**Scheme 15**).[23] The first fluorine was introduced in a regio- and stereoselective manner with $Et_3N•3HF$ at 120 °C by ring-opening of vinyl epoxide **81**. The resultant fluorohydrin **82** was subjected to a symmetrical cross-metathesis reaction to generate a C_2-symmetrical difluorodiol as a single diastereoisomer (>99% ee). Double O-triflation of the free hydroxy groups of this diol, followed by displacement of the triflates with fluoride, using $Et_3N•3HF$ at 50 °C, introduced two additional fluorines to give tetrafluoroalkene **84**, albeit in low yield. Dihydroxylation of this olefin generated two diastereoisomers, **85** and **86**, in a 9:1 ratio, which were separated by chromatography. In each case, the fifth fluorine was introduced by applying Sharpless's cyclic sulfate ring-opening fluorination methodology,[57] with $Et_3N•3HF$ acting as the fluoride ion source, and then the final fluorine atom was installed by dehydroxyfluorination reactions with Deoxo-Fluor®, leading to the desired vicinal hexafluorohexane isomers **89** and **90**.

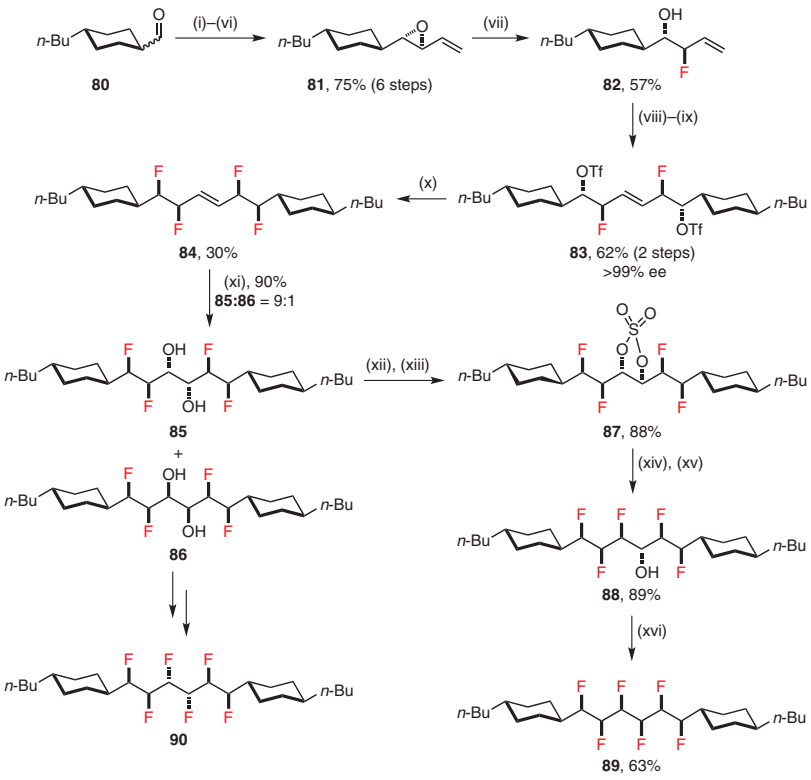
The peripheral cyclohexane rings rendered **89** and **90** as crystalline solids and allowed their X-ray structures to be determined. These structures are particularly insightful in that they reveal a helical



Scheme 13. Synthetic Route to Vicinal Tetrafluorohexane Diastereoisomers **68** and **69**. *(Ref. 21,56)*



Scheme 14. Synthesis of Vicinal Pentafluoroheptane Diastereoisomers. *(Ref. 58)*



(i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt. (ii) KOH, MeOH, Δ. (iii) DIBAL-H, CH_2Cl_2, hexane, –78 °C. (iv) Sharpless epoxidation, –35 °C. (v) DMP (Dess–Martin periodinane), CH_2Cl_2, rt. (vi) Ph_3PCH_2Br, KHMDS, THF, rt. (vii) Et_3N•3HF, MeCN, 120 °C. (viii) Grubbs 2nd gen. cat., CH_2Cl_2, Δ (63%). (ix) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, rt (99%). (x) Et_3N•3HF, Et_3N, THF, 50 °C. (xi) $KMnO_4$, $MgSO_4$, EtOH, CH_2Cl_2, H_2O, 0 °C. (xii) $SOCl_2$, CH_2Cl_2, Py, rt, 1.5 h. (xiii) $NaIO_4$, $RuCl_3$, MeCN, H_2O, 0 °C, 2 h. (xiv) Et_3N•3HF, Et_3N, MeCN, 110 °C. (xv) H_2SO_4, H_2O, THF, rt. (xvi) Deoxo-Fluor®, CH_2Cl_2, reflux, overnight.

Scheme 15. Synthesis of Vicinal Hexafluorohexane Diastereoisomers. *(Ref. 23)*

twist along the chain for the all-syn isomer, **89**, as a result of the stereoelectronic preference to avoid 1,3-C–F bond repulsion. In contrast, the configurations of the C–F bonds in stereoisomer **90** allow the molecule to readily adopt an anti-zigzag carbon-chain conformation, without any 1,3-C–F-repulsive interactions.

Collectively, the vicinal poly(fluoro)alkane motifs described in the preceding paragraphs provide insights into the influence of the C–F bond in determining alkyl-chain conformations in organic molecules. Such insights are important in the design of organic liquid crystals and other performance organic molecules, which require order and polarity but low viscosity.

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Nawaf Al-Maharik received his M.Sc. degree in synthetic chemistry in 1988 from the Technische Hochschule Leuna-Merseburg (THLM; Germany) under the direction of Professor Egon Fanghänel. He obtained his Ph.D. degree in synthetic chemistry in 2000 from the University of Helsinki (Finland), working under the guidance of Professors Tapio Hase and Kristtiina Wähälä. He subsequently joined the group of Professor Lars Engman at Uppsala University (Sweden) and, in 2001, the group of Professor Nigel Botting at the University of St Andrews (Scotland) to work on the synthesis of ^{13}C-labelled complex polyphenols. In 2006, he joined Professor Andrei Nikolaev's group at the University of Dundee (Scotland) to work towards the chemical preparation of GPI anchors and other complex biologically important carbohydrates. In 2010, he joined Professor David O'Hagan's laboratory at the University of St Andrews to work on the synthesis of diastereoisomeric vicinal, polyfluorinated alkanes. His research interests include ^{18}F-labelled radiopharmaceuticals for Positron Emission Tomography (PET) and natural product, tellurium, fluorine, and carbohydrate chemistry.

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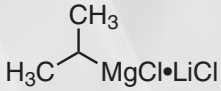

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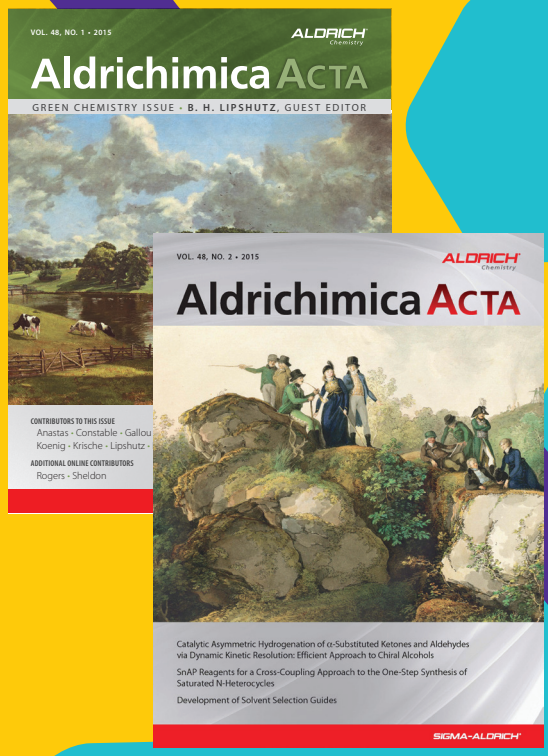

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