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Recent Advances in Intermolecular
Direct Arylation Reactions
Evolution and Applications of Second-Generation
Ruthenium Olefin Metathesis Catalysts



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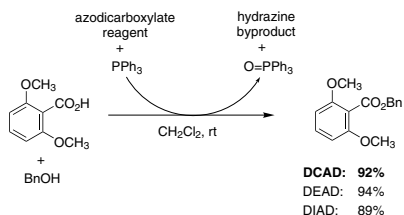
New Products from Aldrich R&D

Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Lipshutz DCAD Coupling Reagent

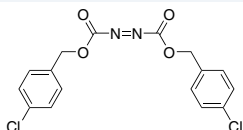
The Mitsunobu reaction is one of the most extensively used coupling reactions in organic synthesis and typically employs azodicarboxylate reagents such as DEAD or DIAD. However, these reagents have drawbacks such as low room-temperature stability and difficulty in removing the hydrazine byproducts. Professor Bruce Lipshutz and co-workers have developed an attractive alternative to the existing reagents: di(4-chlorobenzyl) azodicarboxylate (DCAD). DCAD is a stable solid that has an activity comparable to those of DEAD and DIAD in typical Mitsunobu reactions such as substitutions, esterifications, and etherifications. However, unlike the standard reagents, the hydrazine byproduct can be removed by simple precipitation directly from the reaction mixture, and is easily recycled in high yield to regenerate DCAD.

Lipshutz, B. H. et al. *Org. Lett.* **2006**, 8, 5069.



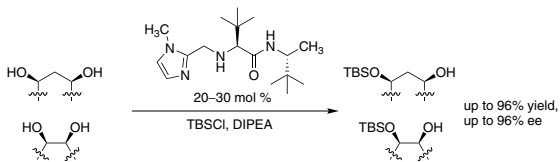
Di(4-chlorobenzyl) azodicarboxylate DCAD

680850 1 g
 $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}_4$ 10 g
FW: 367.18



Hoveyda-Snapper Silylation Catalyst

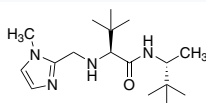
Because of the ease of preparation of *meso*-diols, synthetic methods that can desymmetrize these substrates are critically important. Professors Marc Snapper and Amir Hoveyda at Boston College have reported the first practical enantioselective silylation of *meso*-1,2- and 1,3-diols relying on an amino acid derived organocatalyst. The reactions do not require the rigorous exclusion of air or moisture, and the catalyst can be nearly quantitatively recovered by an aqueous wash. This catalyst greatly increases the efficiency with which optically enriched molecules can be prepared.



Zhao, Y. et al. *Nature* **2006**, 443, 67.

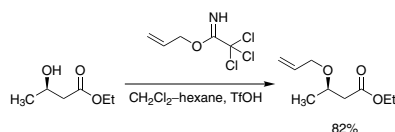
(S)-N-((R)-3,3-Dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1H-imidazol-2-yl)methylamino)butanamide, 97%

680826 1 g
 $\text{C}_{17}\text{H}_{32}\text{N}_4\text{O}$
FW: 308.46



Trichloroacetimidate Reagents

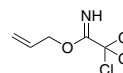
Trichloroacetimidates are useful reagents for protection of alcohols as their allyl and benzyl ethers. We are delighted to offer two new reagents, allyl 2,2,2-trichloroacetimidate and 4-methoxybenzyl 2,2,2-trichloroacetimidate, that have been extensively employed in organic synthesis. These reagents are particularly attractive in applications where base-sensitive functional groups are present that would not tolerate the standard alkoxide alkylation method of alcohol protection.



Clark, J. S. et al. *Tetrahedron* **2006**, 62, 73.

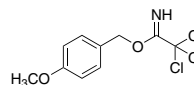
O-Allyl 2,2,2-trichloroacetimidate, 96%

678414 5 g
 $\text{C}_5\text{H}_6\text{Cl}_3\text{NO}$
FW: 202.47



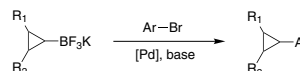
4-Methoxybenzyl 2,2,2-trichloroacetimidate

679585 5 g
 $\text{C}_{10}\text{H}_{10}\text{Cl}_3\text{NO}_2$ 25 g
FW: 282.55



Potassium Cyclopropyltrifluoroborate

Cyclopropyl groups are found in a variety of natural products and are increasingly incorporated into pharmaceuticals such as the broad-spectrum antibiotic ciprofloxacin. Both the Charette¹ and Deng² groups have reported success in the cross-coupling of potassium cyclopropyltrifluoroborates with aryl bromides in the presence of common palladium catalysts. The trifluoroborate salts exhibit enhanced stability and more certain stoichiometry relative to their boronic acid counterparts. However, like boronic acids, post-reaction byproducts are easily removed. We are pleased to add this useful reagent to our ever-growing arsenal of organoboron compounds.



(1) Charette, A. B. et al. *Synlett* **2005**, 11, 1779. (2) Fang, G.-H. et al. *Org. Lett.* **2004**, 6, 357.

Potassium cyclopropyltrifluoroborate

662984 1 g
 $\text{C}_3\text{H}_5\text{BF}_3\text{K}$ 5 g
FW: 147.98



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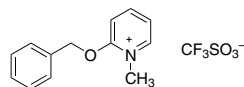
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Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Gregory B. Dudley of Florida State University kindly suggested that we make 2-benzyloxy-1-methylpyridinium triflate. This crystalline, neutral, and stable organic salt is an excellent reagent for the protection of an alcohol as a benzyl ether under mild conditions. Reaction with this reagent can be performed under near-neutral pH, unlike other benzylation protocols, which require strongly acidic or basic reaction media (e.g., the use of benzyl trichloroacetimidate or benzyl halides).^{1,2}

(1) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923. (2) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142.



679674 2-Benzyloxy-1-methylpyridinium triflate 1 g
5 g

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

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

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ABOUT OUR COVER

Panoramic Landscape with Hunters (oil on canvas, 105 × 135 cm) was painted in the mid-1660s by Philips Koninck (1619–1688), one of the great Baroque landscape artists of the Golden Age of Dutch Art (ca. 1600–1680). Although a contemporary of Rembrandt, Koninck is not believed to have studied with him. However, Koninck knew the master and some of his pupils and was certainly familiar with Rembrandt's paintings, which had some influence on him.

This painting illustrates Koninck's method of bringing together details of real-life scenes to create fictional but convincing sweeping landscapes featuring streams, fields, abundant flora, and rural dwellings. The translucent colors of the sky, the receding diagonal lines, and the horizontal striations denoting successive planes that recede into the distance add to the great allure of this landscape.

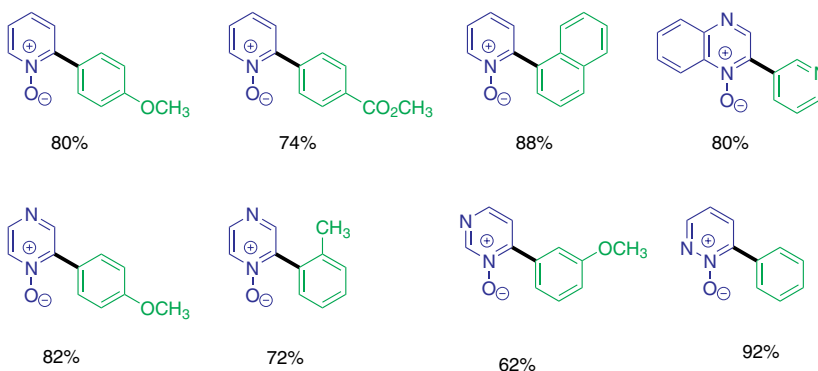
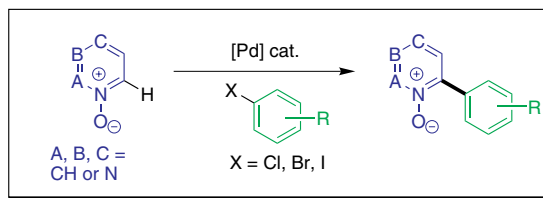


Photograph © Alfred Bader.

This painting is in the private collection of Isabel and Alfred Bader. Dr. Bader is a perennial "chemist collector" and a former Aldrich and Sigma-Aldrich president.

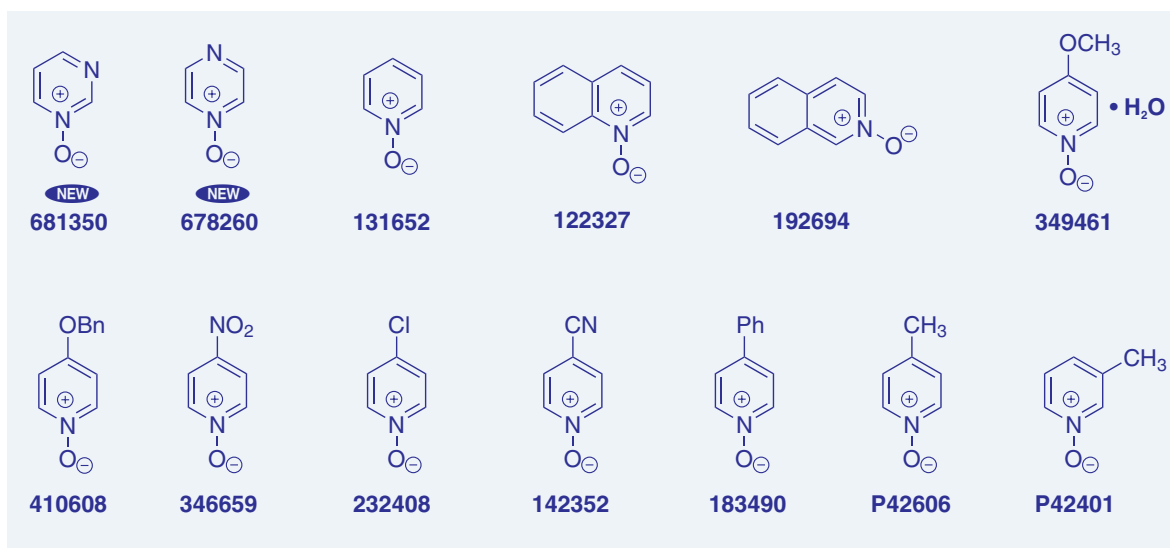
Reagents for Direct Arylation

Pd-catalyzed cross-coupling of organometallic nucleophiles with aryl halides has become the most commonly used method for biaryl synthesis. However, the range of biaryls that can be prepared is limited to those organometallic reagents that are commercially available or easily made. Nitrogen-containing heterocyclic organometallic reagents are often difficult to prepare and success of their coupling reactions can be sporadic. Professor Keith Fagnou and co-workers at the University of Ottawa have developed a novel method for biaryl synthesis by the direct arylation of heterocyclic *N*-oxides.¹⁻³ Yields are typically very good, and the oxide residue is easily reduced to give the free azine or diazine.



References

(1) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (2) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (3) Campeau, L.-C.; Stuart, D.R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.



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Recent Advances in Intermolecular Direct Arylation Reactions



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Mr. David R. Stuart



Professor Keith Fagnou

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Outline

1. Introduction
2. Arylations of Heterocycles
3. Arylations of Simple Arenes
 - 3.1. Directed Reactions
 - 3.2. Nondirected Reactions
4. Conclusions
5. Acknowledgements
6. References

1. Introduction

Biaryl molecules are important building blocks in both materials and medicinal chemistry, and have attracted the attention of the synthetic organic chemistry community for over 100 years.¹ The past quarter century has witnessed the development of transition-metal-catalyzed biaryl cross-coupling reactions that can be performed with a number of organometallics (boron, tin, silicon, magnesium) and a wide range of aryl halides.² While high yields and selectivities can be obtained, the requisite arene preactivation involves several manipulations prior to the cross-coupling, generating waste from reagents, solvents, and purifications. Furthermore, a stoichiometric amount of metal waste is produced from the arene-activating groups upon completion of the cross-coupling. In some cases, not all regioisomers of the organometallic reagents are readily available and, in the worst cases, they may be insufficiently stable to participate in the coupling reaction. For these reasons, there is a compelling need to continue the search for more efficient methods for the preparation of unsymmetrical biaryl molecules.

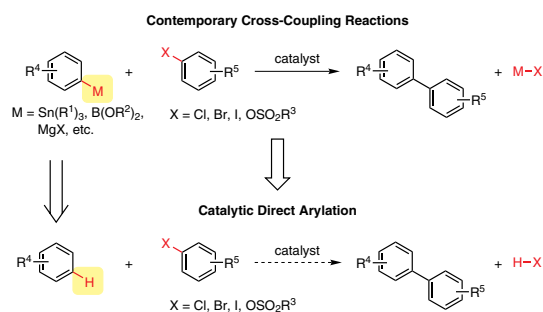
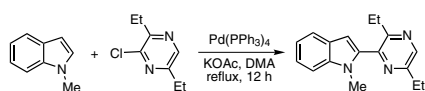
In recent years, direct arylation reactions have emerged as attractive alternatives to traditional cross-coupling methods.³ These reactions substitute one of the preactivated coupling partners with a simple arene. In most cases, the more-difficult-to-prepare organometallic component is replaced, which also reduces the metal waste generated in the overall process (**Scheme 1**). In the past few years, the field of direct arylation has undergone rapid growth and continues to garner worldwide attention. This review will discuss only the most recent advances in the field, with an emphasis on reports

from 2005–2006. Furthermore, only reactions leading to the formation of biaryl compounds will be addressed. For reports prior to these dates, and for catalytic arylation reactions leading to the formation of other product classes, the reader is directed to other excellent reviews of the field.³ Examples have been chosen for their synthetic value and their conceptual advances. The first section outlines recent advances in the direct arylation of heterocyclic substrates. Subsequent sections present advances in reactions with simple arenes, including directed and nondirected reactions.

2. Arylations of Heterocycles

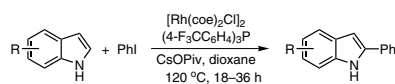
One of the first examples of heterocycles used in the direct arylation was reported by Ohta and co-workers in 1989.⁴ *N*-Alkylindoles were arylated at the 2 or 3 position, depending on the nature of the *N*-substituent (**eq 1**). It was subsequently demonstrated that these reactions could be extended to a number of π -rich heterocycles using similar reaction conditions.^{3d,5} It is commonly accepted that, in direct arylation reactions, π -electron-rich substrates can react via an electrophilic palladation step and that the arylations are facilitated by the highly nucleophilic nature of these arenes.⁶ In recent years, researchers have sought to develop novel strategies that might allow for milder reaction conditions as well as broaden the substrate scope.

In 2005, Sames and co-workers reported the development of C-2 selective indole arylation reactions with palladium and rhodium catalysts. Of note, the rhodium-catalyzed reactions are compatible with unprotected indoles and aryl iodides and afford moderate-to-good yields of 2-arylindoles (**eq 2**).⁷ The proposed catalytic cycle is outlined in **Scheme 2**. The rhodium catalyst first inserts into the aryl iodide to afford a rhodium(III) intermediate. This species was isolated and found to be a competent catalyst for the reactions, further validating this as the first step in the catalytic cycle. This arylrhodium(III) intermediate can then bind and metallate the indole to afford the diarylrhodium(III) species, which can reductively eliminate the product and regenerate the rhodium(I) catalyst. The use of cesium pivalate as the base is key to obtaining high yields. While no insight into the intimate details of the indole

**Scheme 1.** Direct Arylation vs Cross-Coupling Reactions.

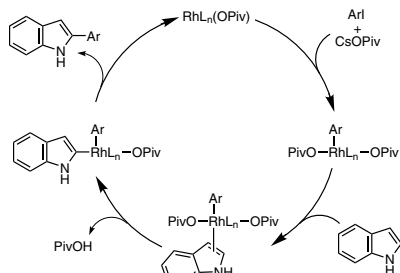
Ref. 4

eq 1

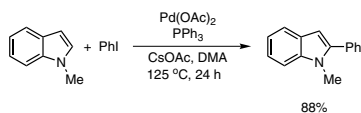


Ref. 7

eq 2

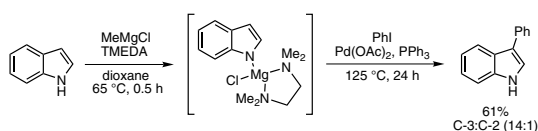


Ref. 7

Scheme 2. C-2 Selective Rhodium-Catalyzed Arylation of Indoles.

Ref. 6, 8

eq 3



Ref. 6

eq 4

metallation step could be provided, the authors postulated that the pivalate may be serving as an intramolecular base.

Sames also reported further studies dealing with palladium-catalyzed indole arylation reactions that enable a wide range of N-substituted indole substrates to be employed.^{6,8} Most of these reactions are selective typically for C-2 of the indole, but a remarkable base effect has been observed with N-H indoles where the proper selection of the base counterion allows for the selective formation of either the C-2 (**eq 3**) or the C-3 arylation isomer (**eq 4**).

The authors have postulated that the observed selectivity arises from a migration of palladium during the metallation event (**Scheme 3**).⁶ Kinetic data and isotope effects support an initial electrophilic palladation at C-3 followed by deprotonation to give the C-3 isomer. If migration of the arylpalladium moiety to C-2 takes place prior to deprotonation, the C-2 regioisomer is obtained instead.

Sanford and co-workers have established an alternative strategy to the site-selective arylation of indoles at the C-2 position.⁹ Instead of exploiting the Pd(0)/Pd(II) catalytic manifold, they developed reactions functioning under a Pd(II)/Pd(IV) redox couple. In these reactions, an initial metallation of indole by a palladium(II) salt is followed by oxidation with a diaryliodonium salt to generate a diarylpalladium(IV) intermediate, which can reductively eliminate the biaryl product and regenerate the catalytically active palladium(II) species (see the related catalytic cycle in Scheme 5 of Section 3.1). Unlike prior studies, which commonly reported heating the reactants to very elevated temperatures, Sanford's arylations can be carried out under remarkably mild conditions in acetic acid at 25 °C (**eq 5**).⁹ A number of substituted indoles participate in the reaction and, if the C-2 position is blocked, reaction at the indole C-3 position occurs in lower yields. It is also possible to perform the reaction with a number of functionalized diaryliodonium salts.

Azoles are another class of heterocycles that have been studied as substrates for the direct arylation reaction. Bergman, Ellman, and co-workers found that rhodium compounds can form carbene complexes with azoles,¹⁰ which has provided a valuable mechanistic entry point for the further development of rhodium-catalyzed direct arylation reactions. The rhodium-carbene intermediates, **1**, have been isolated and are postulated to be crucial to the reactivity (**Scheme 4**).¹⁰ Following the formation of the rhodium-carbene complex, oxidative addition of the aryl iodide leads to the formation of a diarylrhodium(III) species, which can undergo reductive elimination to give the corresponding arylazole. In 2006, Bergman and Ellman also described studies leading to the development of a new catalytic system for the arylation of azoles.¹¹ The new reaction conditions employ aryl bromides, which had been until then rarely utilized in the direct arylation of azoles. Under microwave heating at 250 °C, a number of different azole substrates were used with various aryl bromides to give the arylazoles in moderate-to-high yields (**eq 6**).¹¹

Another rhodium-catalyzed transformation of π -rich heterocycles was reported by Itami and co-workers.¹² The reaction employed an electron-deficient rhodium complex bearing strong π -accepting perfluoroalkylphosphite ligands, which were postulated to favor the electrophilic rhodation of the electron-rich heterocycle. Aryl iodides participated in the reaction with various heterocycles such as thiophenes, furans, pyrroles, and indoles (**eq 7**).¹² Simple arenes were also successfully employed (see Section 3.2).

In contrast to the number of reports of the utilization of π -rich heterocycles in the direct arylation reaction, the use π -deficient heterocycles, such as azines and diazines, is rare. In 2005, Campeau, Rousseaux, and Fagnou reported a high-yielding and site-selective method for the arylation of pyridine *N*-oxides.¹³ The reaction is broadly applicable to a number of aryl bromides and pyridine substrates, and deoxygenation of the 2-arylpiperidine *N*-oxide products gives rapid access to 2-arylpiperidines. The methodology was also extended to other azine *N*-oxides including quinolines and isoquinolines, as well as to diazine *N*-oxides including the *N*-oxides of pyrazines, pyridazines, and pyrimidines (**eq 8**).¹⁴ Competition experiments as well as DFT calculations were consistent with a concerted palladation–deprotonation pathway, which is described in detail in Section 3.2.¹⁵

Recently, Zhuravlev reported a very mild direct arylation reaction between aryl halides and oxazolo[4,5-*b*]pyridines.¹⁶ The arylations were carried out with Pd(OAc)₂/PPh₃ in acetone at 30 °C, and led to the corresponding C-2 products in moderate-to-good yields (**eq 9**). The superior reactivity of these substrates is attributed to the high acidity of the hydrogen that is replaced by the aryl group.

A clear indication of the growing acceptance of the direct arylation methodology by the synthetic community is its use in industry. For example, researchers at Merck & Co. reported in 2005 that the direct arylation of imidazo[1,2-*b*][1,2,4]triazine can be successfully employed as an alternative to the Suzuki cross-coupling reaction in a key fragment coupling reaction for the preparation of a selective GABA agonist (**eq 10**).¹⁷

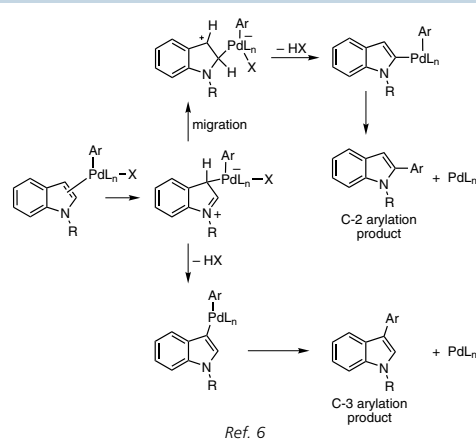
3. Arylations of Simple Arenes

3.1. Directed Reactions

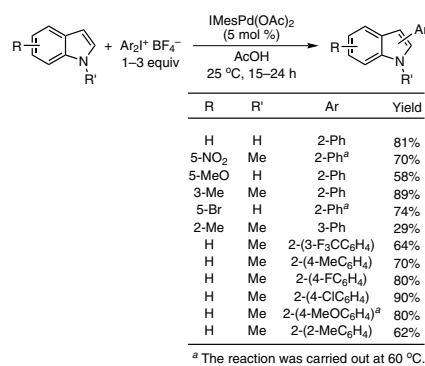
The catalytic direct arylation of simple arenes is challenging due to the attenuated nucleophilicity of the aromatic rings. To promote the necessary substrate–catalyst interactions, Lewis basic directing groups have been used; these groups enable the metallation by bringing the metal into close proximity to the reactive center.

Sanford and co-workers have reported the use of pyridine moieties as efficient directing groups in the Pd-catalyzed direct arylation of 2-arylpiperidines with aryl iodide salts (**eq 11**).¹⁸ They have also demonstrated that a wide variety of other directing groups, including quinolines, pyrrolidinones, oxazolidinones, and acetanilides are compatible. A diverse functionality on the pyridine or the aryl moiety is also tolerated, and the reactions can be carried out in ambient air and moisture and do not require expensive ligands or strong bases. Mechanistic investigations suggest that the arylation proceeds via a cyclopalladated 2-arylpiperidine that is oxidized by the aryl iodide salt to generate a very reactive Pd(IV) intermediate. Reductive elimination of the arylated product regenerates the catalytically active Pd(II) species (**Scheme 5**).¹⁸

Aryl iodides have also been utilized in direct arylation reactions of simple arenes by Daugulis and Zaitsev, who reported the successful Pd(II)-catalyzed diarylation of acylanilides with aryl iodides.¹⁹ Stoichiometric amounts of AgOAc were required for each equivalent of aryl iodide consumed. It was observed that the reaction is faster for electron-rich aryl iodides, contrasting the typical trend observed in Pd(0)/Pd(II) catalytic cycles. Acylanilides with electron-donating substituents react faster than their electron-neutral or electron-poor counterparts, which is consistent with an electrophilic aromatic metallation pathway. A mechanistic proposal has been advanced involving



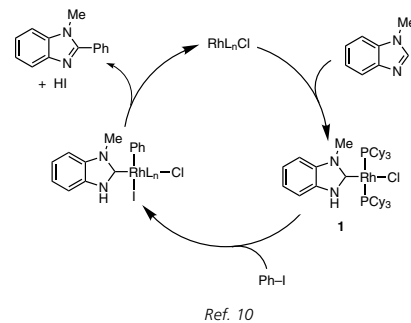
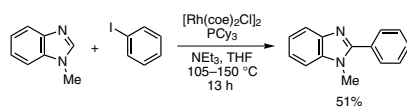
Scheme 3. Mechanistic Rationale for the Observed Regioselectivity in the Arylation of Indoles.



^a The reaction was carried out at 60 °C.

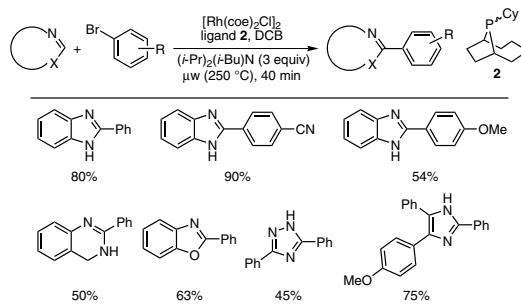
Ref. 9

eq 5



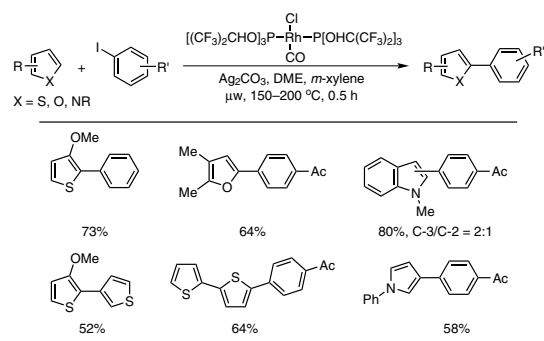
Ref. 10

Scheme 4. Proposed Catalytic Cycle for the Rhodium-Catalyzed Arylation of Azoles.



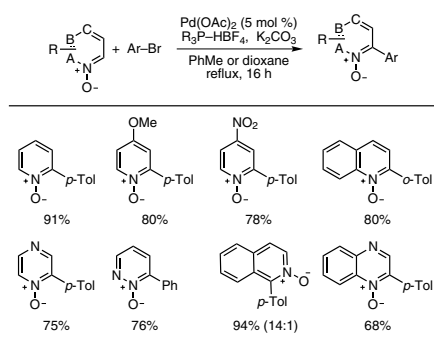
Ref. 11

eq 6



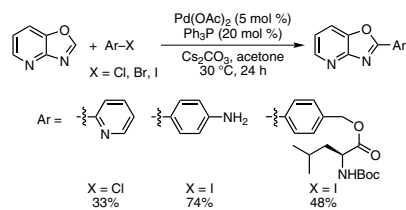
Ref. 12

eq 7



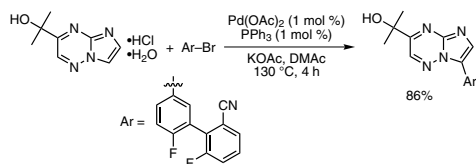
Ref. 14

eq 8



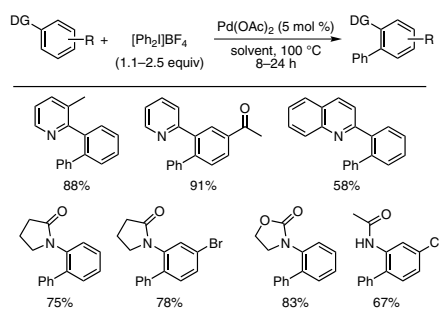
Ref. 16

eq 9



Ref. 17b

eq 10



Ref. 18

eq 11

a cyclopalladated complex that undergoes oxidative addition of the aryl iodide to produce a Pd(IV) intermediate. Pyridines,²⁰ benzamides,²¹ and benzylamines²² have all been successfully used as directing groups (**eq 12**).¹⁹⁻²²

Ackermann has also reported the use of pyridines and other Lewis basic groups as directing groups in direct arylation reactions. Importantly, these reactions were carried out successfully with aryl chlorides and tosylates by using the appropriate ruthenium catalyst.²³ While such reactivity is now common with other traditional cross-coupling reactions, achieving direct arylation with aryl chlorides and tosylates is exceedingly rare. Both electron-rich and electron-poor aryl chlorides are compatible and afford diarylated products of 2-arylpiperidines in good yields (**eq 13**).^{23a} It is also possible to achieve monoarylation with the ruthenium catalyst if imines derived from acetophenones are utilized as substrates. Conveniently, the products are then isolated as the ketones after hydrolysis of the imines (**eq 14**).²³

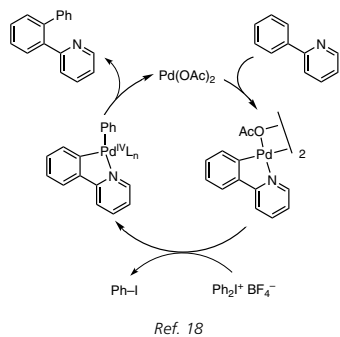
Imines have also been utilized in rhodium-catalyzed direct arylation reactions. In a 2005 report on the development of a rhodium-catalyzed Suzuki-type coupling, Ueura et al. observed that, with arenitriles, benzophenone imines were formed that were subsequently arylated ortho to the imine (**eq 15**).²⁴ When similar reaction conditions were applied directly to the imine, it was possible to isolate a mixture of the mono- and diarylated products (**eq 16**).²⁴

Çetinkaya and co-workers reported the direct ortho arylation of benzaldehyde derivatives with aryl chlorides and bromides (**eq 17**).²⁵ Good yields were obtained through the use of Pd(OAc)₂, an imidazolium salt as a carbene ligand precursor, and Cs₂CO₃ in dioxane at 80 °C. The authors postulated that the aldehyde oxygen was acting as an ortho-directing group. When aryl bromides were employed, diarylation took place and led to 2,6-diarylbenzaldehyde derivatives.

3.2. Nondirected Reactions

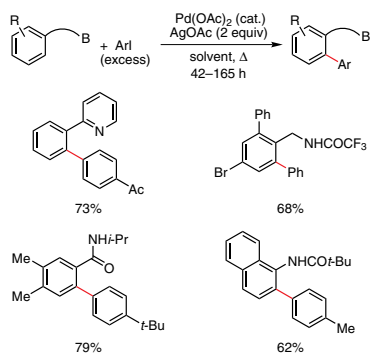
In a 2006 article focusing predominantly on the arylation of heterocycles, Itami and co-workers described direct arylation reactions with anisole and 1,3-dimethoxybenzene.¹² In both cases, the observed regioselectivity was consistent with an electrophilic metallation mechanism occurring preferentially at the para and ortho positions relative to the electron-donating methoxy groups (**Scheme 6**). Given the small number of nondirected reactions of simple arenes in direct arylation, this result shows significant promise for the development of other rhodium-catalyzed direct arylations with simple arenes.

The same year, Fagnou and co-workers explored the direct arylation of perfluorinated arenes. While the π deficiency of these arenes prohibited their use in an electrophilic metallation process, their direct arylation occurred in high yield with 1–5 mol % palladium catalyst in the presence of P(*t*-Bu)₂Me·HBF₄ (**eq 18**).²⁶ It was even possible to achieve reaction with fluorobenzene, albeit in 8% yield. Based on mechanistic studies by Maseras, Echavarren, and co-workers, who described a concerted palladation–deprotonation pathway in intramolecular direct arylation reactions,²⁷ experimental and computational mechanistic studies were performed, which led to the formulation of two possible pathways (**Scheme 7**).²⁶ Pathway A involves a concerted palladation and loss of HBr to afford the diarylpalladium(II) intermediate. Alternatively, an exchange of the bromide ligand with a carbonate anion allows for a related palladation–deprotonation process through transition state **4** (pathway B). Although pathway B was



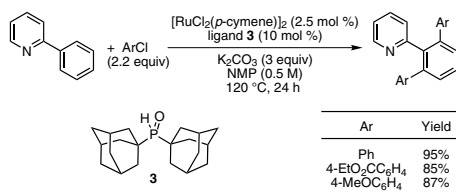
Ref. 18

Scheme 5. Catalytic Cycle of Oxidative Direct Arylation with Diaryliodonium Salts.



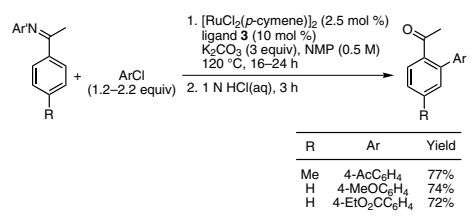
Ref. 19–22

eq 12



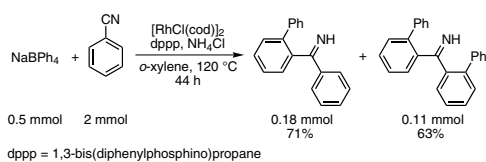
Ref. 23a

eq 13



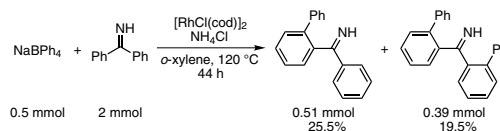
Ref. 23a

eq 14



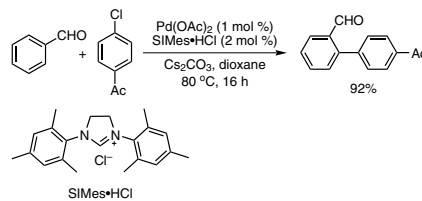
Ref. 24

eq 15



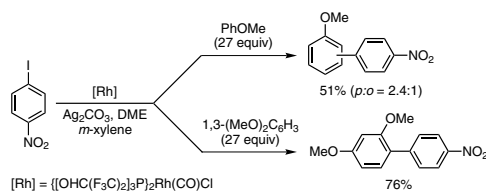
Ref. 24

eq 16



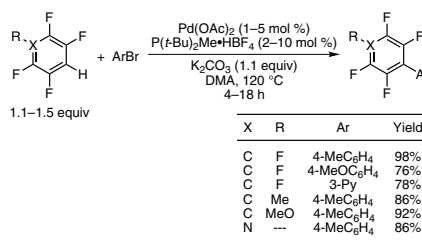
Ref. 25

eq 17



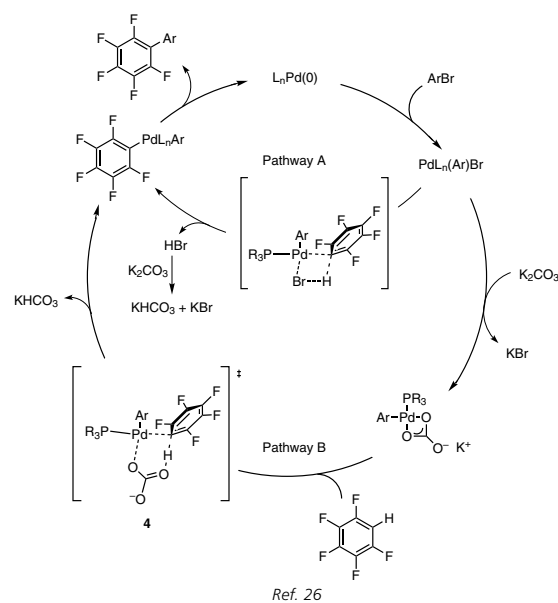
Ref. 12

Scheme 6. Nondirected Reactions of Simple Arenes in the Direct Arylation Reaction.



Ref. 26

eq 18



Ref. 26

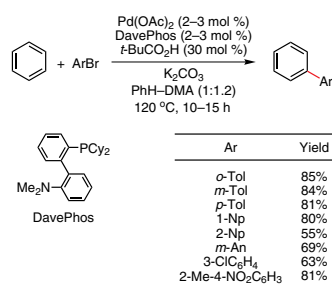
Scheme 7. Proposed Catalytic Cycle for the Direct Arylation of Pentafluorobenzene.

deemed lower in energy by DFT calculations (9.9 kcal/mol vs 23.7 kcal/mol), the near-complete insolubility of K_2CO_3 under the reaction conditions prevented pathway A from being ruled out and provided an enticing clue into how the reaction might be improved.

With the goal of favoring pathway B in more challenging arylations of benzenes, the use of soluble acid co-catalysts was investigated in conjunction with a stoichiometric and insoluble potassium carbonate base. The proper choice of the carboxylic acid was crucial, and the use of 30 mol % PivOH proved to be optimal.²⁸ Using this protocol, a number of aryl bromides were reacted with benzene to afford the biaryl products in high yields (eq 19). The carboxylic acid additive is believed to facilitate the exchange of the bromide ion on the metal for a carboxylate ligand that can undergo a similar concerted palladation-deprotonation (Scheme 8).²⁸

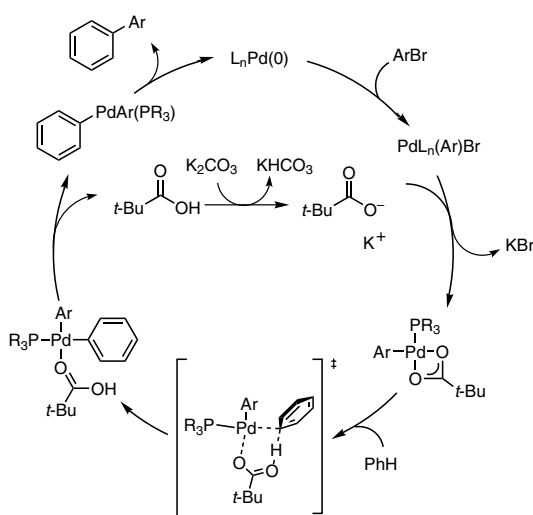
4. Conclusions

Direct arylation reactions are gaining an increasingly convincing track record in the construction of biaryl compounds. The many recent reports have allowed for the use of milder reaction conditions and equimolar amounts of coupling partners. The number of diverse catalysts and mechanisms by which direct arylation reactions can be performed show promise for a more frequent use in everyday organic synthesis and should stimulate



Ref. 28

eq 19



Ref. 28

Scheme 8. Role of Pivalic Acid Co-Catalyst in the Direct Arylation of Benzene.

the development of novel processes with expanded scope and efficacy. This should make these methods increasingly attractive for the preparation of biaryl molecules in an industrial setting.

5. Acknowledgements

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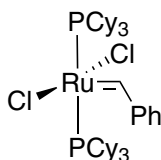
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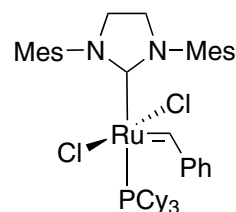
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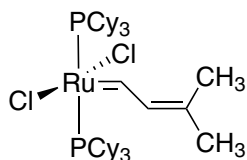
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Grubbs 2nd generation catalyst

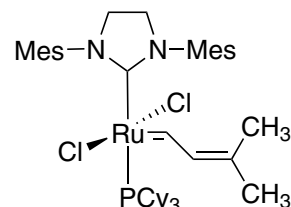
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More active than 1st generation catalysts. Increased activity in RCM and has been employed in challenging CM of sterically demanding or deactivated olefins.



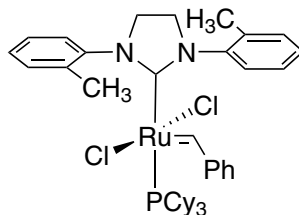
578681

Kinetic and application profile similar to that of Grubbs 1st generation catalyst.



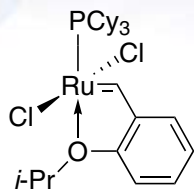
682365 **NEW**

Slower to initiate than Grubbs 2nd generation catalyst, thus potentially useful in exothermic ROMP applications. Typically, reaction temperatures of 50 to 60 °C are employed.



682284 **NEW**

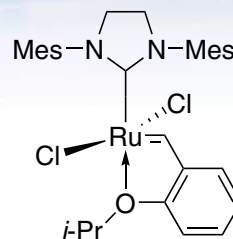
Highly efficient catalyst for the preparation of tetrasubstituted olefins by RCM or CM of sterically hindered olefins.



Hoveyda-Grubbs 1st generation catalyst

577944

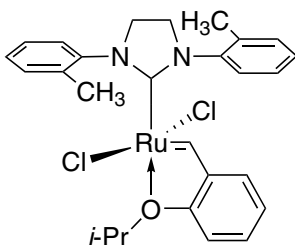
Similar reactivity as Grubbs 1st generation catalyst. Proved to be particularly useful in the industrial production of macrocycles via RCM.



Hoveyda-Grubbs 2nd generation catalyst

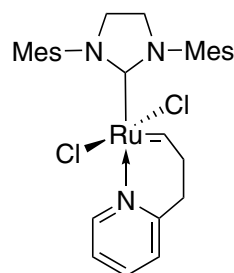
569755

Comparable reactivity to Grubbs 2nd generation catalyst, but initiates more readily at lower temperatures. Efficient for the metathesis of electron-deficient substrates.



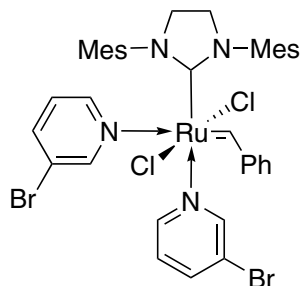
682373 **NEW**

Hoveyda-Grubbs analog of 682284 with similar reactivity profile. Depending on substrate and reaction conditions, may prove more efficient than 682284.



682381 **NEW**

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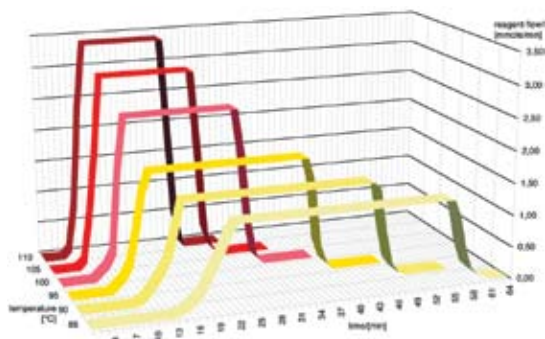
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Evolution and Applications of Second-Generation Ruthenium Olefin Metathesis Catalysts



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Outline

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 - 2.1. Discovery of NHC-Based Olefin Metathesis Catalysts
 - 2.2. Mechanistic Considerations and Development of Second-Generation Derivatives
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 - 5.1. Second-Generation Catalysts Based on Unsymmetrical Alkyl, Aryl-NHC Ligands
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6. Practical Considerations for Using Olefin Metathesis Catalysts
7. Conclusions
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1. Introduction

Olefin metathesis is a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds, and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The widely accepted view that olefin metathesis revolutionized the different fields of synthetic chemistry led to the awarding of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock “for the development of the metathesis method in organic synthesis”.¹ While Chauvin had proposed the “carbene” mechanism to explain how the metathesis process functions^{1a,2} and Schrock had prepared the first well-defined highly active metathesis catalysts,^{1b,3} Grubbs

provided synthetic chemists with active catalysts that could be handled in air and were tolerant of various functional groups, such as esters, amides, ketones, aldehydes, and even protic functionalities like alcohols, water, and acids.^{1c,4}

The Grubbs catalysts are based on a ruthenium atom surrounded by five ligands: two neutral electron-donating entities (e.g., trialkylphosphines, N-heterocyclic carbenes), two mono-anionic groups (e.g., halides), and one alkylidene moiety (e.g., unsubstituted and substituted methylidenes). These catalysts are divided into two categories based on the nature of the neutral ligands: $L_2X_2Ru=CHR$ complexes (where L is a phosphine ligand) were discovered first and are referred to as the first-generation Grubbs catalysts, and $(L)(L')X_2Ru=CHR$ complexes (where L is a phosphine ligand and L' a saturated N-heterocyclic carbene or NHC ligand) were subsequently developed and are referred to as the second-generation Grubbs catalysts (**Figure 1**).

The first-generation Grubbs catalysts have demonstrated attractive functional-group tolerance and handling properties, and have been widely used as highly efficient promoters for ring-opening metathesis polymerizations,⁵ ring-closing metathesis reactions to make disubstituted olefins,⁶ ethenolysis (i.e., cleavage of the carbon–carbon double bond),⁷ cross-metathesis of terminal olefins,⁸ and the preparation of 1,3-dienes via enyne metathesis.⁹ As such, these catalysts and analogues¹⁰ remain very useful and are still employed in important processes, including the ethenolysis of feedstocks derived from bio-renewable seed oils^{7b,c} and the manufacture of macrocyclic hepatitis C therapeutics.¹¹ Nonetheless, the utility of first-generation catalysts is somewhat limited, because they suffer from reduced activity as compared to the more sensitive but highly active Schrock catalysts. Examples of transformations that are poorly or simply not enabled by first-generation Grubbs catalysts include the ring-closing metathesis to form tri- and tetrasubstituted cycloalkenes and the cross-metathesis of sterically hindered or electronically deactivated olefins. Many of these limitations have been addressed through the development of the second-generation Grubbs catalysts, which possess excellent metathesis activity while retaining the

handling characteristics and broad functional-group tolerance of the earlier Grubbs catalysts.

Since their discovery in 1999, second-generation Grubbs systems have rapidly evolved into a large family of catalysts with varying properties. These catalysts have been widely utilized to facilitate new transformations and to allow important applications that extend to a broad range of areas including fine chemicals, pharmaceuticals, and materials. As it is often the case in homogeneous catalysis, there does not exist a single second-generation catalyst that is best for all transformations and applications. In fact, many of the second-generation catalysts have been developed to provide systems with optimal characteristics for specific purposes. Therefore, the aim of this article is to review the evolution of this group of catalysts, point out the properties and specificity of its members, and present some of the very interesting applications enabled by them.

2. Second-Generation Grubbs and Other Early NHC-Based Catalysts

2.1. Discovery of NHC-Based Olefin Metathesis Catalysts

The first examples of NHC-containing, olefin metathesis catalysts were disclosed by Herrmann and co-workers in 1998.¹² These complexes were bis-NHC ruthenium benzylidene species, **1**, where the NHC ligands were unsaturated and contained identical or different, chiral or achiral alkyl substituents on the

nitrogen atoms (**Figure 2**). These systems were originally aimed at tuning the properties of the catalysts by changing the nature of the alkyl substituents on the nitrogen atoms and at producing chiral complexes.¹³ Although they were first thought to be more active than the first-generation catalysts,¹² this notion turned out not to be generally true.¹⁴ A year later, mixed NHC–phosphine ruthenium metathesis catalysts were reported: Herrmann and co-workers had focused on species containing alkyl-substituted unsaturated NHCs, **2**,¹⁵ while the Grubbs¹⁶ and Nolan¹⁷ groups independently developed catalysts derived from aryl-substituted unsaturated NHCs, in particular 1,3-dimesitylimidazol-2-ylidene or IMes, **3**. The mixed NHC–phosphine complexes **2** and **3** were found to possess greater metathesis activity and enhanced thermal stability than the first-generation Grubbs catalysts.^{15a,c,16,17} In particular, compound **3**, developed by Grubbs and Nolan, proved to be an especially efficient catalyst.¹⁸ Other IMes-based systems containing moieties such as vinylidene,¹⁹ allenylidene,²⁰ or indenylidene²¹ were prepared by the Grubbs, Fürstner, and Nolan groups. The allenylidene systems turned out to be inactive in metathesis, while the vinylidene complexes were active but slower than their ruthenium benzylidene analogues, and the indenylidene complexes proved to be “equipotent” to the benzylidene derivatives. Soon after developing the IMes catalyst, the Grubbs group discovered that replacing one phosphine of the first-generation systems with a *saturated* mesityl-substituted NHC (or SIMes) ligand afforded a catalyst with even greater activity than the IMes-based compounds.²² The SIMes catalyst, **4**, commonly referred to as the second-generation Grubbs catalyst, quickly superseded the IMes species because it demonstrated superior efficiency in practically all metathesis reactions.^{23,24}

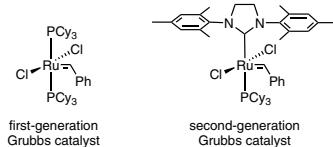


Figure 1. Most Commonly Used First- and Second-Generation Grubbs Catalysts.

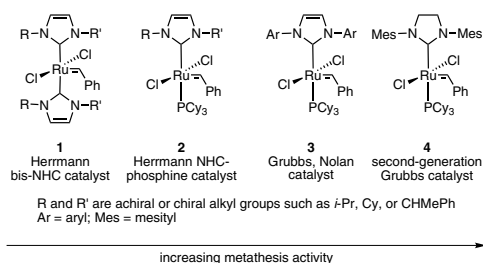
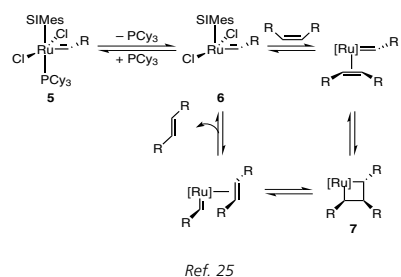


Figure 2. Evolution and Relative Activity of Early NHC-Based Metathesis Catalysts.



Scheme 1. Mechanism of the Metathesis of a Symmetrical Cis Olefin to Its Trans Isomer.

2.2. Mechanistic Considerations and Development of Second-Generation Derivatives

Mechanistic studies of **4** indicated that the catalytic steps involve an initiation event where a 16-electron species, **5**, undergoes reversible phosphine dissociation to furnish a 14-electron, active catalytic complex, **6**. Complex **6** can either rebind a dissociated phosphine or proceed to reversibly coordinate an olefinic substrate to form a ruthenacyclobutane, **7**. The breaking apart of the ruthenacyclobutane follows to expel the new olefinic products (**Scheme 1**).²⁵ In addition, these studies showed that the second-generation catalysts initiate much more slowly than the first-generation ones, and that their enhanced activity is due to the fact that their affinity to coordinate an olefinic substrate in the presence of free phosphine is much greater than that of the first-generation systems.

These mechanistic insights guided Grubbs and co-workers to prepare a family of second-generation catalysts with different initiation rates by varying the detachable phosphine ligands. Depending on the application, it is advantageous to employ catalysts that initiate more or less rapidly. For example, when performing ring-opening olefin metathesis polymerizations (ROMP) of strained cyclic olefinic monomers, slower-initiating catalysts are often desirable because they allow for longer handling of the monomer/catalyst resin before the polymerization starts.²⁶ Conversely, fast-initiating catalysts, able to promote metathesis at reduced temperatures, are useful in applications where low reaction temperatures are required to prevent catalyst decomposition and formation of undesired byproducts.²⁷

Thus, analogues of **4**, such as complexes **8–10** containing tri(*n*-butyl)phosphine, tri(*p*-tolyl)phosphine, and triphenylphosphine, have been synthesized and their phosphine dissociation rates found to vary dramatically with the nature of the phosphine

ligand (**Figure 3**).^{28,29} Indeed, the phosphine dissociation rate of **10** was about 60 times greater, and that of **8** about 170 times smaller, than that of **4** (measured at 80 °C in toluene).^{29,30}

The nature of the halide and alkylidene ligands also has an impact on the catalyst initiation rate. In particular, catalysts containing larger halide ligands initiate more rapidly, while systems with smaller alkylidene moieties (e.g., methylidene) initiate more slowly.^{25b} Similarly, complex **13**, containing a large NHC ligand (i.e., 1,3-bis(2,6-diisopropylphenyl)imidazo lidin-2-yl) and first synthesized by Fürstner and co-workers,³¹ has proved to be a fast initiator and a highly active catalyst (**Figure 4**).^{23,25b,32}

2.3. Applications of Second-Generation Grubbs Catalysts

By virtue of their greatly enhanced activity vis-à-vis their first-generation counterparts, the second-generation catalysts promote the metathesis of sterically demanding or deactivated olefins. In particular, second-generation Grubbs complexes have shown increased activity in ring-closing metatheses (**eq 1–3**),^{22,33,34} and in macrocyclizations.³⁵ They also catalyze challenging cross-metatheses^{1h,36} including the coupling of olefins with α,β -unsaturated carbonyls,³⁷ vinylphosphonates,³⁸ and 1,1-disubstituted alkenes (**Scheme 2**).³⁹

A model for the prediction of the outcome of cross-metathesis reactions has been developed based on the categorization of olefins according to their relative propensity to homodimerize via cross-metathesis and the ability of their homodimers to undergo secondary metathesis.⁴⁰ Based on this model, olefinic substrates are divided into four different types. Whether a certain olefin belongs to one type or another depends on the nature of the metathesis catalyst used (**Table 1**). Cross-metatheses between two olefins of Type I yield product mixtures that correspond to statistical distributions. Additionally, reactions between two olefins of the same type (but not of Type I) give nonselective product mixtures, while reactions between olefins of two different types are selective processes.

The ability of the second-generation catalysts to couple olefins with α,β -unsaturated carbonyls has been utilized to prepare A,B-alternating copolymers by ring-opening insertion metathesis polymerization (ROIMP).⁴¹ Additionally, these catalysts promote the enyne metathesis of alkynes to make interesting 1,3-dienes (**eq 4,5**).^{9,34,42,43} Finally, second-generation systems are often the catalysts of choice for the preparation of novel ROMP polymers, including ROMP-based immobilized reagents and scavengers.⁴⁴

3. Phosphine-Free, SIMes-Based Second-Generation Catalysts

A phosphine-free catalyst, **14**, containing an SIMes and a chelating benzylidene ether ligand has been introduced by Hoveyda and co-workers (**Figure 5**).^{45,46} This complex shows efficiencies similar to the Grubbs systems, but has slightly different substrate specificities. It is a particularly efficient catalyst for metatheses involving highly electron-deficient substrates such as acrylonitrile and fluorinated alkenes.⁴⁷

Other phosphine-free catalysts of the Hoveyda type have been prepared by introducing different substitution patterns on the chelating benzylidene ether ligand. Thus, Blechert and co-workers have reported complexes bearing more sterically hindered chelating ligands (**15** and **16**),⁴⁸ while Grela and co-workers have disclosed benzylidene ether moieties with

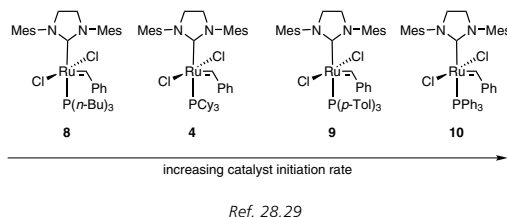


Figure 3. Effect of the Nature of the Phosphine Ligand on the Initiation Rate of the Second-Generation Catalyst.

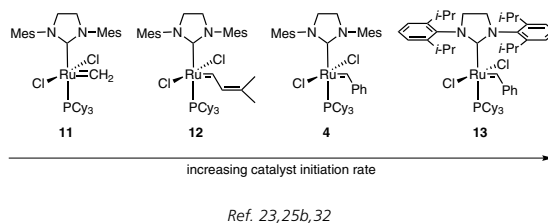
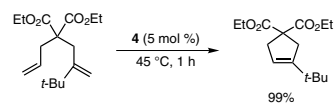
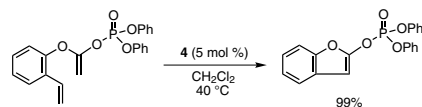


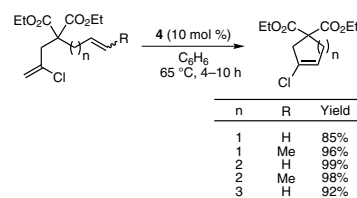
Figure 4. Influence of the Nature of the Alkylidene and NHC Ligands on the Initiation Rate of the Second-Generation Catalyst.



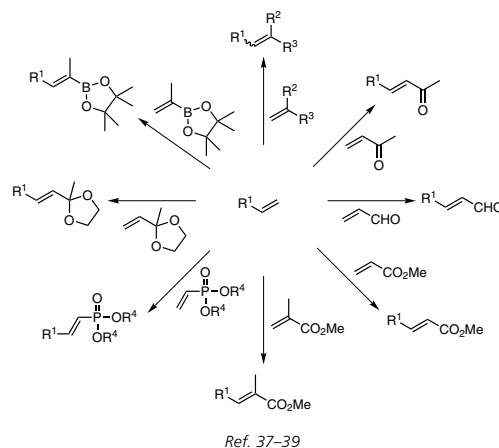
eq 1



eq 2



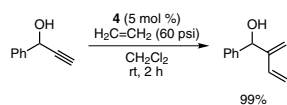
eq 3



Scheme 2. Cross-Metatheses Catalyzed by Second-Generation Grubbs Catalysts.

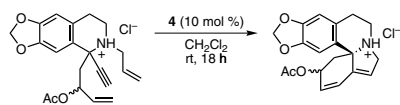
Table 1. Olefin Categories Based on Their Metathesis Reactivity

Olefin Type	First-Generation Grubbs Catalysts	Second-Generation Grubbs Catalysts
Type I (facile homodimerization; homodimers are readily consumable)	terminal olefins; allyl silanes; 1° allylic alcohols, ethers, and esters; allyl boronate esters; allyl halides	terminal olefins, 1° allylic alcohols and esters; allyl boronate esters; allyl halides; styrenes (without large ortho substituents); allyl phosphonates; allyl silanes; allyl phosphine oxides; allyl sulfides; protected allylic amines
Type II (more difficult homodimerization; homodimers sparingly consumable)	styrenes; 2° allylic alcohols; vinyl dioxolanes; vinyl boronates	styrenes (with large ortho substituents); acrylates; acrylamides; acrylic acid; acrolein; vinyl ketones; unprotected 3° allylic alcohols; vinyl epoxides; 2° allylic alcohols; perfluorinated alkane olefins
Type III (no homodimerization)	vinyl siloxanes	1,1-disubstituted olefins; non-bulky trisubstituted olefins; vinyl phosphonates; phenyl vinyl sulfone; 4° allylic hydrocarbons; protected 3° allylic alcohols
Type IV (spectator substrates: do not undergo cross-metathesis)	1,1-disubstituted olefins; di-substituted α,β -unsaturated carbonyls; 4° allylic carbon-containing olefins; perfluorinated alkane olefins; protected 3° allylic amines	olefins with vinylic nitro group; protected trisubstituted allylic alcohols



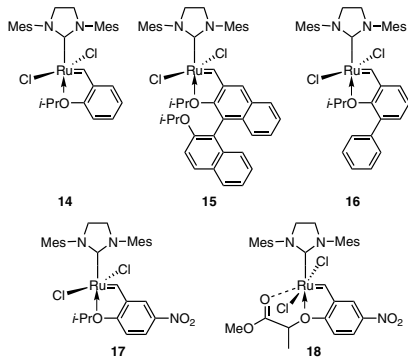
Ref. 42

eq 4

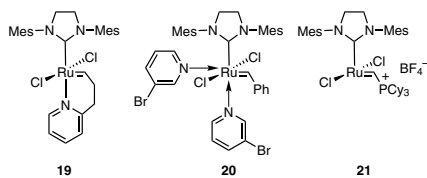


Ref. 43

eq 5



Ref. 45,48,49

Figure 5. Phosphine-Free, SIMes-Based Second-Generation Catalysts.

Ref. 50,52,55

Figure 6. Very Slow and Very Fast Initiating, Second-Generation Catalysts.

electron-withdrawing substituents in the position para to the alkoxy group to make catalysts such as compounds **17** and **18**.⁴⁹ Both of these steric and electronic alterations of the original ligand have resulted in faster-initiating catalysts than the parent Hoveyda complex **14**, presumably because the ether ligands in species **15–18** dissociate faster from the ruthenium than the ether ligand in catalyst **14**.

4. Slow- and Fast-Initiating NHC-Based Catalysts

Additional tuning of the initiation rates led to the development of exceptionally slow- and exceptionally fast-initiating metathesis catalysts. Thus, complex **19** (Figure 6) is a latent phosphine-free initiator, but a highly active catalyst once it has initiated.^{50,51} As such, complex **19** is a useful promoter for the ROMP of strained cyclic olefinic monomers such as dicyclopentadiene.²⁶ On the other hand, catalyst **20** is a very fast phosphine-free initiator,⁵² which has proved useful for the production of polymers with narrow polydispersities and for the synthesis of block copolymers.^{53,54}

Catalysts such as compound **21**, developed by Piers and co-workers, are extremely fast initiators and are capable of catalyzing the ring-closing metathesis of terminal dienes at 0 °C.⁵⁵ The ability of Piers's systems to turn over at very low temperatures has proved useful in very elegant mechanistic studies resulting in the direct observation of olefin metathesis metallacyclobutane intermediates,⁵⁶ and has made them ideal candidates for low-temperature applications.

5. Other Recent Developments in the Design of Second-Generation Catalysts

5.1. Second-Generation Catalysts Based on Unsymmetrical Alkyl, Aryl-NHC Ligands

Second-Generation-type systems bearing unsymmetrical saturated NHC ligands, substituted with an alkyl group on one nitrogen atom and an aryl group on the other, were initially investigated by Mol and co-workers, who prepared the mixed 1-adamantyl,mesityl complex **22** (Figure 7).⁵⁷ This compound turned out to be an extremely poor metathesis catalyst, presumably because of the large steric hindrance resulting from the adamantyl substituent.⁵⁷

More recently, Blechert's research group reported the preparation of mixed methyl,mesityl and ethyl,mesityl systems of the Grubbs and Hoveyda–Grubbs types (**23** and **24**).⁵⁸ These complexes demonstrated activities comparable to the Grubbs and Hoveyda–Grubbs analogues **4** and **14** in the metathesis of several common substrates. However, catalyst **24** performed much more poorly than **14** in a challenging cross-metathesis with acrylonitrile.⁵⁸ Additionally, complex **23** gave lower *E/Z* ratios than **4** and **14** in various cross-metatheses. While this specificity may prove useful in certain applications, it is also an additional hint that mixed alkyl,aryl systems tend to be less active than bisaryl ones.⁵⁹

5.2. Chiral, Second-Generation Ruthenium Metathesis Catalysts⁶⁰

Although the syntheses of the first ruthenium metathesis catalysts with chiral, saturated NHC ligands (e.g., complex **25**) go back to the time of the discovery of the second-generation catalysts,²² asymmetric metatheses affording appreciable enantiomeric excesses were not achieved until chiral complexes such as **26** and **27** were developed by the Grubbs and Hoveyda groups, respectively (Figure 8).^{61,62} Complex **26** effectively catalyzed the desymmetrizing RCM of prochiral trienes to

afford enantiomeric excesses ranging from 13% to 90%.⁶¹ Catalyst **27** led to high enantioselectivities in the asymmetric, tandem, ring-opening metatheses–cross-metatheses of tricyclic norbornene derivatives.⁶² However, complex **27** is altogether a less active catalyst and requires elevated reaction temperatures and prolonged reaction times. Hoveyda and co-workers have subsequently reported analogs of **27** with enhanced catalytic activity using lower catalyst loadings.⁶³ More recently, Grubbs and collaborators developed highly active analogues of catalyst **25** (e.g., **28**) that can induce chirality with greater efficiency than **25**.⁶⁴

5.3. Immobilized, Second-Generation Catalysts and Related Developments

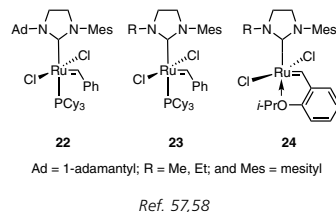
Considerable research efforts have been applied to immobilizing second-generation catalysts on various supports.⁶⁵ Many of the systems prepared involve the attachment of the ruthenium complex via its alkylidene moiety.^{45,66} This approach, by its nature, does not lead to a permanent anchoring of the system on the support, but rather to a controlled release of the catalytic species into the reaction solution. Depending on the specific systems employed, the released metal species have been observed to partially return and reattach themselves to the support.⁴⁵ Other approaches consist of attaching the ruthenium catalysts via the NHC or the anionic ligands.^{66,67} The most noteworthy examples of this approach are the catalysts immobilized on silica, polymers, or monolithic supports developed by Buchmeiser and co-workers.⁶⁸ Using similar strategies, Grubbs and co-workers have prepared an active, water-soluble catalyst by connecting the NHC ligand to a poly(ethylene glycol) chain.⁶⁹ A related development was recently reported by the Gladysz group, who prepared a second-generation Grubbs catalyst bearing a fluorinated phosphine ligand and used it in biphasic reactions.⁷⁰

5.4. Second-Generation Catalysts for the Metathesis of Hindered Olefins

The most exciting recent additions to the family of second-generation catalysts concern the metathesis of hindered olefins and, in particular, RCM to form tetrasubstituted cycloalkenes. While catalysts **2**, **3**, **4**, and **14** have enabled several such transformations,^{15c,16,23,24} RCM to make tetrasubstituted, five-membered-ring olefins (e.g., RCM of dimethylmalonates) had remained especially challenging until very recently. Indeed, catalysts **4** and **14** gave a 6% and a 17% conversion, respectively, in the RCM of diethyl dimethylmalonate after 4 days at 30 °C.²³ The best catalyst systems for making tetrasubstituted, five-membered cycloalkenes, the unsaturated NHC-based catalysts (e.g., complexes **2** and **3**), gave a modest 31% conversion after 4 days at 30 °C.²³ As a result, an extensive search for improved catalysts for the metathesis of hindered olefins was undertaken. Complexes **29–31**, prepared by Grubbs and co-workers (Figure 9),^{71–73} are more efficient catalysts for such transformations than **2–4** and **14**. For example, **29–31** all afford high conversions (~90%) in the RCM of diethyl dimethylmalonate after 24 hours at 60 °C.^{72,73} However, attempts to optimize and scale up the preparation of these catalysts revealed that they would be relatively difficult and expensive to produce at scale.⁷⁴ Most recently, catalysts **32** and **33** were developed and the scope of their utility investigated. These complexes proved to be the most efficient catalysts in the benchmark RCM of dimethylmalonates, affording greater than 95% conversion in less than 1 hour (eq 6).⁷⁵

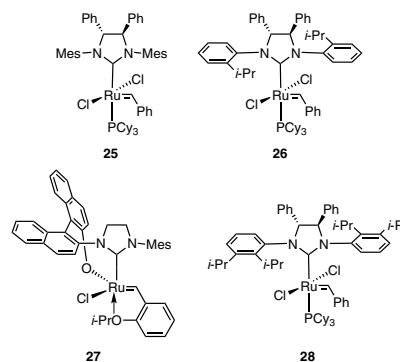
6. Practical Considerations for Using Olefin Metathesis Catalysts

Many of the first- and second-generation Grubbs and Hoveyda–Grubbs catalysts discussed so far are commercially available. Olefin metathesis reactions catalyzed by these ruthenium-based catalysts can be conducted in neat olefinic substrates or in solvents of varied polarities. Toluene and dichloromethane are most commonly used, but 1,2-dichloroethane, chlorinated benzenes, diethyl ether, tetrahydrofuran, ethyl acetate, acetone, and methanol may also be employed. Of further utility,



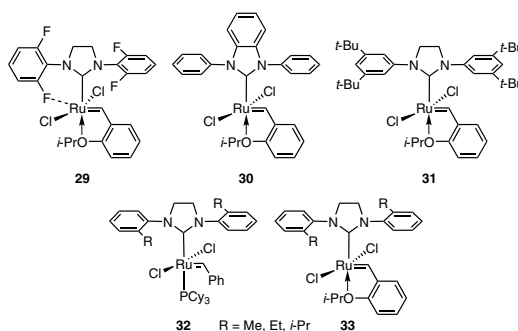
Ref. 57,58

Figure 7. Second-Generation Catalysts Based on Unsymmetrical Alkyl, Aryl-Substituted NHCs.



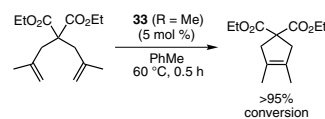
Ref. 22,61,62,64

Figure 8. Examples of Chiral Ruthenium Olefin Metathesis Catalysts.



Ref. 71,72,73,75

Figure 9. Highly Efficient Catalysts for the Metathesis of Hindered Olefins.



Ref. 75

eq 6

solvents and substrates do not need to be anhydrous. Although ruthenium-based catalysts are relatively robust to oxygen, degassing the reaction solvents and olefinic substrates before adding the catalysts is recommended. Additionally, improved efficiencies may be obtained upon further purification of the olefinic substrates by filtration through silica gel or activated alumina.

Reaction temperatures of about 30 to 50 °C are typical for second-generation Grubbs and Hoveyda–Grubbs catalysts (i.e., complexes **4** and **14**, respectively). Catalysts **8**, **12**, and **19** will usually require higher temperatures (e.g., about 50 to 60 °C for **12**, and about 60 to 80 °C for **8** and **19**) to perform adequately, while catalysts **10** and **20** may be used at lower temperatures (e.g., about 10 °C for **10**, and about 0 °C for **20**). **Table 2** summarizes the specificities of different catalysts. Optimal catalyst and substrate loadings may vary depending on the metathesis reaction, the catalyst, and the reaction conditions, but typical loadings are in the range of 0.1–5 mol %. Finally, upon completion of the metathesis reaction, the catalyst can be removed from the products or from the organic phase by employing published methods.⁷⁶

7. Conclusions

Although first-generation olefin metathesis catalysts such as the first-generation Grubbs and Hoveyda–Grubbs systems remain extremely useful tools in synthetic chemistry, the introduction and evolution of the second-generation catalysts have greatly widened the scope of chemical transformations enabled by metathesis reactions. The second-generation Grubbs (e.g., **4** and **12**) and

Hoveyda–Grubbs (e.g., **14**) catalysts have opened the way to new metathesis applications including the formation of trisubstituted cycloalkenes via RCM and the polymerization and cross-metathesis of sterically hindered or electronically deactivated olefins. Moreover, many second-generation catalysts have been developed to address additional needs of synthetic chemists. Slow-initiating, phosphine-containing (e.g., **8**) and phosphine-free (e.g., **19**) catalysts were designed for the controlled ROMP of strained cyclic olefins, while fast-initiating phosphine-containing (e.g., **10**) and extremely fast-initiating phosphine-free (e.g., **20**) systems may be used in low-temperature metathesis processes or in the production of polymers with narrow polydispersities. Additionally, recently developed systems that contain small, saturated NHC ligands (e.g., **32** and **33**) are very efficient at promoting the metathesis of hindered alkenes, even RCM to form tetrasubstituted, five-membered-ring cyclic olefins. By opening these new avenues, catalysts **32** and **33** promise to lead to new exciting applications.

Together, compounds **4**, **8**, **10**, **12**, **14**, **19**, **20**, **32**, and **33**, along with the first-generation Grubbs and Hoveyda–Grubbs complexes, constitute a powerful tool kit that allows synthetic chemists to perform most metathesis transformations currently facilitated by the class of ruthenium-based olefin metathesis catalysts. These catalysts have enabled and will continue to enable the preparation of previously unattainable molecules and materials in all fields of chemistry and materials science.

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Table 2. Specificities of Olefin Metathesis Catalysts


Catalyst	Comments
First-generation Grubbs	Useful in the ROMP of strained cyclic olefins, in the ethenolysis of internal olefins, as well as in the ADMET, CM, and RCM of terminal olefins.
First-generation Hoveyda–Grubbs	Possesses reactivity similar to that of first-generation Grubbs. Especially useful in the industrial production of macrocycles via RCM.
4	Known as the second-generation Grubbs catalyst and is considerably more active than the first-generation catalysts. Has shown increased activity in RCM and has been employed in challenging CMs of sterically demanding or deactivated olefins, including 1,1-disubstituted olefins and α,β -unsaturated carbonyls. Typically used at 30–50 °C.
8	A much slower initiator than 4 and requires higher reaction temperatures (e.g., 60–80 °C).
10	A faster initiator than 4 and can therefore be used at lower temperatures than 4 (e.g., 10–30 °C).
12	Slower to initiate than 4 , but faster than 8 . Requires reaction temperatures of typically 50 to 60 °C.
14	Known as the second-generation Hoveyda–Grubbs catalyst and possesses reactivity comparable to that of 4 . However, it initiates more readily at lower temperatures (e.g., 5–30 °C), depending on the other reaction conditions such as catalyst loading and substrate concentration. Is also an efficient catalyst for the metathesis of highly electron-deficient substrates such as acrylonitrile.
19	A latent initiator that possesses the high activity of second-generation catalysts once it has initiated. Was developed mainly for industrial ROMP applications, in which longer monomer or catalyst resin handling times are desired. Its latency could also prove useful in other applications.
20	A much faster initiator than 4 and can therefore be used at lower temperatures (e.g., ~0 °C), depending on the other reaction conditions. It tends to be less soluble than 4 in nonpolar solvents, and is generally less stable than 4 in solution. Has been employed in the production of block copolymers and polymers with narrow polydispersities.
32 (R = Me)	A highly efficient catalyst for the metathesis of hindered olefins. Is particularly useful in the preparation of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins.
33 (R = Me)	This is the Hoveyda–Grubbs analogue of 32 (R = Me). Is also useful in the synthesis of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins. Depending on the substrate and reaction conditions, it may prove more efficient than 32 (R = Me).

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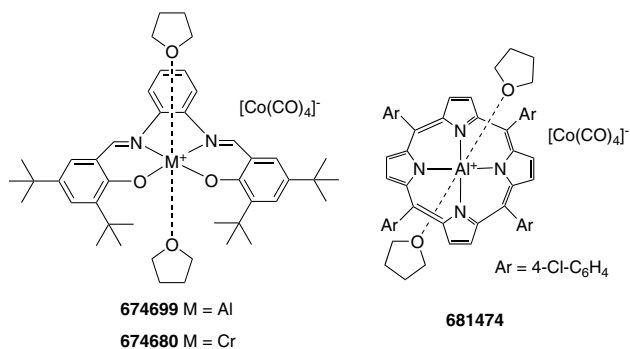
About the Authors

Yann Schrodi was born in 1972 in Strasbourg, Alsace, France. He obtained a B.S. degree in chemistry in 1994 and an M.S. degree in transition-metal chemistry in 1995 from L'Université Louis Pasteur Strasbourg, where he worked under the supervision of Professor John A. Osborn. After serving in the French military for ten months, he spent five years in the laboratory of Professor Richard R. Schrock at MIT, where he earned his Ph.D. degree in inorganic chemistry in 2001. Dr. Schrodi joined Materia, Inc., in 2001, where he is currently leading the Catalyst Research and Development Group. Notable achievements of this group under his leadership and in collaboration with Professor Robert H. Grubbs include the development of several new olefin metathesis catalysts, such as highly active but latent catalysts for ring-opening metathesis polymerizations, highly efficient and selective ethenolysis catalysts, and highly efficient catalysts for the production of tetrasubstituted olefins. Dr. Schrodi is a coauthor on several publications and patents in the area of homogeneous catalyst development and catalytic process development.

Richard L. Pederson was born in 1962 in Albert Lea, Minnesota. He earned his B.S. degree in chemistry in 1985 from the University of Wisconsin-River Falls, where he did research under Professor John Hill. He worked under the supervision of Professor Chi-Huey Wong at Texas A&M University, earning his Ph.D. degree in organic chemistry in 1990. He joined Bend Research, Inc. in Bend, Oregon, where, in 1997, he and Professor Robert H. Grubbs patented the production of insect pheromones using ruthenium metathesis catalysts. Dr. Pederson has spent the last twelve years in entrepreneurial start-ups using olefin metathesis to develop new routes to insect pheromones and pharmaceutical intermediates, while also managing numerous projects and technical personnel. In 2000, he joined Materia, Inc., to start up the Fine Chemicals Group, where he is the Director of Fine Chemicals R&D. Dr. Pederson is the author of numerous patents and publications, including key patents related to the production of chelating metathesis ligands and the use of metathesis in the production of insect pheromones. 

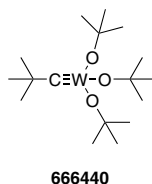
Coates Carbonylation Catalysts

These complexes are efficient and versatile carbonylative ring-expansion catalysts that have been applied in the synthesis of various lactones and cyclic anhydrides.¹⁻³



New Schrock Alkyne Metathesis Catalyst

Tris(*tert*-butoxy)(2,2-dimethylpropylidene)tungsten(VI) has emerged as an effective alkyne metathesis catalyst under fairly mild conditions. The usefulness of this catalyst is illustrated by the concise and stereoselective synthesis of *cis*-civetone—a valuable, macrocyclic, olfactory compound.⁴

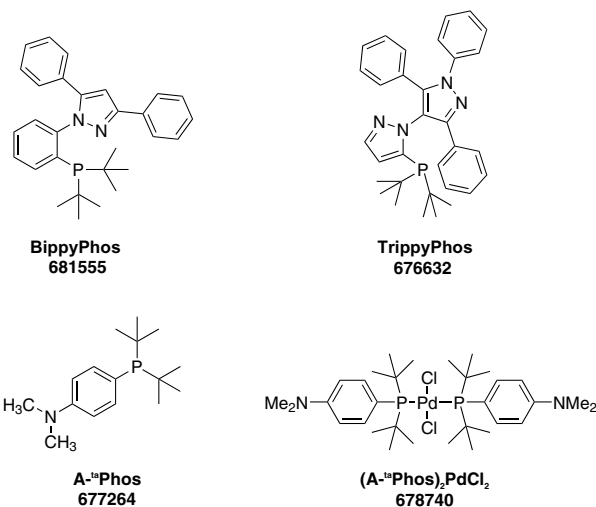


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New Efficient Systems for Cross-Coupling

Developed at pharmaceutical companies, these non-proprietary ligands and catalyst are efficient in mediating Pd-catalyzed aminations⁵ or Suzuki–Miyaura cross-coupling reactions.⁶



Nanoparticulate Pd and Rh

Nanoparticulate palladium in an aluminum hydroxide matrix (**674133**) is a versatile, recyclable, and amphiphilic heterogeneous catalyst that can be applied to a variety of reactions with low catalyst loadings.⁷ Nanoparticulate rhodium entrapped in a highly porous and fibrous boehmite matrix (**679488**) has been used in the facile and mild hydrogenation of a variety of arenes, can be recovered effortlessly by simple filtration, and reused several times without a noticeable loss of activity.⁸⁻⁹

Other Metal Catalysts

- 679771** (2-Biphenyl)di-*tert*-butylphosphinegold(I) chloride, 98%
677876 Trichloro(pyridine)gold(III), 97%
677892 Tetrakis(acetonitrile)copper(I) tetrafluoroborate, 97%
679763 Bis(dibenzylideneacetone)platinum(0)

New Chiral Technologies from Sigma-Aldrich



ChiroSolv™ Kits

ChiroSolv™ kits are 96-well format kits that enable rapid screening of resolving agents and solvents for chiral separation. Each of these ready-to-use disposable kits contains a combination of eight resolving agents and twelve solvents. Racemates that can be separated include: acids, bases, alcohols, amino acids, aldehydes, and ketones. Optimum resolution that typically requires over two months can be achieved within one day.

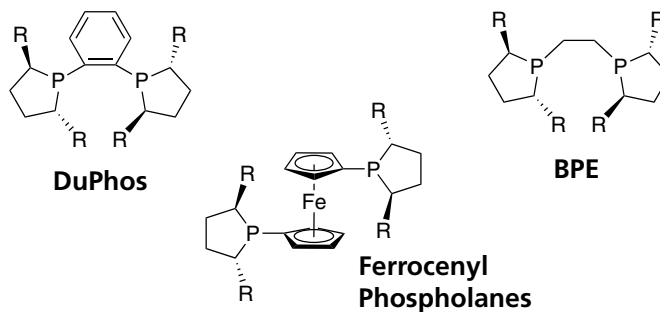
Available in three Acid Series kits (**681431**, **681423**, **681415**) and three Base Series kits (**681407**, **681393**, **681377**). For more information visit sigma-aldrich.com/chirosolv.

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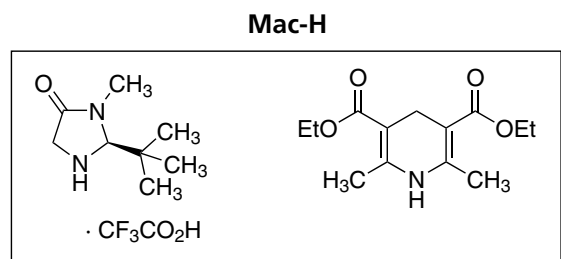
Available in either enantiomeric form with Me, Et, and *i*-Pr substituents. For a detailed product listing, visit sigma-aldrich.com/phospholane.

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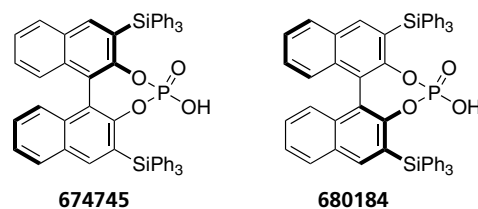
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MacMillan TiPSY Catalysts have been used in the first direct enantioselective organocatalytic reductive amination reaction.

MacMillan TiPSY Catalysts



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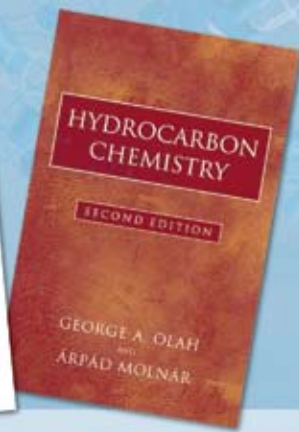
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- Seams heat-sealed for strength
- Two-hand configuration
- Convenient clip closure

Cat. No.	Size	Opening (in.)	W X L (in.)	Gas Ports
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Z564400	Mini	22	27 x 17	2
Z564419	Small	22½	27 x 27	2
Side Entry				
Z564427	Mini	12	20 x 20	4
Z564435	Small	12	30 x 20	2
Dual-Side Entry				
Z564443	Mini	12	20 x 20	2
Z564451	Small	12	30 x 20	2

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CHEMICAL SYNTHESIS

Handbook of Metathesis, 3-Volume Set

R. H. Grubbs, Ed., Wiley-VCH, 2003, 1234 pp. Hardcover. There is probably no name more closely linked to metathesis than that of Robert H. Grubbs of the California Institute of Technology. His pioneering work has led to the success of this important and fascinating reaction, and, in this comprehensive three-volume set, he presents all of its important aspects. The team of contributing authors reads like a "Who's Who" of metathesis. The handbook is clearly divided into three major topics: catalyst developments, organic synthesis applications, and polymer synthesis.

Z551570-1EA

Modern Organonickel Chemistry

Y. Tamaru, Ed., Wiley-VCH, 2005, 346 pp. Hardcover. Nickel catalyzes many unique reactions and thus enormously widens the scope of feasible transformations in organic chemistry. Over the past few years, interest in organonickel chemistry has grown such that it is now just as keen as that in organopalladium chemistry. Yet, while there are numerous books on the latter topic, a book specializing in organonickel chemistry is long overdue. This volume covers the many discoveries made over the past 30 years. Active researchers working at the forefront of organonickel chemistry provide a comprehensive review of the topic, including Nickel-Catalyzed Cross-Coupling Reactions, Reactions of Alkenes Including Allylnickel Complexes, Reactions of Alkynes, Reactions of Dienes and Allenes, Cycloisomerization; Carbonylation and Carboxylation, Asymmetric Synthesis, and Heterogeneous Catalysis.

Z705802-1EA

Handbook of Heterocyclic Chemistry, 2nd Edition

A. R. Katritzky and A. F. Pozharskii, Pergamon Press, 2000, 758 pp. Hardcover. Heterocyclic chemistry is the largest of the classical divisions of organic chemistry. Heterocyclic compounds are widely distributed in nature, playing a vital role in the metabolism of living cells. Their practical applications range from extensive clinical use to fields as diverse as agriculture, photography, biocide formulation, and polymer science. The range of known heterocyclic compounds is enormous, encompassing the whole spectrum of physical, chemical, and biological properties. This handbook is illustrated throughout with thousands of clearly drawn chemical structures and contains over 1500 chemical figures and reactions. The highly systematic coverage given to the subject makes this handbook one of the most authoritative single-volume accounts of modern heterocyclic chemistry available.

Z515213-1EA

Hydrocarbon Chemistry, 2nd Edition

G. A. Olah and Á. Molnár, Wiley, 2003, 871 pp. Hardcover. *Hydrocarbon Chemistry* begins by discussing the general aspects of hydrocarbons, the separation of hydrocarbons from natural sources, and the synthesis from C1 precursors with recent developments for possible future applications. Each successive chapter deals with a specific type of hydrocarbon transformation. The second edition includes a new section on the chemical reduction of carbon dioxide—focusing on catalytic, ionic, electrocatalytic, photocatalytic, and enzymatic reductions—as well as a new chapter on new catalysts and activation methods, combinatorial chemistry, and environmental chemistry.

Z550949-1EA

Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, 2nd Revised and Enlarged Edition, 2-Volume Set

M. Beller and C. Bolm, Eds., Wiley-VCH, 2004, 1344 pp. Hardcover. Already in its second edition, over 70 internationally renowned authors cover the vast range of possible applications for transition metals in industry as well as academia. This two-volume work presents the current state of research and applications in this economically and scientifically important area of organic synthesis. Over 1,000 illustrations and a balanced presentation allow readers fast access to a thorough compilation of applications, making this an indispensable reference for everyone working with such metals.

Z703451-1EA

Supported Catalysts and Their Applications

D. C. Sherrington and A. P. Kybett, Eds., Royal Society of Chemistry, 2001, 278 pp. Hardcover. The need to improve both the efficiency and environmental acceptability of industrial processes is driving the development of heterogeneous catalysts in commodity, specialty and fine chemicals, as well as in pharmaceuticals and agrochemicals. This book discusses aspects of the design, synthesis, and application of solid-supported reagents and catalysts, including supported reagents for multistep organic synthesis, selectivity in oxidation catalysis, mesoporous molecular sieve catalysts, and the use of Zeolite Beta in organic reactions. In addition, the two discrete areas of heterogeneous catalysis (inorganic oxide materials and polymer-based catalysts) that were developing in parallel are now shown to be converging.

Z555517-1EA

Handbook of Organopalladium Chemistry for Organic Synthesis, 2-Volume Set

E. Negishi, Ed., Wiley, 2002, 3424 pp. Hardcover. This is the authoritative reference on organopalladium compounds, designed for synthetic chemists. Transition metals and their complexes represent one of the most important groups of catalysts for organic reactions. Among these, palladium has emerged as one of the most versatile catalysts in modern organic synthesis. Negishi assembles contributions from several dozen international authorities on the use of palladium reagents and catalysts. The handbook's contents are organized by reaction type, which provides maximum utility to the synthetic chemist.

Z513865-1EA

Microwaves in Organic and Medicinal Chemistry (Methods and Principles in Medicinal Chemistry Series, Volume 25)

C. O. Kappe and A. Stadler, Eds., Wiley-VCH, 2005, 422 pp. Hardcover. The authors of this guide are experts on the use of microwaves for drug synthesis, as well as having extensive experience in teaching courses held under the auspices of ACS and IUPAC. In this handy source of information for any practicing synthetic chemist, they focus on common reaction types in medicinal chemistry, including solid-phase and combinatorial methods. They consider the underlying theory and the latest developments in microwave applications, and include a variety of examples from the recent literature, as well as less common applications that are equally relevant for organic and medicinal chemists.

Z704679-1EA

Modern Rhodium-Catalyzed Organic Reactions

P.A. Evans, Ed., Wiley-VCH, 2005, 496 pp. Hardcover. Rhodium is an extremely useful metal due to its ability to catalyze an array of synthetic transformations. Hydrogenation, C–H activation, allylic substitution, and numerous other reactions are catalyzed by this metal, which presumably accounts for the dramatic increase in the number of articles that have recently emerged on the topic. P. Andrew Evans has assembled an internationally renowned team to present the first comprehensive coverage of this important area. The book features contributions from leaders in the field of rhodium-catalyzed reactions, and thereby provides a detailed account of the most current developments.

Z705810-1EA

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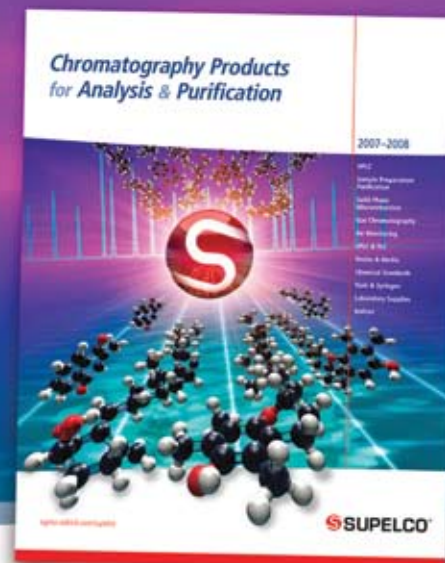
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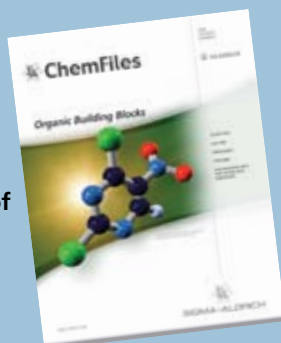


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