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Nucleophilic Chiral Phosphines: Powerful and Versatile Catalysts for Asymmetric Annulations

Silanediol Recognition in Catalysis, Sensing, and Drug Discovery

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"You Could Not Step Twice into the Same River"[1]

Dr. S. J. Firsan

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As the *Aldrichimica Acta* gears up to celebrate its golden jubilee in 2017, we are reminded of a seemingly paradoxical statement that the Greek philosopher *Heraclitus of Ephesus* (c. 540 – c. 480 BC) is believed to have famously made and repeated in several forms. The statement is paraphrased today often as, *"The Only Thing That Is Constant Is Change."* Perhaps the *Aldrichimica Acta*'s secret for success for close to 50 years has been its ability to embrace these two opposites: the *constants* (what our customers and readers have come to appreciate, value, and love) and the *changes* (adapting to rapidly changing academic, business, and technology environments).

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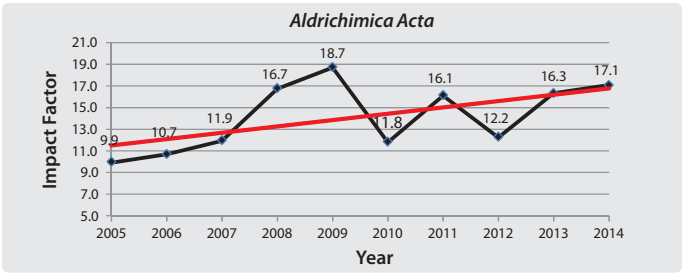

Footnotes

(1) One interpretation of this statement is that *"some things stay the same only by changing"*; see Heraclitus. In *The Stanford Encyclopedia of Philosophy* [Online]; Center for the Study of Language and Information (CSLI), Stanford University, Stanford, CA, 2015. http://plato.stanford.edu/entries/heraclitus/ (accessed Feb 10, 2016).

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(1) Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9851. (2) Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X.-H. ; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514.

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En route pour la pêche (Setting Out to Fish) (oil on canvas, 78.7 × 122.9 cm) was painted in 1878 by John Singer Sargent (1856, Florence, Italy–1925, London, England), the famed expatriate American artist. Sargent received his general education at home and his formal artistic training first in Florence and then in Paris, before apprenticing in the studio of the prominent French portraitist Carolus-Duran. Sargent traveled widely in Europe, studying the work of such masters as Hals, Rembrandt, van Dyck, Reynolds, and Velásquez. He was strongly influenced by Carolus-Duran and Monet, and was himself a powerful inspiration for later generations of American portraitists. Unlike many other artists, he achieved fame and commercial success at a young age and was blessed with both for the rest of his life.

Detail from ***En route pour la pêche***. Photo courtesy National Gallery of Art, Washington, DC.

Although better known for his famous portraits of high society members on both sides of the Atlantic, Sargent's first love was for seascapes, of which this work is a beautiful and early example executed when Sargent was only 22 years old. It portrays residents in the village of Cancale, on the northern coast of Brittany, walking to the beach on a sunny day to collect shellfish and fish at low tide.* This seemingly casual and easy composition was actually methodically planned with preparatory sketches and drawings and was invested with a great deal of effort by the young artist, who intended it for exhibition that year at the prestigious Paris Salon. The influence of Monet, whom Sargent met in Paris two years before he completed this piece, is clearly visible.

This painting is part of the Corcoran Collection at the National Gallery of Art, Washington, DC.

** A twin seascape, **Fishing for Oysters at Cancale**, was created by Sargent at about the same time and is currently in the Museum of Fine Arts, Boston. These two works depict the same locale and scene and share many elements, but they differ in significant ways. To find out more, visit.* ***Aldrich.com/acta491***

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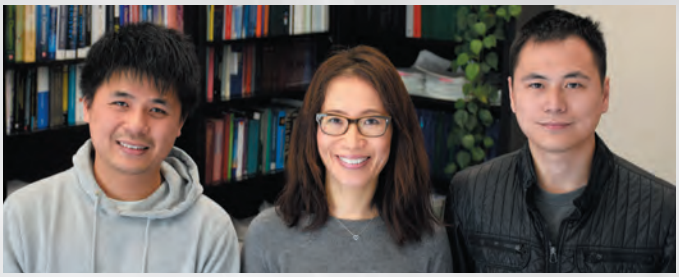

From left to right: Yi Chiao Fan, Professor Ohyun Kwon, and Lingchao Cai

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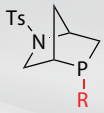
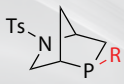
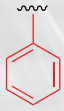


endo



exo

Phenyl



798363 (endo)
798371 (exo)

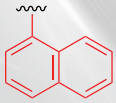
4-Methoxyphenyl

798444 (endo)
798746 (exo)

4-Fluorophenyl

798355 (exo)

1-Naphthyl



798436 (endo)
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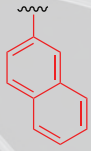
2-Naphthyl



798428 (endo)
798347 (exo)

References:
(1) Xiao, Y.; Guo, H.; Kwon, O. *Aldrichimica Acta* **2016,** *49,* 3.
(2) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012,** *3,* 2510.
(3) Henry, C. E.; Xu, Q.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014,** *136,* 11890.

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Nucleophilic Chiral Phosphines: Powerful and Versatile Catalysts for Asymmetric Annulations


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Prof. H. Guo


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Keywords. chiral phosphines; annulation; cyclization; asymmetric catalysis; organocatalysis.

Abstract. Recent advances in chiral-phosphine-catalyzed asymmetric annulation reactions; including annulations of allenes, alkynes, Morita–Baylis–Hillman (MBH) carbonates, and ketenes; and their applications in the synthesis of bioactive molecules and natural products are reviewed.

Outline

1. Introduction

A wide variety of nucleophilic phosphine-catalyzed annulation reactions have been established as reliable and powerful tools for the synthesis of carbo- and heterocycles from simple starting materials.[1] Asymmetric variants, including [2 + 2], [3 + 2], [3 + 3], [4 + 1], and [4 + 2] annulations, have also been achieved[1] and demonstrated in dozens of applications in organic synthesis.[2,3] A few phosphine-catalyzed annulations serve as key steps in the total synthesis of several bioactive natural products such as (+)-ibophyllidine, hirsutine, ricciocarpin-A, hirsutene, alstonerine, and macroline.[2] In addition, a variety of novel heterocyclic compounds have also been synthesized using phosphine-catalyzed [3 + 2] and [4 + 2] annulations as important reaction steps. Some of these compounds show diverse bioactivities and potential as drug candidates (**Figure 1**).[3]

Typically, the catalytic cycle is initiated by addition of the Lewis basic phosphine to the electrophilic center of the allene, MBH carbonate, alkyne, or alkene, leading to the formation of a zwitterionic intermediate.[1] The zwitterionic intermediate reacts with a variety of electrophilic reagents, resulting in a number of phosphine-catalyzed annulation reactions (**Scheme 1**). It is worth noting that the phosphonium intermediates from 1-acetoxy-2,3-butadiene act as 1,4-bis-electrophilic acceptors of nucleophilic reagents. Moreover, in the past three decades, hundreds of chiral phosphines have been designed and prepared for use in asymmetric catalysis, and most were utilized as chiral ligands of metal catalysts. Normally, all chiral tertiary phosphines could be employed as chiral catalysts for nucleophilic phosphine catalysis. However, most chiral phosphines that were originally designed as ligands for metal-catalyzed reactions are triarylphosphines which are weak nucleophiles. Furthermore, these phosphines are acyclic and without a rigid structure,

and thus result in poor stereoselectivity in nucleophilic organocatalytic reactions. Therefore, only a very limited number of commercially available chiral phosphines could be used in asymmetric nucleophilic phosphine catalysis. In most of the chiral-phosphine-catalyzed asymmetric annulation reactions, cyclic and multifunctional chiral phosphines displayed better catalytic activity and stereoselectivity than acyclic chiral phosphines. Consequently, the design and synthesis of cyclic and multifunctional chiral phosphines have become a key target in the development of phosphine-catalyzed asymmetric reactions. Such chiral phosphines, developed in the past decade and exhibiting excellent catalytic activity in annulation reactions, are shown in **Figures 2** and **3**. Some of these chiral phosphines such as **A1**–**A5**, **C2**–**C4**, **C16**–**C18** and **M6** are commercially available.

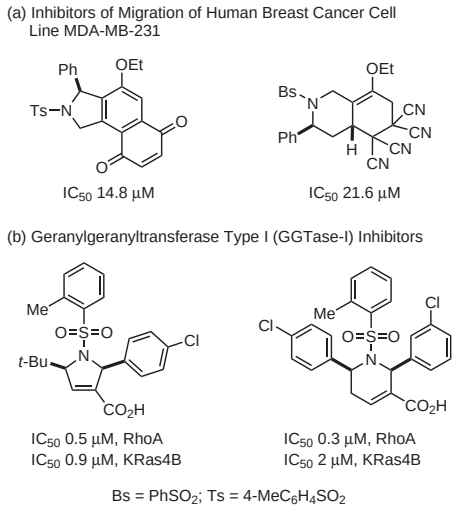
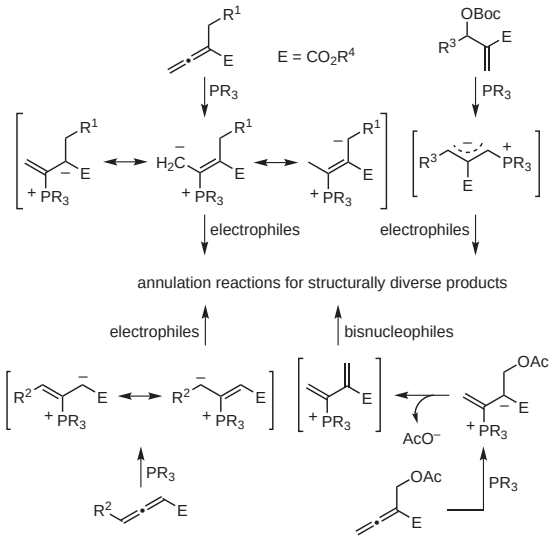


Figure 1. Examples of Bioactive Compounds Synthesized with Phosphine-Catalyzed Annulations as Key Reaction Steps. *(Ref. 3a,f)*



Scheme 1. Principal Modes of Nucleophilic Phosphine Catalysis.

Herein, the applications of chiral phosphines in asymmetric organocatalytic annulation reactions will be highlighted according to the type of annulation reaction and phosphine acceptor. The application of chiral phosphines in other types of reaction such as allylic substitution, Michael addition, γ-umpolung addition, and acylation of alcohols, will not be included in this review.

2. Asymmetric [3 + 2] Annulations of Allenes

2.1. With Alkenes

The chiral-phosphine-catalyzed, asymmetric [3 + 2] annulation of allenoates with electron-deficient alkenes to form cyclopentenes is the most studied annulation reaction in the area of nucleophilic phosphine organocatalysis, and it provides important chiral five-membered-ring carbocycles commonly found in natural and unnatural bioactive molecules.[1] In 1995, Lu reported the first achiral phosphine-catalyzed [3 + 2] annulation of allenoates with electron-deficient alkenes.[4] Following this pioneering contribution, Zhang and co-workers achieved the first asymmetric [3 + 2] annulation of allenes with electron-deficient alkenes by employing rigid, bicyclic chiral phosphines as catalysts. The reactions employing **C1** worked efficiently under mild conditions to give chiral cyclopentene derivatives in 75–92% yield and 69–93% ee

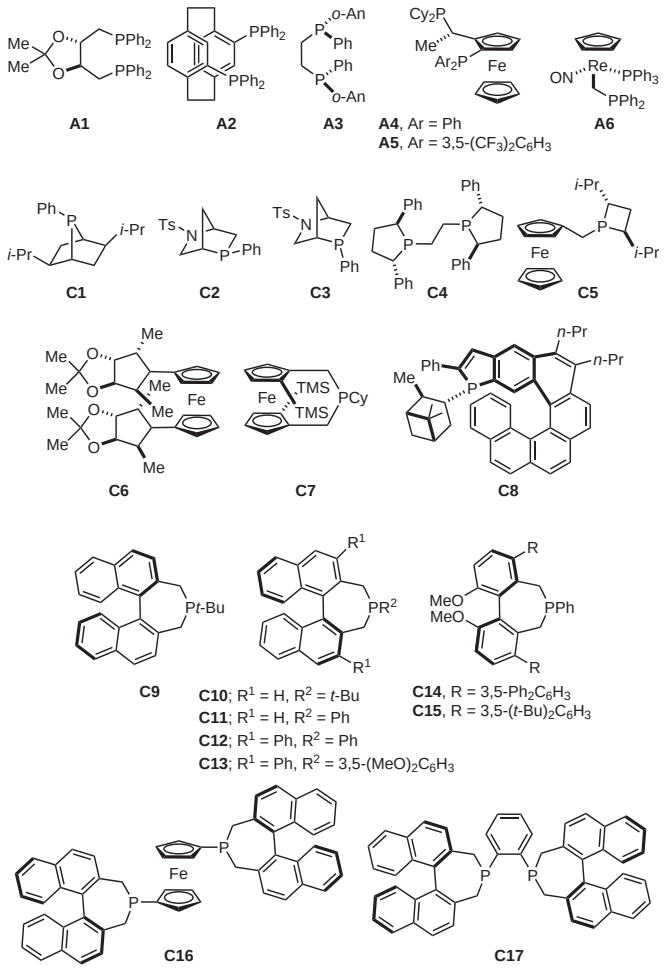


Figure 2. Chiral Phosphines Exhibiting Excellent Activity in Asymmetric Nucleophilic Phosphine Catalysis.

(**eq 1**).[5] This exciting work did not, however, generate sufficient interest in chiral-phosphine-catalyzed asymmetric reactions, especially ones catalyzed by chiral cyclic phosphines, and was overlooked for nearly ten years.

Almost a decade later, Wilson and Fu disclosed the next successful example of nucleophilic-phosphine-catalyzed asymmetric annulation.[6] Chiral cyclic phosphine **C9**, which incorporates a rigid binaphthyl skeleton, catalyzed the enantioselective [3 + 2] annulation of ethyl allenoate with various α,β-unsaturated enones, affording highly functionalized cyclopentenes with two contiguous stereocenters (**eq 2**).[6] In particular, **C9** promoted the reaction with a trisubstituted enone to form a spirocyclic compound bearing adjacent quaternary and tertiary stereocenters in 97% yield and 89% ee. In contrast, acyclic chiral phosphine (*S*,*S*)-DIOP (**A1**) catalyzed the asymmetric [3 + 2] annulation of allenic ketones with a diverse array of exocyclic enones, affording the spirocyclic compounds with only moderate enantioselectivities (≤ 77% ee).[7]

Using 3-butynoates instead of allenoates as substrates, the commercially available acyclic, chiral catalyst (*R*,*R*)-DIPAMP (**A3**) catalyzed the asymmetric [3 + 2] annulation with various α,β-unsaturated enones, providing highly functionalized cyclopentenes in 66–95% yield and with 81–99% ee.[8] Control experiments revealed that under phosphine catalysis conditions, 3-butynoate initially isomerizes to the allenoate, which subsequently undergoes the [3 + 2] annulation with the enones. Compared with Fu's catalytic system,[6] this system, featuring a tandem isomerization–annulation, led to better yields and ee's. Especially interesting is the observation that this acyclic chiral catalyst, not the cyclic ones, was the best catalyst for this annulation.

Employing **C12**, Fujiwara and Fu achieved the asymmetric [3 + 2] annulation between a wide array of γ-substituted racemic allenes and hetroatom-substituted olefins, affording functionalized cyclopentenes with adjacent quaternary and tertiary stereocenters in satisfactory yields and with good regio- (rr = 8:1 to 50:1) and stereoselectivities (up to 98% ee) (**eq 3**).[9] The catalytic system is quite versatile and compatible with various nitrogen-, phosphorus-, oxygen-, and sulfur-substituted olefins. Notably, diverse allenamides also worked well in this reaction. The authors proposed that the chiral microenvironment of **C12** was amplified by its 3,3'-diphenyl substituents.

The intramolecular, enantioselective [3 + 2] annulation of various allenes, tethered with electron-deficient alkenes, was also accomplished by Fu's group by utilizing chiral tertiary phosphines **C10**–**C13** as catalysts. The reaction afforded bicyclic compounds with three contiguous tertiary stereocenters in good yields (56–95%) and with moderate-to-high enantioselectivities (86–98% ee).[10] This method could be applied to different classes of trisubstituted olefins containing

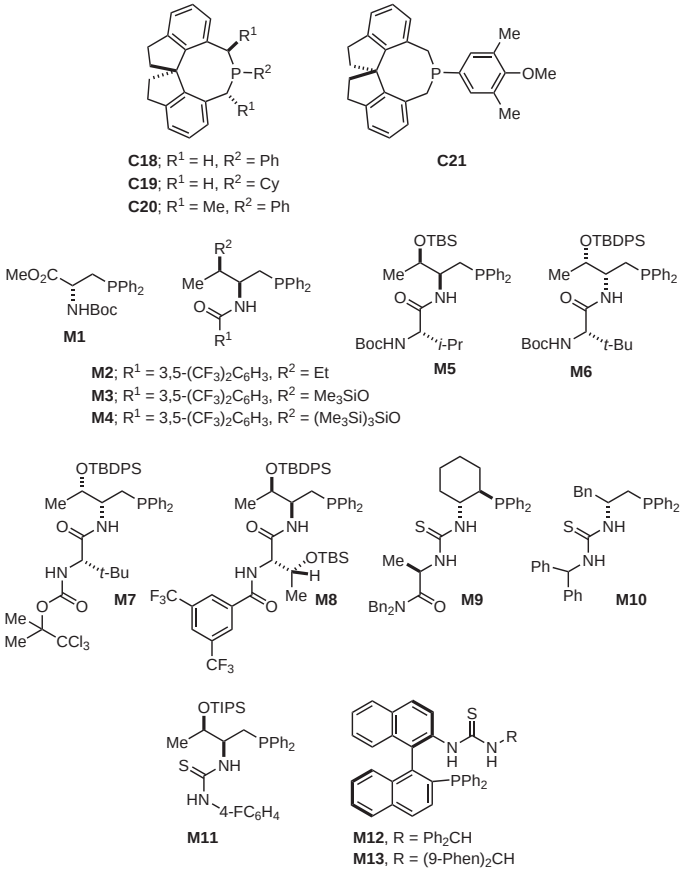
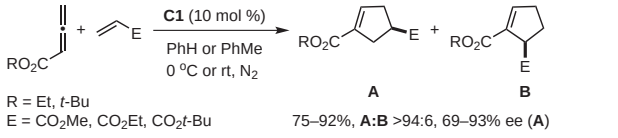
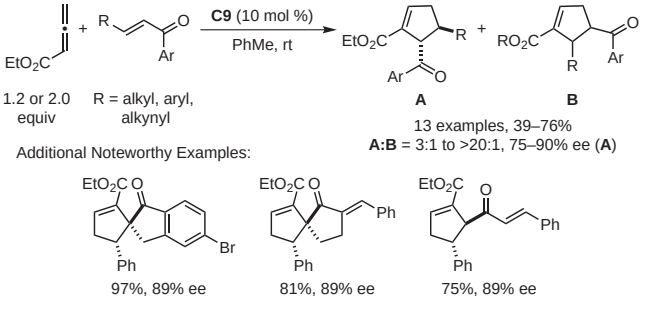


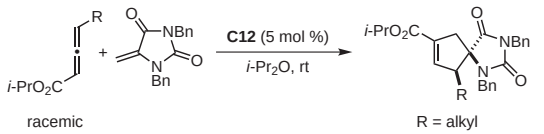
Figure 3. Additional Chiral Phosphines Exhibiting Excellent Activity in Asymmetric Nucleophilic Phosphine Catalysis.



eq 1 *(Ref. 5)*



eq 2 *(Ref. 6)*



eq 3 *(Ref. 9)*

a variety of linkers between the allene and the alkene functional groups, to afford the desired products with a quaternary stereocenter. Using this protocol, many useful scaffolds—widely found in bioactive compounds, including fused pyrrolidine, benzannulated diquinane, and quinolin-2-one derivatives—were generated in very good yields and ee's.

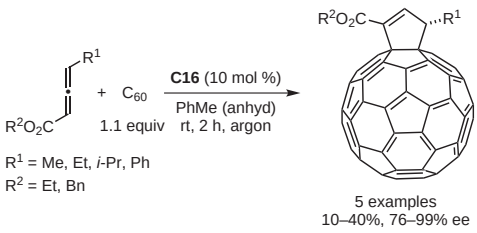
Besides the above-mentioned examples, a variety of activated alkenes including 2-aryl-1,1-dicyanoalkenes,[11a] methyleneindolinones,[11b] 4-substituted 2,6-diarylidenecyclohexanones,[11c] 2,4-diarylidenebicyclo[3.1.0]hexan-3-ones,[11c] olefinic azlactones,[11d] [60]fullerene,[11e] and 4,4-dicyano-2-methylenebut-3-enoates,[11f] underwent asymmetric [3 + 2] annulation with allenes to give the corresponding cyclopentene derivatives. Interestingly, in the presence of chiral phosphine (*S*,*S*)-*f*-binaphane **C16**, [60]fullerene underwent [3 + 2] annulation with allenoates under mild conditions, giving rise to enantiomerically pure carbocyclic fullerene derivatives in remarkably high ee's (**eq 4**).[11e]

Once the excellent catalytic capability of chiral cyclic phosphines was recognized, the design and synthesis of chiral cyclic phosphines with novel skeletons became one of most important research topics in the area of nucleophilic phosphine catalysis. Marinetti and co-workers have developed a new class of very interesting, planar chiral ferrocene-derived phosphines (e.g., **C7**), that possess beneficial properties such as good air-stability, ease of handling, and decent nucleophilicity.[12] These chiral phosphines displayed very broad substrate scope and could be applied in asymmetric [3 + 2] annulations of various activated alkenes—such as methyleneindolinones,[11b] 4-substituted 2,6-diarylidenecyclohexanones,[11c] 2,4-diarylidenebicyclo[3.1.0]hexan-3-ones,[11c] fumarate esters,[12a,12b] α,β-unsaturated ketones,[12a–12c] exocyclic enones,[12a–12c,12e] 2-oxo-2*H*-chromene-3-carboxylates[12d] and 3-(2-nitrophenyl)-acrylate[12d]—leading to a variety of functionalized cyclopentenes, cyclopentenylphosphonates, spirooxindoles, cyclopentene-fused chromanones, dihydroquinolinones, and heterocyclic spiranes with high ee's.

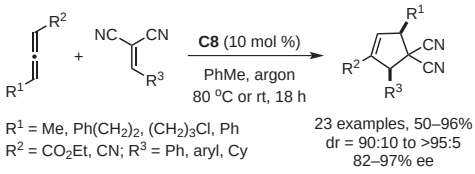
More recently, Marinetti's group designed and synthesized **C8**, a new helically chiral phosphine, and successfully employed it for the enantioselective [3 + 2] annulation between a wide range of γ-substituted allenoates or γ-substituted buta-2,3-dienenitriles and arylidene- or alkylidenemalononitriles, affording the corresponding cycloadducts in high yields, good regio- and diastereoselectivities, and uniformly high ee's (82–97%) (**eq 5**).[13] It is worth noting that, in the presence of 10 mol % of **C8**, the enantioselective [3 + 2] cyclization of cyanoallenes with arylidenemalononitriles at room temperature led to the corresponding cyclopentenes in high yields, excellent regio- and diastereoselectivities, and with 83–88% ee. The reaction represents the first example of a highly enantioselective phosphine-catalyzed cyclization of cyanoallenes. The effective stereochemical control of the organocatalytic process induced by the helically chiral phosphine demonstrated that the chiral helical structure could be a useful template for the design of chiral phosphine catalysts.

Although several cyclic phosphines displayed excellent catalytic activities and enantioselectivities, the asymmetric variants of many achiral phosphine-catalyzed annulations could not be achieved by these chiral cyclic phosphines. Inspired by multifunctional chiral organocatalysts; particularly amino acid, peptide-, and thiourea-based systems;[14] multifunctional chiral phosphines were designed and constructed by attaching a nucleophilic phosphine and a hydrogen-bonding moiety onto a chiral backbone. The phosphine and hydrogen-bonding moiety synergistically activate the substrates in an assembled chiral environment, providing excellent catalytic activities and enantioselectivities that could not be accomplished by using conventional chiral phosphines lacking hydrogen-bonding moieties.[11] Interest in chiral multifunctional phosphines was sparked in 2007 by Cowen and Miller who first reported α-amino acid based phosphine catalyst **M1** for the asymmetric [3 + 2] annulation of allenoates with various cyclic and acyclic enones (**eq 6**).[15] The corresponding cyclopentene derivatives were obtained with excellent regioselectivity and high enantioselectivities. It is worth noting that single amino acid based phosphines displayed better catalytic activities than di-, tri-, and tetrapeptide-based catalysts. The proposed transition state shows that the formation of the zwitterionic intermediate from the reaction of allenoate with the phosphine moiety, and the consequent intramolecular hydrogen bonding, exert dual control on the activity and stereoselectivity.

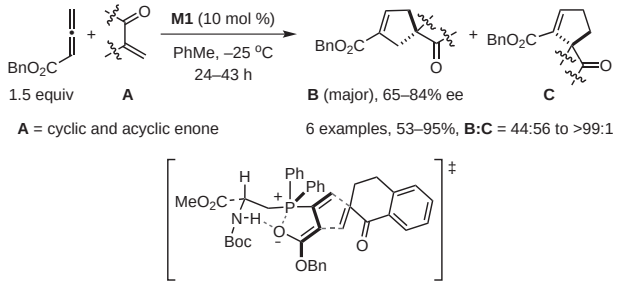
In 2010, Zhao and co-workers reported a novel single amino acid based chiral *N*-acyl aminophosphine **M2**.[16] Using 10% mol of **M2**, the asymmetric [3 + 2] annulation of various arylidenemalononitriles with allenoate proceeded smoothly to give various chiral cyclopentene derivatives as single regioisomers in 79–99% yield 80–99% ee, and with excellent diastereoselectivities.[16] In particular, with 2-cyano-3-



eq 4 *(Ref. 11e)*



eq 5 *(Ref. 13)*



eq 6 *(Ref. 15)*

arylacrylates bearing two different electron-withdrawing functional groups as substrates, chiral cyclopentenes bearing adjacent quaternary and tertiary stereocenters could be obtained in exclusive regioselectivity and high diastereo- and enantioselectivities. Interestingly, γ-substituted racemic allenoates underwent the catalytic [3 + 2] annulation reaction, leading to a dynamic kinetic asymmetric transformation to afford the desired products in high yields and with moderate diastereoselectivities and good enantioselectivities.

A new family of dipeptide-derived chiral phosphines has been developed by Lu and co-workers for asymmetric [3 + 2] annulation reactions.[17] Among them, phosphine **M7** displayed remarkably high activities, catalyzing the asymmetric [3 + 2] annulation of allenoates with acrylates in a rapid (≤0.5 h in most instances) and regiospecific manner to afford functionalized cyclopentenes containing quaternary stereocenters in 61–97% yield and 68–94% ee (**eq 7**).[17a] A proposed transition state model reveals that the phosphonium enolate intermediate approaches the acrylate from its *Re* face to yield the major stereoisomer. Since this kind of chiral phosphine contains a dipeptide moiety, its structure can be easily tuned. A series of dipeptide-derived chiral phosphines with diverse structures have been constructed and evaluated for the asymmetric [3 + 2] annulation of allenes with acrylamides and maleimides, giving rise to the desired chiral functionalized cyclopentenes.[17b,c]

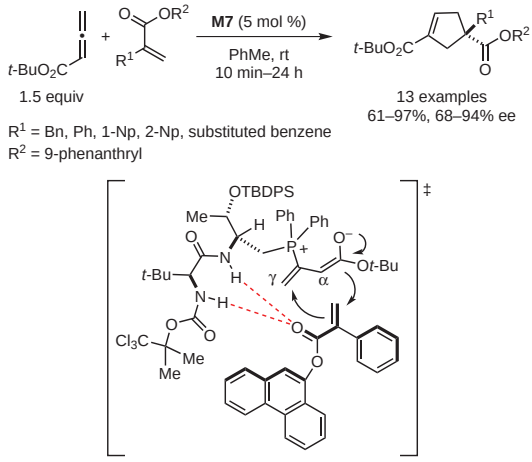
2.2. With Imines

Functionalized pyrrolines are important units in many bioactive compounds and natural products, and Lu and co-workers first reported the achiral phosphine-catalyzed [3 + 2] annulation of allenes with activated imines to form such pyrrolines.[18] However, developing the asymmetric variant of the reaction proved quite challenging, since acyclic (**A2**, **A6**) and cyclic (**C5**, **C10**, **C11**) chiral phosphines—which had displayed excellent activities and enantioselectivities in asymmetric [3 + 2] annulations of allenes with activated alkenes[10]—delivered poor results in the annulation of allenes with imines.[19]

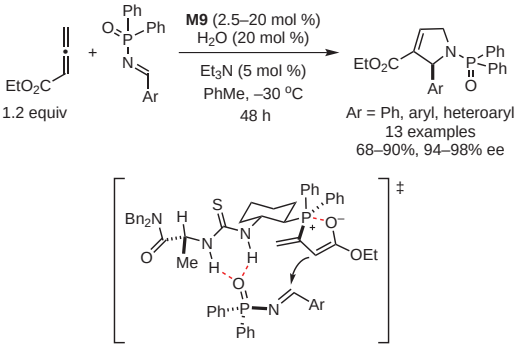
A huge leap forward in the development of enantioselective [3 + 2] annulations of allenoates with imines was achieved in 2008 by Jacobsen's group who used a multifunctional catalyst, **M9**, bearing a phosphine fragment, a thiourea moiety, and an amino acid residue. In the presence of **M9**, a wide range of aromatic *N*-diphenylphosphinoylimines underwent asymmetric [3 + 2] annulations with allenoate, affording 2-aryl-2,5-dihydropyrrole derivatives in high yields (68–90%) and with excellent enantioselectivities (94–98% ee) (**eq 8**).[20] Unfortunately, aliphatic imines were unsuitable substrates since they underwent decomposition under the optimal reaction conditions. On the basis of the proposed transition state, the high enantioselectivity observed could be attributed to synergetic activation and enantioinduction of both the phosphine moiety—which accounts for activation of the allenoate and the enantioinduction—and the thiourea unit, which plays the dual roles of activating the imine and stereochemically controlling the association of the phosphoryl substituents of the imine. The catalytic amounts of triethylamine and water required were indispensable for enhancing the reaction rate. Water is believed to promote proton transfer, while triethylamine probably facilitates the regeneration of the phosphine catalyst.

The limitation of the imine scope was overcome by Lu's team, who utilized dipeptide-derived phosphine **M6** as chiral catalyst to convert a wide range of alkyl, vinyl, and aryl imines into the corresponding 3-pyrroline derivatives in good yields and with nearly perfect enantioselectivities (**eq 9**).[21] With this reaction as a key step, a concise formal synthesis of the alkaloid (+)-trachelanthamidine was accomplished by the same group, highlighting the synthetic value of this methodology.

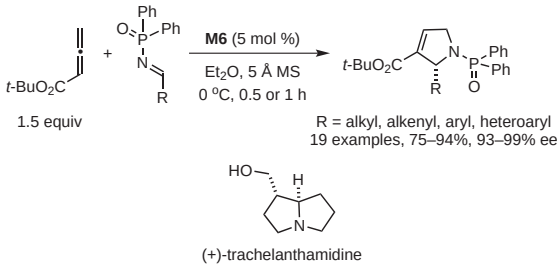
Recently, our group designed and synthesized a new class of rigid [2.2.1] bicyclic chiral phosphines, **C2** and **C3**, from commercially available *trans*-4-hydroxy-L-proline.[22] These chiral cyclic phosphines are highly effective catalysts for the asymmetric [3 + 2] annulation of γ-substituted allenoates with imines, providing substituted pyrrolines in



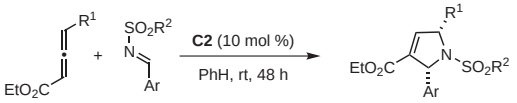
eq 7 *(Ref. 17a)*



eq 8 *(Ref. 20)*

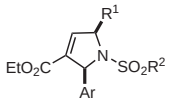


eq 9 *(Ref. 21)*

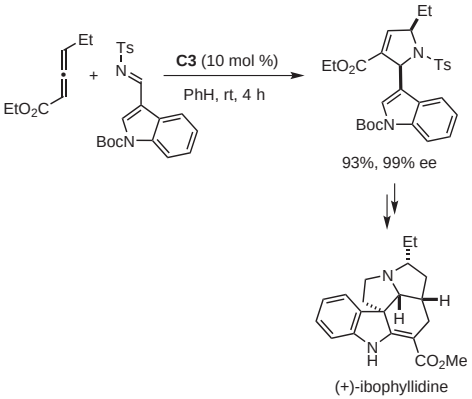


R^1= Me, Et, *i*-Pr, *t*-Bu, *c*-Pent, Cy; Ar = Ph, substituted benzene; SO_2R^2 = Ns

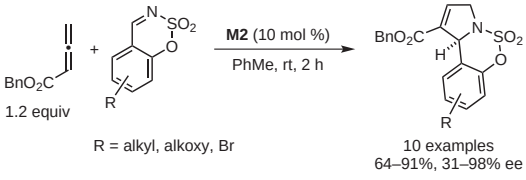
Using **C3** under identical conditions, (+)-pyrrolines were obtained:



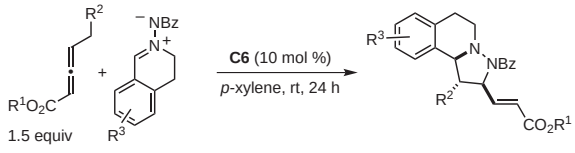
eq 10 *(Ref. 22)*



Scheme 2. A **C3**-Catalyzed Asymmetric [3 + 2] Annulation as a Key Step in the First Enantioselective Total Synthesis of the Indole Alkaloid (+)-Ibophyllidine. *(Ref. 2h)*



eq 11 *(Ref. 23)*



R^1 = Me, *t*-Bu, *t*-$BuCH_2$, Bn
R^2 = Bn, Ph, substituted benzene
R^3 = H, Me, 5,8-Me_2, *t*-Bu, F, Br

eq 12 *(Ref. 25)*

high yields and with excellent enantioselectivities (**eq 10**).[22] Compared with the above two kinds of multifunctional chiral phosphine (**M6** and **M9**), which only catalyzed the reaction of 2,3-butadienoate, **C2** and **C3** extended the scope of allenes to include γ-substituted allenoates. A demonstration of the utility of this chemistry has been the first enantioselective total synthesis (15 steps, 13% overall yield) of the indole alkaloid (+)-ibophyllidine via a **C3**-catalyzed asymmetric [3 + 2] annulation (93%, 99% ee) of an indole-derived *N*-tosylaldimine and 4-ethyl-2,3-butadienoate at rt (**Scheme 2**).[2h] The reaction was also performed on a 30 g scale to provide the optically pure pyrroline (94%, 97% ee) without loss of activity and enantioselectivity.

In the presence of amino acid based, bifunctional chiral phosphine **M2**, sulfamate-derived cyclic imines undergo asymmetric [3 + 2] annulation reactions with allenoate, providing sulfamate-fused dihydropyrroles in good yields and with moderate-to-excellent enantioselectivities (≤91%, ≤98% ee) (**eq 11**).[23]

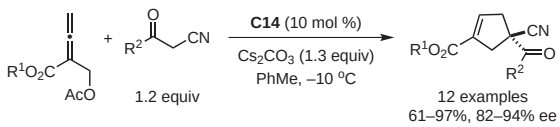
2.3. With Azomethine Imines

In the past five years, the phosphine-catalyzed annulation of 1,3-dipoles with allenes or Morita–Baylis–Hillman (MBH) carbonates has emerged as a powerful tool for the synthesis of bioactive heterocyclic compounds.[24] Several asymmetric variants of the reaction have been reported. For example, the **C19**-catalyzed asymmetric [3 + 2] annulation of a cyclic *N,N'*-azomethine imine with allenoate affords a chiral tetrahydropyrazolopyrazolone in 56% yield and 89% ee.[24a] The asymmetric [3 + 2] annulation of C,N-cyclic azomethine imines with γ-substituted allenoates has also been achieved in the presence of (*S*)-Me-*f*-KetalPhos (**C6**), providing a variety of functionalized tetrahydroisoquinoline (a moiety widely found in pharmaceutically important compounds) derivatives in good yields and with high diastereo- and enantioselectivities (**eq 12**).[25]

3. Asymmetric [4 + x] Annulations of Allenes

3.1. With Bisnucleophiles (x = 1)

The phosphine-catalyzed [4 + 1] annulation reaction is an expedient alternative approach for the synthesis of five-membered-ring carbocycles and heterocycles, and has received considerable attention.[1] Based on the achiral phosphine-catalyzed [4 + 1] annulation of allenoates with bisnucleophiles developed by Tong and co-workers,[26] Fu's group accomplished its asymmetric version with the biphenyl-derived phosphines **C14** and **C15**.[27] In the presence of phosphine **C14**, the asymmetric [4 + 1] annulation of allenoate with a variety of α-cyano-substituted carbonyl compounds afforded functionalized (*S*)-cyclopentenes bearing an all-carbon quaternary stereocenter in high yields (61–97%) and good ee values (82–94%) (**eq 13**).[27] For α-cyano-substituted sulfones, phosphine oxides, and phosphonates, however, **C15** was a more effective catalyst, enabling the efficient synthesis of the corresponding enantioenriched (*R*)-cyclopentene



R^1 = Ph_2CH; R^2 = alkyl, Cy, MeO, Ph, aryl, heteroaryl, NR^3R^4

eq 13 *(Ref. 27)*

derivatives (5 examples; 88–97%, 84–94% ee). Very recently, using chiral spirophosphine catalyst **C20**, Kramer and Fu reported the [4 + 1] annulation of various sulfonamides with a wide range of γ-alkyl-substituted allenes, giving the (*S*)-5-alkyl-substituted dihydropyrrole products in good yields and ee's (14 examples; 67–95%, 83–93% ee).[28]

Pyrazolones are bisnucleophiles and one-carbon synthons, and 4-spiro-5-pyrazolones are a class of compounds with potential biological significance. Lu and co-workers disclosed an efficient [4 + 1] annulation for the synthesis of optically enriched pyrazolones in the presence of L-threonine-derived, O-silylated phosphine **M3**. A wide range of chiral spiropyrazolones were obtained at room temperature in 57−88% yield and 85−92% ee (**eq 14**).[29] The reaction also served as the key step in the synthesis of a chiral inhibitor of type-4 phosphodiesterase.

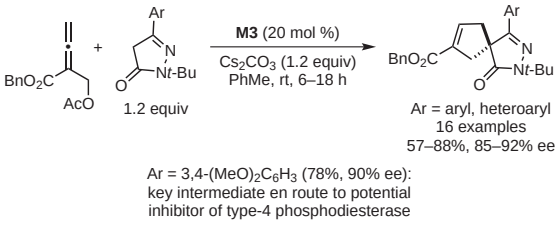
3.2. With Alkenes (x = 2)

Only limited examples of the phosphine-catalyzed [4 + 2] annulation had been reported prior to 2007, when our group disclosed the first achiral phosphine-catalyzed [4 + 2] annulation of allenoates with activated alkenes.[30] Five years later, Lu and co-workers reported the first highly enantioselective variant employing bifunctional phosphines derived from chiral amino acids, **M4**, or dipeptides, **M6**.[31] Highly functionalized cyclohexenes and 3-spirocyclohexene-2-oxindoles were obtained in very high yields and with excellent diastereo- and enantioselectivities (**eq 15**).[31] 3-Spirocyclohexene-2-oxindoles are biologically significant structures in natural products and therapeutically useful agents. At about the same time, Zhao and co-workers reported a highly asymmetric [4 + 2] annulation between activated alkenes and α-substituted allenoates that is catalyzed by an analogue of the bifunctional chiral phosphine **M2**. The reaction afforded various optically active cyclohexenes with three neighboring carbon stereocenters in high yields and with excellent enantioselectivities.[32]

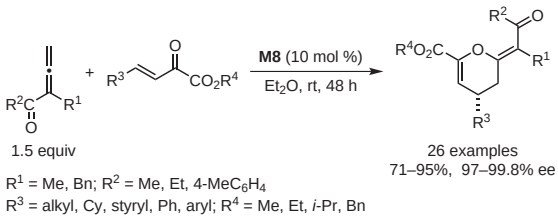
Very recently, Lu's group developed another novel [4 + 2] annulation between allenones and β,γ-unsaturated α-keto esters by using dipeptide-based bifunctional phosphines as chiral catalysts (**eq 16**).[33] In the presence of 10 mol % of the L-threonine-derived bifunctional phosphine **M8**, a wide range of β,γ-unsaturated α-keto esters bearing aryl, heteroaryl, vinyl, and alkyl substituents underwent cyclizations with various allene ketones, generating the desired 3,4-dihydropyrans in good yields with nearly perfect enantioselectivities (≥99% ee in most cases). Moreover, the dihydropyran motif in the product could readily be transformed into bioactive compounds, demonstrating the significant synthetic value of the reaction.

3.3. With Imines (x = 2)

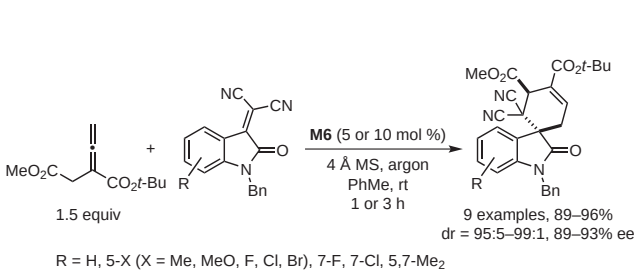
In 2003, our group reported the PBu_3-catalyzed [4 + 2] annulation of allenoates and *N*-tosylimines.[34] The asymmetric variant was disclosed two years later by Wurz and Fu who employed the binaphthyl-based chiral cyclic phosphine **C9** as catalyst to generate a range of chiral functionalized tetrahydropyridines in moderate-to-excellent yields (42–99%) with excellent enantio- (ee ≤ 99%) and diastereoselectivities (dr ≤ 99:1) (**eq 17**).[35] This asymmetric [4 + 2] annulation served as the key step in the synthesis of the bridged tetracyclic framework of the *Alstonia* class of indole alkaloids.[35] Later, Zhao and co-workers also accomplished this asymmetric reaction by utilizing bifunctional *N*-acylaminophosphine **M2**.[36] For some activated imines, the bifunctional phosphine displayed a catalytic capability superior to that of Fu's chiral cyclic phosphine system in terms of yield, ee, or both. In the presence of amino acid derived, thiourea-based multifunctional chiral phosphine[37a] or cyclic phosphine (*R*)-SITCP (**C18**),[37b] cyclic aldimines and ketimines underwent asymmetric [4 + 2] annulations with allenoates, leading to the formation of tetrahydropyridines with good enantioselectivities.[37]



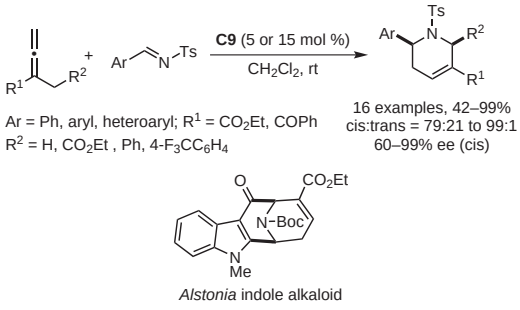
eq 14 *(Ref. 29)*



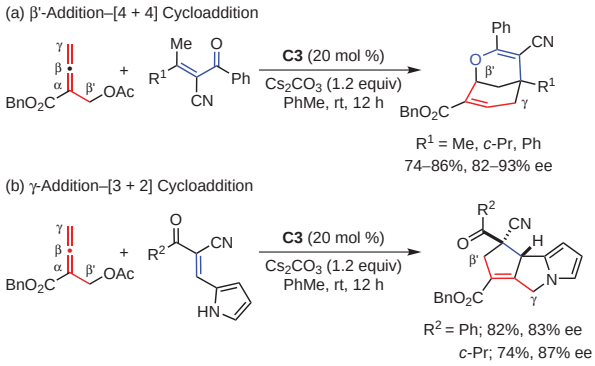
eq 16 *(Ref. 33)*



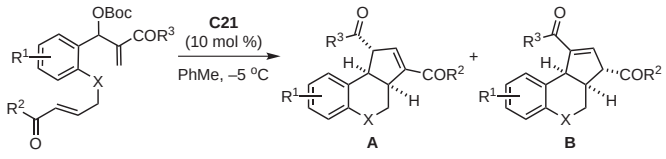
eq 15 *(Ref. 31)*



eq 17 *(Ref. 35)*



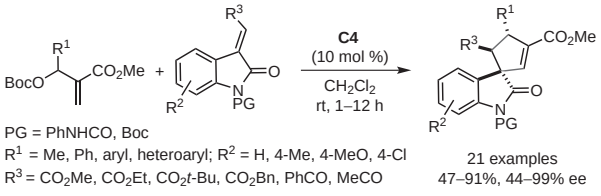
Scheme 3. β′-Addition–[4 + 4] Annulation and γ-Addition–[3 + 2] Annulation of Allenes with Enones. *(Ref. 38)*



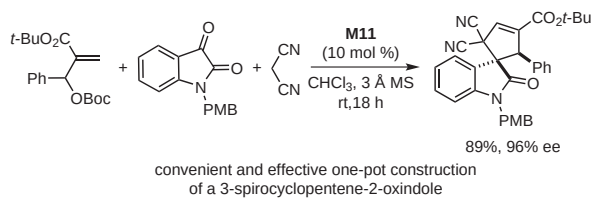
Conditions	A+B	A:B	ee
No additive	76–98%	25:75 to >95:5	77 to >99% (**A**)
$Ti(O\textit{i}\text{-}Pr)_4$ (20 mol %)	76–99%	8:92 to <5:95	77–92% (**B**)

X = O, C; R^1 = H, 4-Cl, 4-Br, 2-MeO; R^2, R^3 = Me, MeO, EtO

eq 18 *(Ref. 40)*



eq 19 *(Ref. 41a)*



eq 20 *(Ref. 42)*

4. Addition–Annulation Domino Reaction of Allenes with Enones

Most recently, Tong and co-workers developed two novel classes of phosphine-catalyzed addition–annulation domino reactions of β'-acetoxyallenoate with 2-acyl-3-methylacrylonitriles (β′-addition–[4 + 4] annulation) and 2-acyl-3-(2-pyrrole)acrylonitriles (γ-addition–[3 + 2] annulation),[38] affording 2-oxabicyclo[3.3.1]nonanes (e.g., ≤86%, ≤93% ee with Kwon's phosphine **C3**) and cyclopenta[a]pyrrolizines (e.g., 74–82%, 83–87% ee with **C3**), respectively (**Scheme 3**).[38] The oxabicyclononanes and cyclopentapyrrolizines are two ubiquitous frameworks in natural products and biologically active compounds. Some preliminary results of their asymmetric variants were also reported.

5. Asymmetric Annulations of MBH Carbonates

5.1. [3 + 2] Annulation with Alkenes

Besides activated allenes and alkynes, Morita–Baylis–Hillman (MBH) carbonates are often employed as versatile substrates for the phosphine-catalyzed annulations.[1,39] Tang, Zhou, and co-workers have found that spirocyclic chiral phosphines can efficiently promote the intramolecular asymmetric [3 + 2] cyclization of MBH carbonates and electron-deficient alkenes (**eq 18**).[40] In the presence of 10 mol % (*S*)-DMM-SITCP **C21**, a variety of α,β-unsaturated carbonyl compounds were transformed in toluene at –5 °C into the optically active benzobicyclo[4.3.0] products **A** in 76–98% yield and with 77–95% ee. Interestingly, the addition of 20 mol % of $Ti(O\textit{i}\text{-}Pr)_4$, under otherwise identical conditions, inhibited the isomerization process, leading to the regioisomeric benzobicyclo[4.3.0] compounds **B** as major products in almost identical optical purities (77–92% ee) to those of **A**.

In 2011, aiming to develop new, highly enantioselective methods for the direct construction of the spirocyclopenteneoxindole scaffold, Barbas and co-workers discovered a novel highly efficient asymmetric [3 + 2] annulation between methyleneindolinones and MBH carbonates.[41a] In the presence of 10 mol % (+)-Ph-BPE (**C4**), the annulation between a wide range of Boc- and carbamoyl-protected methyleneindolinones and various MBH carbonates occurred readily, yielding polyfunctionalized spirocyclopenteneoxindoles in moderate-to-excellent yields (63–85%) and good ee's (91–99%) (**eq 19**). Aryl-substituted MBH carbonates reacted much better than methyl-substituted ones. Following this study and using the same catalytic system, the same group achieved the asymmetric [3 + 2] annulation of MBH carbonates with methylene benzofuranone derivatives, affording a wide range of polysubstituted spirocyclopentenebenzofuranones in high yields and with good-to-excellent enantioselectivities.[41b]

Lu and co-workers synthesized biologically important 3-spirocyclopentene-2-oxindoles with two contiguous quaternary centers by employing asymmetric [3 + 2] annulations between MBH carbonates and activated isatin-based alkenes catalyzed by amino acid derived chiral phosphines.[42] In the presence of catalyst **M11**, the reactions proceeded in very high yields and with good enantioselectivities. This reaction is synthetically appealing, since it can be conveniently and equally effectively performed in a one-pot manner. For example, simply mixing the isatin, malononitrile (precursors of activated alkene), and MBH carbonate produces the corresponding spirooxindole with the same enantioselectivity as that acquired in the reaction between activated alkenes and MBH adducts, albeit in slightly diminished yields (**eq 20**). Shi and co-workers found that chiral bifunctional thiourea-based phosphine catalyst **M12** could catalyze the same reaction, giving the corresponding cycloadduct as the major product in 92% yield and with a 9:1 diastereomeric ratio and 74% ee.[43]

The asymmetric [3 + 2] annulation between MBH carbonates and maleimides, giving functionalized bicyclic imides, has been achieved with the amino acid derived chiral phosphine catalyst **M5** in excellent yields and with high enantio- and diastereoselectivities.[44] With the versatile and powerful thiourea-based chiral phosphine **M10** as catalyst, Shi's group effected asymmetric [3 + 2] annulations of MBH carbonates with various activated alkenes, including maleimides,[45a] trifluoroethylidenemalonates,[45b] and 2-arylideneindane-1,3-diones,[45c] providing the functionalized cyclopentenes in moderate-to-excellent yields, diastereoselectivities, and enantioselectivities.

5.2. [4 + 1] Annulation with Dienes

While allenes function as four-carbon synthons in the [4 + 1] annulation under phosphine catalysis, MBH carbonates serve as one-carbon synthons in the same reaction. In the presence of 20 mol % of the bifunctional phosphine **M13** and 4 Å molecular sieves, the asymmetric [4 + 1] annulation of MBH carbonates with activated dienes proceeded smoothly in toluene at room temperature. A wide range of functionalized cyclopentenes bearing quaternary carbon stereocenters were thus prepared in 29–92% yield with 66–98% ee, albeit requiring very long reaction times (up to 7 days) (**eq 21**).[46] Those substrates bearing bulky substituents were not compatible with the reaction conditions, leading to low yields or ee's.

5.3. [3 + 3] Annulation with Azomethine Imines

The phosphine-catalyzed [3 + 3] annulation is a very useful alternative to the [4 + 2] annulation for the synthesis of biologically important six-membered-ring carbocycles and heterocycles. However, this type of reaction, especially the asymmetric variant, has met with limited success.[1] Most recently, the first phosphine-catalyzed asymmetric [3 + 3] annulation of MBH carbonates with C,N-cyclic azomethine imines was achieved using the commercially available spirocyclic chiral phosphine **C18** as catalyst under mild conditions.[47] The reaction yielded a novel class of pharmaceutically interesting 4,6,7,11b-tetrahydro-1*H*-pyridazino[6,1-*a*]isoquinoline derivatives in high yields and with good-to-excellent diastereoselectivities and outstanding enantioselectivities (98 to >99% ee) (**eq 22**). Moreover, the reaction could be scaled up without significant loss of diastereoselectivity, enantioselectivity, or yield.

6. Asymmetric [2 + 2] Annulation of Ketenes

Ketenes, analogues of allenes, can also undergo phosphine-catalyzed annulations, whereby they generally function as binary synthons. In the presence of 10 mol % of (*R*)-binaphane (**C17**), disubstituted ketenes underwent asymmetric [2 + 2] annulations with *N*-tosyl arylimines in dichloromethane or tetrahydrofuran, giving the corresponding *trans*-β-lactams in moderate-to-excellent ee's (≤98%), diastereoselectivities (dr ≤ 99:1), and yields (up to >99%) (**eq 23**).[48] Very interestingly, with (*S*,*Rp*)-JosiPhos **A4** or **A5** as chiral catalyst, ketenes underwent asymmetric homodimerization, namely formal [2 + 2] annulations, affording chiral β-lactones in high yields (≤99%) and with good-to-excellent ee's (≤96%).[49]

7. Miscellaneous Annulations through Domino Reactions

In addition to the annulations employing allenes, alkynes, MBH carbonates, and ketenes described in the preceding sections, phosphine-catalyzed asymmetric annulations can also be achieved by domino reactions. These transformations allow the rapid construction of carbocyclic and heterocyclic molecules from readily available starting materials in two or more steps in a single operation. By utilizing acyclic, cyclic, and multifunctional chiral phosphines as catalysts, several asymmetric annulations have been accomplished through domino aza-MBH–Michael,[50] tandem RC–Michael,[51] double-Michael,[52] and tandem Michael addition–Wittig olefination.[53] These asymmetric annulations are described in the cited references, and will not be discussed in this review.

8. Conclusions and Outlook

In summary, nucleophilic chiral phosphines—including acyclic, cyclic, and multifunctional phosphines—especially the latter two types, display powerful and versatile catalytic capabilities. Under catalysis by these phosphines, various asymmetric annulations have been developed, which serve as very valuable tools in the synthesis of a significant number of bioactive molecules and natural products. Although huge strides in the area of nucleophilic chiral-phosphine-catalyzed asymmetric annulations have been made, many challenges still remain, necessitating a continued vigorous research effort in the design and synthesis of chiral phosphines with novel skeletons.

9. Acknowledgments

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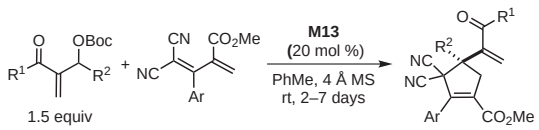

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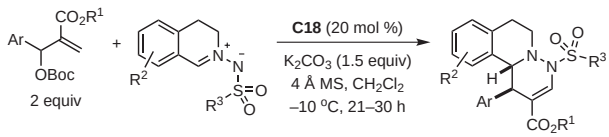

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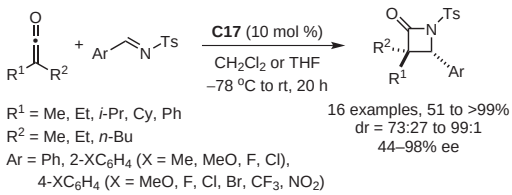

eq 23 *(Ref. 48)*

10. References

(1) For selected reviews on phosphine-promoted annulations, see: (a) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. (b) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (c) Wang, S.-X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, 2766. (d) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (e) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (f) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (g) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089 (DOI: 10.3762/bjoc.10.218).

(2) (a) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (b) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (c) Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289. (d) Koech, P. K.; Krische, M. J. *Tetrahedron* **2006**, *62*, 10594. (e) Webber, P.; Krische, M. J. *J. Org. Chem.* **2008**, *73*, 9379. (f) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (g) Sampath, M.; Lee, P.-Y. B.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1988. (h) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510. (i) Villa, R. A.; Xu, Q.; Kwon, O. *Org. Lett.* **2012**, *14*, 4634. (j) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. *Org. Lett.* **2012**, *14*, 5388.

(3) (a) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (b) Watanabe, M.; Fiji, H. D. G.; Guo, L.; Chan, L.; Kinderman, S. S.; Slamon, D. J.; Kwon, O.; Tamanoi, F. *J. Biol. Chem.* **2008**, *283*, 9571. (c) Lu, J.; Chan, L.; Fiji, H. D. G.; Dahl, R.; Kwon, O.; Tamanoi, F. *Mol. Cancer Ther.* **2009**, *8*, 1218. (d) Chan, L. N.; Fiji, H. D. G.; Watanabe, M.; Kwon, O.; Tamanoi, F. *PLoS ONE* **2011**, *6*, e26135. (e) Choi, J.; Mouillesseaux, K.; Wang, Z.; Fiji, H. D. G.; Kinderman, S. S.; Otto, G. W.; Geisler, R.; Kwon, O.; Chen, J.-N. *Development* **2011**, *138*, 1173. (f) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem.–Eur. J.* **2011**, *17*, 649. (g) Cruz, D.; Wang, Z.; Kibbie, J.; Modlin, R.; Kwon, O. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6769.

(4) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.

(5) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.

(6) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426.

(7) Wallace, D. J.; Sidda, R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, *72*, 1051.

(8) Sampath, M.; Loh, T.-P. *Chem. Sci.* **2010**, *1*, 739.

(9) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.

(10) Lee, S. Y.; Fujiwara, Y.; Nishiguchi, A.; Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 4587.

(11) (a) Schuler, M.; Voituriez, A.; Marinetti, A. *Tetrahedron: Asymmetry* **2010**, *21*, 1569. (b) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.–Eur. J.* **2010**, *16*, 12541. (c) Pinto, N.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Chem. Commun.* **2011**, *47*, 1015. (d) Steurer, M.; Jensen, K. L.; Worgull, D.; Jørgensen, K. A. *Chem.–Eur. J.* **2012**, *18*, 76. (e) Marco-Martinez, J.; Marcos, V.; Reboredo, S.; Filippone, S.; Martin, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5115. (f) Zhang, X.-N.; Shi, M. *ACS Catal.* **2013**, *3*, 507.

(12) (a) Voituriez, A.; Panossian, A.; Fleury-Brégeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (b) Voituriez, A.; Panossian, A.; Fleury-Brégeot, N.; Retailleau, P.; Marinetti, A. *Adv. Synth. Catal.* **2009**, *351*, 1968. (c) Pinto, N.; Neel, M.; Panossian, A.; Retailleau, P.; Frison, G.; Voituriez, A.; Marinetti, A. *Chem.–Eur. J.* **2010**, *16*, 1033. (d) Neel, M.; Gouin, J.; Voituriez, A.; Marinetti, A. *Synthesis* **2011**, 2003. (e) Duvvuru, D.; Pinto, N.; Gomez, C.; Betzer, J.-F.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Adv. Synth. Catal.* **2012**, *354*, 408.

(13) Gicquel, M.; Zhang, Y.; Aillard, P.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 5470.

(14) (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759.

(15) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988.

(16) Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4467.

(17) (a) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726. (b) Han, X.; Wang, S.-X.; Zhong, F.; Lu, Y. *Synthesis* **2011**, 1859. (c) Zhao, Q.; Han, X.; Wei, Y.; Shi, M.; Lu, Y. *Chem. Commun.* **2012**, *48*, 970.

(18) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549.

(19) (a) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (b) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335. (c) Fleury-Brégeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920. (d) Pinto, N.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146. (e) Panossian, A.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2008**, 3826.

(20) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

(21) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767.

(22) Henry, C. E.; Xu, Q.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, *136*, 11890.

(23) Yu, H.; Zhang, L.; Yang, Z.; Li, Z.; Zhao, Y.; Xiao, Y.; Guo, H. *J. Org. Chem.* **2013**, *78*, 8427.

(24) (a) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (b) Jing, C.; Na, R.; Wang, B.; Liu, H.; Zhang, L.; Liu, J.; Wang, M.; Zhong, J.; Kwon, O.; Guo, H. *Adv. Synth. Catal.* **2012**, *354*, 1023. (c) Liu, J.; Liu, H.; Na, R.; Wang, G.; Li, Z.; Yu, H.; Wang, M.; Zhong, J.; Guo, H. *Chem. Lett.* **2012**, *41*, 218. (d) Li, Z.; Yu, H.; Liu, H.; Zhang, L.; Jiang, H.; Wang, B.; Guo, H. *Chem.–Eur. J.* **2014**, *20*, 1731. (e) Li, Z.; Yu, H.; Feng, Y.; Hou, Z.; Zhang, L.; Yang, W.; Wu, Y.; Xiao, Y.; Guo, H. *RSC Adv.* **2015**, *5*, 34481.

(25) Wang, D.; Lei, Y.; Wei, Y.; Shi, M. *Chem.–Eur. J.* **2014**, *20*, 15325.

(26) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550.

(27) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183.

(28) Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803.

(29) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643.

(30) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632.

(31) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231.

(32) Xiao, H.; Chai, Z.; Cao, D.; Wang, H.; Chen, J.; Zhao, G. *Org. Biomol. Chem.* **2012**, *10*, 3195.

(33) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *137*, 54.

(34) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

(35) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.

(36) Xiao, H.; Chai, Z.; Wang, H.-F.; Wang, X.-W.; Cao, D.-D.; Liu, W.; Lu, Y.-P.; Yang, Y.-Q.; Zhao, G. *Chem.–Eur. J.* **2011**, *17*, 10562.

(37) (a) Yu, H.; Zhang, L.; Li, Z.; Liu, H.; Wang, B.; Xiao, Y.; Guo, H. *Tetrahedron* **2014**, *70*, 340. (b) Takizawa, S.; Arteaga, F. A.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Asian J. Org. Chem.* **2014**, *3*, 412.

(38) Gu, Y.; Hu, P.; Ni, C.; Tong, X. *J. Am. Chem. Soc.* **2015**, *137*, 6400.

(39) (a) Liu, T.-Y.; Xie, M.; Chen, Y.-C. *Chem. Soc. Rev.* **2012**, *41*, 4101. (b) Rios, R. *Catal. Sci. Technol.* **2012**, *2*, 267. (c) Xie, P.; Huang, Y. *Org. Biomol. Chem.* **2015**, *13*, 8578.

(40) Wang, Q.-G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 1914.

(41) (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (b) Albertshofer, K.; Tan, B.; Barbas, C. F., III. *Org. Lett.* **2013**, *15*, 2958.

(42) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837.
(43) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348.
(44) Zhong, F.; Chen, G.-Y.; Han, X.; Yao, W.; Lu, Y. *Org. Lett.* **2012**, *14*, 3764.
(45) (a) Deng, H.-P.; Wang, D.; Wei, Y.; Shi, M. *Beilstein J. Org. Chem.* **2012**, *8*, 1098 (DOI: 10.3762/bjoc.8.121). (b) Deng, H.-P.; Wei, Y.; Shi, M. *Adv. Synth. Catal.* **2012**, *354*, 783. (c) Hu, F.; Wei, Y.; Shi, M. *Tetrahedron* **2012**, *68*, 7911.
(46) Zhang, X.; Deng, H.-P.; Huang, L.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 8664.
(47) Zhang, L.; Liu, H.; Qiao, G.; Hou, Z.; Liu, Y.; Xiao, Y.; Guo, H. *J. Am. Chem. Soc.* **2015**, *137*, 4316.
(48) Chen, S.; Salo, E. C.; Wheeler, K. A.; Kerrigan, N. J. *Org. Lett.* **2012**, *14*, 1784.
(49) Ibrahim, A. A.; Wei, P.-H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901.
(50) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725.
(51) (a) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825. (b) Jin, Z.; Yang, R.; Du, Y.; Tiwari, B.; Ganguly, R.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 3226.
(52) Khong, S. N.; Kwon, O. *Molecules* **2012**, *17*, 5626.
(53) Ye, L.-W.; Wang, S.-B.; Wang, Q.-G.; Sun, X.-L.; Tang, Y.; Zhou, Y.-G. *Chem. Commun.* **2009**, 3092.

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Ohyun Kwon, Professor of Chemistry and Biochemistry at UCLA, received her B.S. and M.S. degrees in 1991 and 1993, respectively, from Seoul National University. After receiving her Ph.D. degree in 1998 from Columbia University and, following a postdoctoral stint at Harvard University, Kwon started her independent career in 2001 at UCLA. She has played key roles in establishing phosphinocatalysis as one of the main areas of organocatalysis research, and is recognized as one of the leaders in the field.

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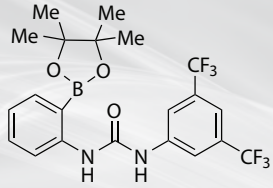

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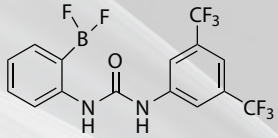

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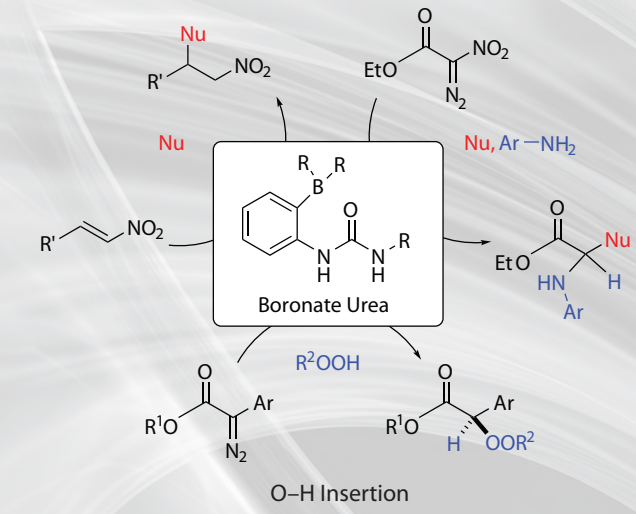

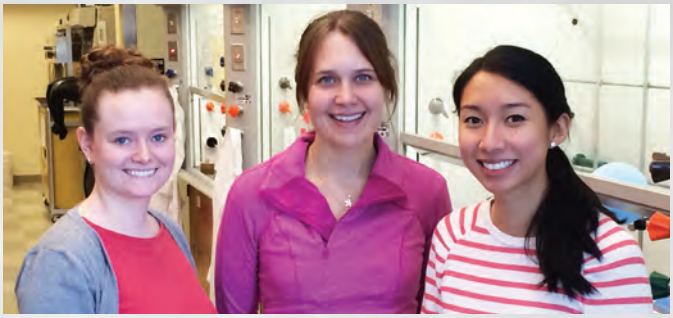

From left to right: Andrea Hardman-Baldwin, Professor Anita Mattson, and Veronica Dunham

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References:
(1) Wieting, J. M.; Hardman-Baldwin, A. M.; Visco, M. D.; Mattson, A. E. *Aldrichimica Acta* **2016,** *49,* 15.
(2) So, S. S.; Oottikkal, S.; Badjić, J. D.; Hadad, C. M.; Mattson, A. E. *J. Org. Chem.* **2014,** *79,* 4832.
(3) Nickerson, D. M.; Angeles, V. V.; Auvil, T. J.; So, S. S.; Mattson, A. E. *Chem. Commun.* **2013,** *49,* 4289.
(4) Fisher, T. J.; Mattson, A. E. *Org. Lett.* **2014,** *16,* 5316.

Silanediol Recognition in Catalysis, Sensing, and Drug Discovery†


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Keywords. silanediol; catalysis; molecular recognition; anion binding; hydrogen bonding.

Abstract. Inherent chemical properties of silanediols, such as their excellent hydrogen-bonding abilities, enable these remarkable molecules to provide platforms for the development of new chemical tools. This review describes advances in catalysis, sensing, and drug discovery that are made possible by the molecular recognition abilities of the silanediol functional group.

Outline

1. Introduction

The silanediol functional group has been inspiring scientific investigations for more than a century.[1] Unlike their carbon counterparts, which typically eliminate water to form carbonyl compounds, silanediols are more stable than their corresponding silanones (**Figure 1**).[2] Silanediols exist predominantly as stable hydrates, which gives rise to unique chemical reactivities and enables their use for innovative solutions in specialized sensors, stereoselective catalysis, and drug design.

The self-condensation of silanediols into silicone polymers may be their most widespread application.[3] As a result of their desirable properties, such as low surface tension and high thermal stability, silicon polymers play an important role in society. The ease of polymerization of silanediols via self-condensation correlates directly with the steric bulk of the substituents on silicon: the more bulky the substituent, the less likely the polymerization.[4] In fact, monomeric silanediols can be rather stable if the organic substituents on silicon are sufficiently bulky.

Owing to the high acidity and relatively high basicity of the hydroxyl group, silanediols, like all organosilanols, participate readily in hydrogen bonding.[4,5] Silanediols form hydrogen bonds often through self-association with more bulky silanediols forming discrete cyclic dimers, while unhindered silanediols participate in an infinite number of hydrogen-bonded structures. Besides self-recognition, the silanediol functional group engages a variety of suitable neutral and anionic guest molecules in hydrogen-bonding complexes. The powerful intermolecular recognition abilities of the silanediol functionality are emerging as central tools in a number of applications, such as catalysis, sensing, and drug discovery.

A number of articles have surveyed the synthesis, properties, and medicinal chemistry of silanediols and, therefore, these topics are not covered in detail in this review.[4–7] The intent of this article is to focus on recent advances that capitalize on the utility of silanediol recognition. The first section of this review covers self-recognition of silanediols as it applies to catalysis and supramolecular structures. The following section focuses on silanediol anion recognition as a function for sensing and enantioselective catalysis. Silanediol–enzyme recognition as a tool for drug discovery is briefly highlighted in the third section. Finally, the prospects of silanediol recognition as a chemical tool are considered.

2. Self-Recognition of Silanediols

2.1. Silanediol Self-Recognition Patterns

Interest in the self-recognition of silanediols has withstood the test of time. Early work in this area demonstrated the formation of infinite sheets from unhindered silanediols like diethylsilanediol[8] and diallylsilanediol.[9] More moderately hindered species, such diphenylsilanediol, were found to organize themselves into hydrogen-bonded columns.[10] Discrete hexamers, tetramers, and dimers have been formed from bulky silanediols, such as $(Me_3Si)_3CSiF(OH)_2$.[4]

2.2. Catalysis via Silanediol Self-Association

The long-standing history supporting the self-recognition properties of silanediols has recently inspired the Franz group to probe their utility in catalysis and supramolecular assembly. In 2011, while studying a silanediol-catalyzed Diels–Alder reaction, this research group captured interesting molecular-recognition preferences of a small family of diarylsilanediols in the solid state.[11] For example, when crystallized alone, dimesitylsilanediol (**1**) formed a linear network; but, in the presence of a Lewis basic carbonyl compound (e.g., benzaldehyde), two self-associated silanediols crystallized with two carbonyl compounds (**2**, **Figure 2**).[11] Silanediol **1** demonstrated moderate levels of carbonyl activation in the hetero-Diels–Alder reaction of Rawal's diene and methacrolein (**Scheme 1**, Part (a)).[11] Subsequent work by Franz's group demonstrated silanediol dimers may be acting as catalysts for the activation of nitroalkenes in their reactions with indoles and *N*,*N*-dimethyl-*meta*-anisidine (Scheme 1, Part (b)).[12] Based on these studies, Franz's team proposed that the principal mode by which the silanediol activates *trans*-β-nitrostyrene proceeds via the self-recognition complex **4**. These workers further proposed that the dimeric silanediol intermediates possess enhanced acidity of the hydroxyl protons relative to the monomeric silanediols, and thus show improved catalytic performance.

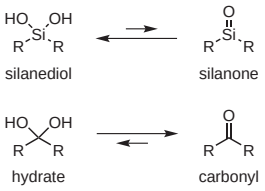


Figure 1. Stability of Silanediols vs That of Hydrates (*gem*-Diols).

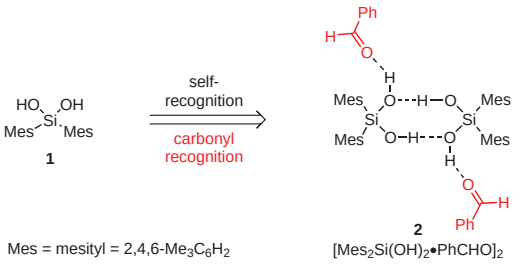
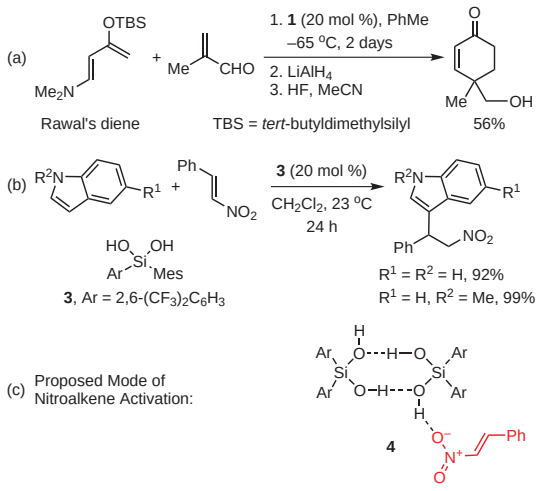


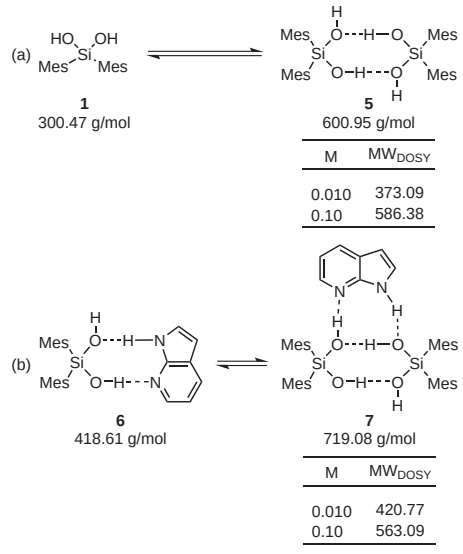
Figure 2. Molecular-Recognition Preferences of Dimethylsilanediol in the Solid State. *(Ref. 11)*



Scheme 1. Silanediol Catalysis via Hydrogen Bonding of (a) Carbonyl Compounds and (b) Nitroalkenes. *(Ref. 11,12)*

2.3. Evidence for Silanediol Self-Association

Franz and co-workers found additional evidence for silanediol self-association when exploring the supramolecular assembly of silanediols with select bifunctional heterocycles.[13] Diffusion-Ordered Spectroscopy (DOSY) experiments found the average molecular weight of aggregates in a 0.10 M solution of dimesitylsilanediol (**1**) in C_6D_6 to be 586.38 g/mol, suggesting a significant portion of the silanediols were self-associating. Diluting the solution to a concentration of 0.01 M significantly decreased the level of self-association as evidenced by the average molecular weight of aggregates dropping to 373.09 g/mol (**Scheme 2**, Part (a)).[13] When a neutral organic molecule was added, that was capable of both donating and accepting hydrogen bonds (e.g., 7-azaindole), self-association of the silanediol seemed to be interrupted, and DOSY NMR studies indicated the existence at 0.01 M of predominantly a 1:1 association of **6** and **7** (Scheme 2, Part (b)). Through the course of their studies, Franz and co-workers consistently observed that, in the presence of select Lewis basic species, silanediols tend to dimerize in such a way as to produce both hydrogen-bond donor and acceptor sites.



Scheme 2. Self-Association Patterns of Silanediols at Low and High Concentrations: (a) in the Absence and (b) in the Presence of a Self-Association Disruptor. *(Ref. 13)*

3. Silanediol Anion Recognition

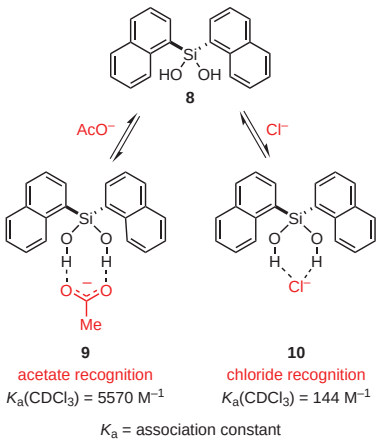
3.1. Silanediols as Sensors

Unequivocal evidence demonstrating the ability of dinaphthylsilanediol **8** to recognize anionic guest molecules including acetate, chloride, and bromide, through hydrogen-bonding interactions was published in 2006 by Kondo, Unno, and co-workers (**Scheme 3**).[14] Using data collected from NMR binding-titration studies and X-ray crystal structures, a 1:1 binding stoichiometry with dual hydrogen-bonding mode of action was proposed for acetate (**9**) and halides (**10**). No silanediol dimerization was observed in the solid state. According to the experimental data, silanediol binding to acetate [$K_a(CDCl_3)$ = 5570 M^{-1}] is stronger than to chloride [$K_a(CDCl_3)$ = 144 M^{-1}] and bromide [$K_a(CDCl_3)$ = 50 M^{-1}]. Although functioning in a similar manner as the well-established thioureas,[15] silanediols offer a unique template to develop innovative families of molecular sensors and hydrogen-bond-donor catalysts. While the advantages of this underdeveloped moiety are not yet fully delineated, silanediols may offer enhanced activity via their distinct shape, flexibility, and inherent propensity to form hydrogen bonds.

Upon further investigations, Kondo's group established the photostability of di(1-pyrenyl)silanediol (**11**) and proceeded to evaluate its binding affinity via UV-Vis and fluorescence spectral titrations in CH_3CN (**eq 1**).[16] When AcO^- and $H_2PO_4^-$ anions were titrated into a solution of silanediol **11** in CH_3CN, a significant increase in fluorescence intensity was detected at two wavelengths (377 and 396 nm) as well as a significant decrease in intensity of the signals at 382.5 and 450 nm. These observations are important because they suggest that silanediol **11** could serve as a ratiometric fluorescent sensor for biologically relevant anions. Ratiometric fluorescent sensors are of interest as they may provide an analysis technique potentially leading to reliable, precise results due to the built-in self-calibration abilities of the sensor.[17] The association constants in the fluorescence spectral titrations of **11** with AcO^- and $H_2PO_4^-$ in CH_3CN were calculated, via nonlinear curve fitting regression, to be 3.16 ± 0.17 x 10^4 and 1.26 ± 0.13 x 10^4 mol^{-1} dm^3, respectively.

3.2. Silanediols as Anion-Binding Catalysts

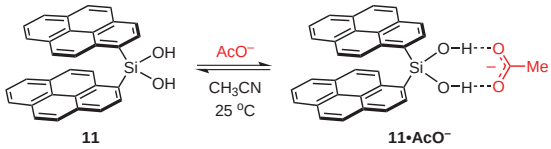
In addition to sensing, the anion-recognition abilities of silanediols can be taken advantage of in the context of catalysis. Anion-binding catalysis is an emerging reaction platform in which a complex consisting of a neutral receptor and anionic guest molecule operates to control the transition state of the major reaction pathway.[18,19] In 2013, we first demonstrated the promise of silanediols in anion-binding catalysis. Our investigations established that achiral silanediol **8** catalyzed the addition of silyl ketene acetal **15** to isoquinoline, plausibly via ion-pair **14**, to give rise to **16** in 74% yield (**Scheme 4**).[20,21]



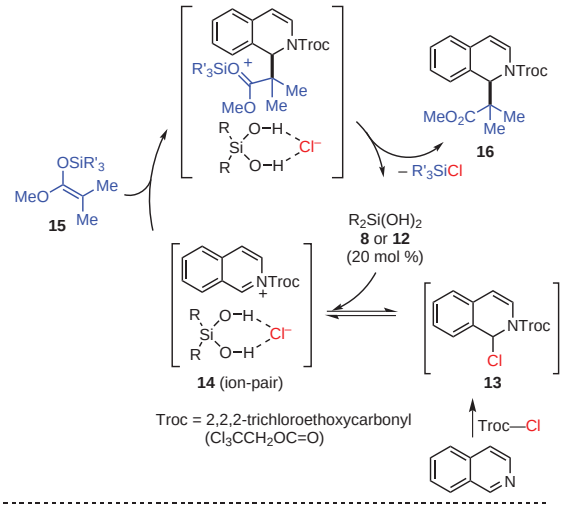
Scheme 3. Silanediol Anion Recognition. *(Ref. 14)*

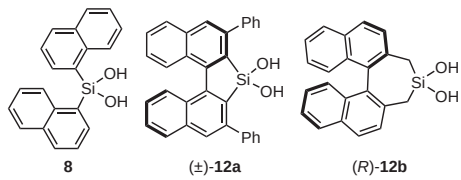
3.3. Enantioselective Silanediol Anion-Binding Catalysis

With the catalytic abilities of the silanediol established in the *N*-acyl Mannich reaction, attention was directed toward the design and application of chiral, enantiopure silanediol catalysts that would be capable of controlling the stereochemical outcome. It is worth noting that enantioselective, anion-binding catalysis with a silanediol had not been reported before. Based upon the success of dinaphthylsilanediol (**8**), we focused our efforts first on developing silanediols from the 1,1'-bi-2-naphthol (BINOL) scaffold. Not only does the BINOL backbone resemble that of **8**, BINOL is readily accessible in enantiopure form and easy to modify.[22] To this end, racemic silanediol **12a**[23] was prepared



eq 1 *(Ref. 16)*





R'	T, t (in PhMe)	**16** (with **8**)	**16** [with (±)-**12a**]	**16** [with (*R*)-**12b**)]
TBS	–78 °C, 40 h	74%	50%	71% (18% ee)
TIPS	–55 °C, 6 h	___	___	55% (28% ee)

TIPS = triisopropylsilyl [(*i*-Pr)$_3$Si]; TBS = *tert*-butyldimethylsilyl (*t*-BuMe$_2$Si)

Scheme 4. Silanediol Anion-Binding Catalysis in the *N*-Acyl Mannich Reaction. *(Ref. 20)*

and found to provide a modest 50% yield of the desired product, **16** (Scheme 4). Further investigations found that the enantiopure silanediol **12b** containing extra methylene groups between the aromatic system and the silanediol functionality was more active, affording a 71% yield of product and a promising 18% enantiomeric excess. This was the first report of enantiomeric excess observed in a reaction catalyzed by a silanediol. The enantiocontrol of the reaction is proposed to derive from the nucleophilic addition of silyl ketene acetal **15** to chiral ion-pair **14**. Although further investigations are required to identify the noncovalent interactions involved in the transition state of the preferred reaction pathway, studies on related systems likely proceeding by anion-binding catalysis suggest that a number of intermolecular forces (i.e., hydrogen bonding, π–π stacking, general-base, etc.) are potentially involved.[24]

We set out to improve the stereocontrol in this transformation by introducing aromatic substituents into the BINOL backbone in order to offer increased stabilization for potential noncovalent interactions, such as π–π and π-cation stacking. These interactions take place in the ion-pair involved in the transition state of the major reaction pathway. Established literature procedures, or modification thereof, allowed for the preparation of a small family of BINOL-derived precursors, **19**, for the synthesis of the requisite silanediols (**Scheme 5**).[25] Subjecting intermediates **19** to a silacyclization protocol, developed in our laboratory, led to silanediols **12c–e** via dimethoxysilanes **20**. The assessment of **12c–e** in anion-binding catalysis found that the highest stereocontrol in the *N*-acyl Mannich reaction is achieved with tetraphenylsilanediol **12c**. At –55 °C, silanediol **12c** (20 mol %) gave rise to **16** in 69% yield and with 66% enantiomeric excess (**eq 2**).[25] If the loading of silanediol **12c** is increased to 50 mol % and the reaction temperature reduced to –78 °C, an enantiomeric excess of nearly 80% is observed. The rather dramatic enhancement in enantioselectivity from the initial 18% ee to a respectable 80% ee, achieved in large part through the tuning of the silanediol structure, provides good evidence supporting the ability to strategically design silanediols to achieve optimal performance in reactions likely proceeding though anion-binding catalysis.

The role of the silanediol catalyst in *N*-acyl Mannich reactions was probed experimentally. Silanediol–chloride recognition was suggested by NMR binding-titration studies with **12c** and tetrabutylammonium chloride: a binding constant of 310 M^{-1} was found in $CDCl_3$ (eq 2). A Job plot analysis found a silanediol-to-chloride ratio of 1:1. Solid-state data obtained from a co-crystal of achiral silanediol **8** with isoquinoline HCl salt suggested that the ion-pair is involved in a network of non-covalent interactions that may include π–π and π-cation stacking in addition to hydrogen bonding. The pK_a(DMSO) value of the optimal catalyst was found to be 18.7 ± 0.3, a value that falls within the same range as known hydrogen-bond-donor (HBD) catalysts that are thought to operate through anion-binding reaction pathways.[21,26,27]

3.4. Silanediol-Catalyzed Carbon Dioxide Fixation

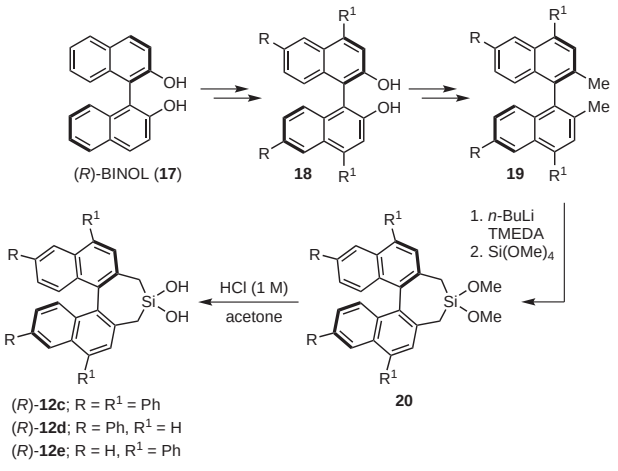
The anion-binding ability of silanediols prompted our group to explore silanediols as catalysts for the insertion of carbon dioxide into aryl and alkyl epoxides to generate cyclic carbonates (**Scheme 6**).[28,29] Using dinaphthylsilanediol (**8**) and tetrabutylammonium iodide as co-catalysts, a variety of cyclic carbonates (**21**) were isolated in excellent yields (73–97%). Notably, the mild reaction conditions enabled chirality transfer from enantiopure epoxides. The study also highlighted the importance of the dual hydrogen-bonding nature of the silanediol; monosilanols, ureas, and thioureas were all found to be inferior catalysts under identical reactions conditions.

4. Silanediol Recognition of Enzyme Active Site

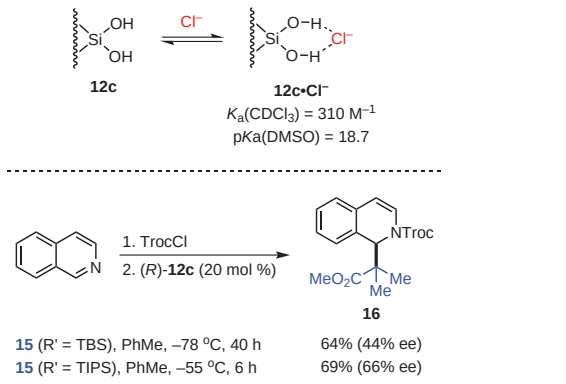
Innovative directions in drug discovery have centered on silanediol recognition of proteases. The stable silanediol functional group is proposed to mimic the tetrahedral transition state of amide hydrolysis, thereby operating to inhibit the protease via recognition of its active site. Recent and thorough reviews already exist that document the promise of silanediols as carbonyl hydrate mimics.[6,7] It is not the intent here to provide a comprehensive coverage of this area; however, this review would not be complete without including highlights of the role of silanediols in metalloprotease recognition.

4.1. Recognition of Thermolysin

The enzyme recognition abilities of silanediols is nicely demonstrated in the specific case of the metalloprotease thermolysin.[30] Sieburth and co-workers demonstrated that silanediol **22** inhibits thermolysin at levels that are competitive with those of the known phosphinic acid inhibitor **23** (**Figure 3**).[30] Silanediol **22** has an inhibition constant, K_i, of 41 nM, which is comparable to the level of inhibition achieved with phosphinic acid **23** (K_i = 10 nM). Both functional groups are believed to inhibit thermolysin by binding to a zinc cation central to the active site of thermolysin. At physiological pH, the phosphinic acid functional group is anionic and therefore has the benefit of an intrinsic Coulombic



Scheme 5. Synthesis of Stabilized, Enantiopure Silanediols. *(Ref. 25)*



eq 2 *(Ref. 25)*

attraction to the Zn^{2+} at the heart of the active site of thermolysin. The silanediol remains neutral and therefore lacks any Coulombic attraction to the zinc cation making the competitive level of inhibition between these two moieties all the more impressive. In addition, the charge-neutrality of the silanediol at physiological pH is advantageous in terms of cell-membrane permeability.

Solid-state data of each inhibitor in the active site of thermolysin gives further insight into structural differences and important interactions with distal residues.[31] Analysis of the crystal structure of silanediol **22** in the active site of thermolysin reveals histidine 231 is 0.3 Å closer to the silanediol oxygen than the equivalent oxygen in the crystal structure between an analogous phosphonamidate and thermolysin. Histidine 231 is believed to play a critical role in the enzymatic activity of thermolysin, and this interaction is a testament to the ability of a silanediol to not only bind to the metal center of the enzyme, but also to effect conformational change in crucial distal residues.

4.2. Recognition of Angiotensin-Converting Enzyme (ACE)

The promise of silanediols in the recognition of the active site of the metalloprotease angiotension-converting enzyme (ACE) was also reported by Sieburth and co-workers.[32] Investigations took inspiration from the known ketone inhibitor **24**: four diastereomeric silanediols were prepared and evaluated as inhibitors of ACE (**25**, **Figure 4**).[32] The data suggests silanediols can be incorporated into small molecules for the purpose of ACE inhibition. Recent computational work suggests that the silanediol can recognize the active site through binding to zinc.[33] Sieburth and co-workers have noted the difficulties encountered during the synthesis of complex silanediol protease inhibitors and the streamlining of their syntheses is an ongoing focus of research in their laboratory as well as in the laboratories of others.[6,7a,b,34]

5. Conclusions and Outlook

While the silanediol functional group has been the inspiration for scientific studies for a good part of a century, it is only relatively recently that the molecular recognition abilities of silanediols have been capitalized on as a chemical tool. In this context, silanediols have promise as therapeutic agents, sensors, and catalysts.

However, before the full potential of silanediols can be realized, there are obstacles to overcome. First, more general and robust methodologies to synthesize silanediols are needed. There are surprisingly few complex silanediols reported in the literature and, therefore, not many routes to these useful compounds are available. The formation of the carbon–silicon bond can often be the most demanding aspect of the synthesis. To this end, there are limited methods available to construct carbon–silicon bonds and these strategies are often not general enough to be applicable to the functional group requirements of a silanediol synthesis. If the target is an enantiopure silanediol, the pool of available methods narrows even further.

After silanediol synthesis, the next hurdle to overcome may be the current limited understanding of the relationship of silanediol structure to activity. Whether the silanediol is operating as a medicinal agent, sensor, or catalyst, a great deal remains to be learned about their properties including their acidities, intermolecular binding, stability, and ability to stabilize noncovalent interactions.

The gap in knowledge about silanediol structure and function presents exciting opportunities for investigations and discovery. As silanediols become a more widely utilized chemical tool, their strategic design may enable the catalysis of unique reactivity patterns, development of specialized sensors, and the discovery of novel therapeutics.

6. References

(†) Portions of this manuscript are adapted from Wieting, J. M. Silanediol-Catalyzed Stetreoselective Functionalization of Heterocycles. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 2015.

(1) For early reports of silanediols, see: (a) Dilthey, W.; Eduardoff, F. *Ber. Dtsch. Chem. Ges.* (presently *Eur. J. Inorg. Chem.*) **1904**, *37*, 1139. (b) Martin, G.; Kipping, F. S. *J. Chem. Soc.* **1909**, *95*, 302.

(2) Raabe, G.; Michl, J. In *The Chemistry of Organic Silicon Compouds*, Part 2; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, U.K., 1989; pp 1015–1142.

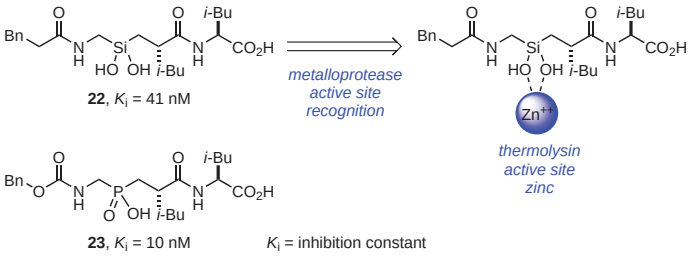
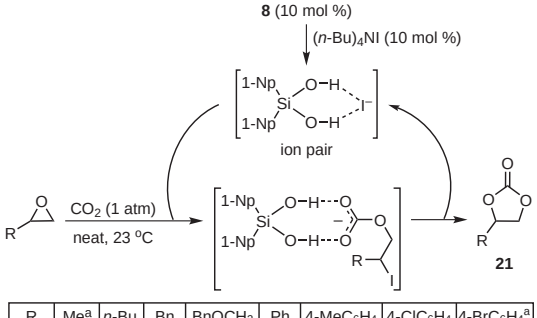


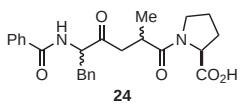
Figure 3. Silanediol Recognition of Thermolysin Active Site. *(Ref. 30)*



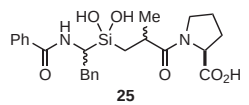
R	Me[a]	*n*-Bu	Bn	$BnOCH_2$	Ph	$4\text{-}MeC_6H_4$	$4\text{-}ClC_6H_4$	$4\text{-}BrC_6H_4$[a]
Yield	74%	82%	96%	96%	93%	97%	88%	73%

[a] In toluene at 40 °C for 18 h.

Scheme 6. Silanediols as Sustainable Catalysts for the Metal-Free Fixation of Carbon Dioxide Under Mild Conditions. *(Ref. 28)*



Bn	Me	IC_{50}
····Bn	—Me	1 nM
—Bn	—Me	8.2 nM
····Bn	····Me	46 nM
—Bn	····Me	3200 nM



Bn	Me	IC_{50}	Relative Potency
····Bn	—Me	3.8 nM	3.8
—Bn	—Me	19 nM	2.3
····Bn	····Me	207 nM	4.5
—Bn	····Me	72 nM	0.023

IC_{50} = half maximal inhibitory concentration

Figure 4. Silanediol Recognition of Angiotensin-Converting Enzyme (ACE). *(Ref. 32d)*

(3) Rochow, E. G. *Silicon and Silicones*; Springer-Verlag: Heidelberg, Germany, 1987.
(4) Lickiss, P. D. *Adv. Inorg. Chem.* **1995**, *42*, 147.
(5) Chandrasekhar, V.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847.
(6) For a review on synthetic approaches to silanediols, see Min, G. K.; Hernández, D.; Skrydstrup, T. *Acc. Chem. Res.* **2013**, *46*, 457.
(7) For reviews that include information on the synthesis and medicinal aspects of silanediols, see: (a) Sieburth, S. McN.; Chen, C.-A. *Eur. J. Org. Chem.* **2006**, 311. (b) Sieburth, S. McN. In *Bio-Inspired Silicon-Based Materials*; Zelisko, P. M., Ed.; Advances in Silicon Science Series, Vol. 5; Matisons, J., Series Ed.; Springer: Dordrecht, The Netherlands, 2014; pp 103–123. (c) Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388.
(8) Kakudo, M.; Watase, T. *J. Chem. Phys.* **1953**, *21*, 167.
(9) (a) Kakudo, M.; Kasai, P. N.; Watase, T. *J. Chem. Phys.* **1953**, *21*, 1894. (b) Kasai, N.; Kakudo, M. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 605.
(10) Fawcett, J. K.; Camerman, N.; Camerman, A. *Can. J. Chem.* **1977**, *55*, 3631.
(11) Tran, N. T.; Min, T.; Franz, A. K. *Chem.—Eur. J.* **2011**, *17*, 9897.
(12) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Org. Lett.* **2012**, *14*, 186.
(13) Tran, N. T.; Wilson, S. O.; Franz, A. K. *Chem. Commun.* **2014**, *50*, 3738.
(14) Kondo, S.; Harada, T.; Tanaka, R.; Unno, M. *Org. Lett.* **2006**, *8*, 4621.
(15) For examples of solid-state evidence of ureas recognizing Lewis basic functional groups through hydrogen-bonding interactions, see: (a) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415. (b) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896. (c) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.
(16) Kondo, S.; Bie, Y.; Yamamura, M. *Org. Lett.* **2013**, *15*, 520.
(17) Lee, M. H.; Kim, J. S.; Sessler, J. L. *Chem. Soc. Rev.* **2015**, *44*, 4185.
(18) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.
(19) For examples of reactions plausibly proceeding through hydrogen-bond-donor-catalyzed anion binding, see: (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434. (b) Zurro, M.; Asmus, S.; Beckendorf, S.; Mück-Lichtenfeld, C.; Mancheño, O. G. *J. Am. Chem. Soc.* **2014**, *136*, 13999. (c) Yeung, C. S.; Ziegler, R. E.; Porco, J. A., Jr.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 13614. (d) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 14084. (e) Mancheño, O. G.; Asmus, S.; Zurro, M.; Fischer, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 8823.
(20) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, *52*, 11321.
(21) For a similar reaction catalyzed by a thiourea, see Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700.
(22) (a) Brunel, J. M. *Chem. Rev.* **2007**, *107*, PR1–PR45. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.
(23) Schafer, A. G.; Wieting, J. M.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 5228.
(24) For examples of noncovalent interactions proposed in anion-binding transition states of thiourea-catalyzed reactions, see: (a) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817. (b) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678. (c) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.
(25) Wieting, J. M.; Fisher, T. J.; Schafer, A. G.; Visco, M. D.; Gallucci, J. C.; Mattson, A. E. *Eur. J. Org. Chem.* **2015**, 525.
(26) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.
(27) For recent examples of anion-binding thiourea catalysts with a pK_a(DMSO) ~20, see: (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745.
(28) Hardman-Baldwin, A. M.; Mattson, A. E. *ChemSusChem* **2014**, *7*, 3275.
(29) For recent examples of hydrogen-bond-donor-catalyzed carbon dioxide fixation, see: (a) Wilhelm, M. E.; Anthofer, M. H.; Cokoja, M.; Markovits, L. I. E.; Herrmann, W. A.; Kühn, F. E. *ChemSusChem* **2014**, *7*, 1357. (b) Büttner, H.; Steinbauer, J.; Werner, T. *ChemSusChem* **2015**, *8*, 2655. (c) Gennen, S.; Alves, M.; Méreau, R.; Tassaing, T.; Gilbert, B.; Detrembleur, C.; Jerome, C.; Grignard, B. *ChemSusChem* **2015**, *8*, 1845.
(30) Kim, J.; Sieburth, S. McN. *J. Org. Chem.* **2004**, *69*, 3008.
(31) Juers, D. H.; Kim, J.; Matthews, B. W.; Sieburth, S. McN. *Biochemistry* **2005**, *44*, 16524.
(32) (a) Sieburth, S. McN.; Nittoli, T.; Mutahi, A. M.; Guo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 812. (b) Wa Mutahi, M.; Nittoli, T.; Guo, L.; Sieburth, S. McN. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (c) Kim, J.; Hewitt, G.; Carroll, P.; Sieburth, S. McN. *J. Org. Chem.* **2005**, *70*, 5781. (d) Kim, J.; Sieburth, S. McN. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2853.
(33) Šramko, M.; Garaj, V.; Remko, M. *J. Mol. Struct.: THEOCHEM* **2008**, *869*, 19.
(34) Bo, Y.; Singh, S.; Duong, H. Q.; Cao, C.; Sieburth, S. McN. *Org. Lett.* **2011**, *13*, 1787.

About the Authors

Joshua Wieting was born in 1987 in Appleton, Wisconsin. He was a part of the honors intern program at the University of Wisconsin-Stevens Point, performing two and a half years of undergraduate research in the laboratory of Professor Nathan Bowling. In 2010, he graduated from UW-SP with a B.S. degree in chemistry, and enrolled in the Ph.D. program at The Ohio State University, studying under the mentorship of Professor Anita E. Mattson. Josh's graduate research has focused on the development of silanediols as a new class of asymmetric hydrogen-bond donors that function specifically as anion-binding catalysts.

Andrea Hardman-Baldwin was born in 1989 in Harrison, Arkansas. She received her bachelor's degree in chemistry from Harding University in 2011 while working under the mentorship of Professor Carl B. Hollandsworth. In June of 2011, she moved to The Ohio State University to begin graduate studies with Professor Anita E. Mattson. Andi's research is centered on the synthesis and functionalization of heterocycles by utilizing new classes of hydrogen-bond donors that function as organocatalysts.

Michael Visco was born in 1990 in Malden, Massachusetts. He received his B.S. degree in chemistry from the University of Rhode Island while conducting undergraduate research in Professor Brenton DeBoef's group. In January of 2013, he began his graduate studies under the guidance of Professor Anita E. Mattson at The Ohio State University, where he is investigating the design and development of chiral silanediols and their applications in asymmetric anion-binding catalysis.

Anita Mattson received her B.S. degree in 2002 from Northern Michigan University, where she studied polarity reversal catalysis in the context of radical reactions with Professor Frankie Ann McCormick. She then joined Northwestern University as a graduate student in Professor Karl Scheidt's research group, where she developed new thiazolium-based strategies for acyl anion addition reactions. In 2007, she completed the requirements for her Ph.D. degree, and transitioned to Professor Michael Crimmins's group at the University of North Carolina at Chapel Hill as a National Institutes of Health postdoctoral fellow investigating a highly convergent approach toward hemibrevetoxin B. Mattson joined the faculty in the Department of Chemistry and Biochemistry at The Ohio State University in 2009. Her current research program focuses on the design of new families of organic catalysts, the development of methodologies for metal-free synthesis, and the synthesis of naturally occurring molecules.

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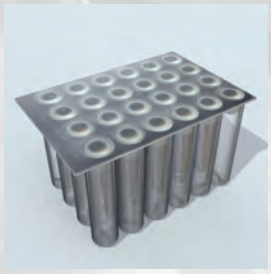

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Amidine-Based Catalysts (ABCs): Design, Development, and Applications

Advancing Sustainable Catalysis with Magnetite. Surface Modification and Synthetic Applications

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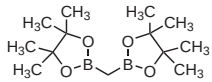
(1) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (2) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708. (3) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455.



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Udit Batra, Ph.D.
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ABOUT OUR COVER

Detail from ***Giant Magnolias on a Blue Velvet Cloth***. Photo courtesy National Gallery of Art, Washington, DC.

Martin Johnson Heade (1819–1904) painted ***Giant Magnolias on a Blue Velvet Cloth*** (oil on canvas, 38.4 × 61.5 cm) ca. 1890 when he was already in his early seventies and after he had settled in St. Augustine, FL, following a life as an itinerant artist. Not much is known about his formal education or early artistic training, save for the possibility that he might have been instructed by Edward and Thomas Hicks, two local artists. A two-year stay in Italy in his early twenties and a later close interaction with J. F. Kensett, B. Champney, and many artists from the Hudson River School round out his artistic development. Especially influential on Heade was F. E. Church, who was a lifelong friend and who likely stimulated Heade's interest in tropical themes.

Heade travelled to Europe twice and made several trips to Central and South America. Although he is now viewed as one of the more important American artists of the nineteenth century, Heade achieved only moderate success during his lifetime. His artistic interests ranged from portraits early in his career, to seascapes and romantic tropical scenery in his mid-career,* to still lifes of subtropical flowers in his later years.

Giant Magnolias on a Blue Velvet Cloth is considered one of his finest in a series of still lifes of flowers from the Southern United States, so much so that the U.S. Postal Service reproduced this painting on a 2004 stamp to honor Heade. What makes this composition so striking are the luxuriously rendered magnolias and the contrast between the brightly lit flowers and leaves and the dim background. The suggestion has even been made that the full blooms and rich colors of the magnolias and the fragrance they evoke are perhaps stand-ins for nudes gracefully lounging on plush sofas.

This painting is a gift of The Circle of the National Gallery of Art in Commemoration of its 10th Anniversary, National Gallery of Art, Washington, DC.

** Another one of Heade's finest compositions was featured on the cover of an earlier Aldrichimica Acta issue. To find out which issue and learn more about another of Heade's major artistic themes, visit* ***Aldrich.com/acta492***

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(1) Gallou, F.; Isley, N. A.; Ganic, A.; Onken, U.; Parmentier, M. *Green Chem.* **2016**, *18*, 14.
(2) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2012**, *45*, 3.
(3) Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack E. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 10952.

Amidine-Based Catalysts (ABCs): Design, Development, and Applications

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Keywords. acylation; asymmetric organocatalysis; Lewis base catalysis; kinetic resolution; catalyst design.

Abstract. Since their discovery in 2003, amidine-based catalysts have found numerous applications in asymmetric catalysis, particularly in enantioselective acyl transfer and related modes of catalysis. This account presents an update of this rapidly growing area of research.

Outline

1. Introduction

Several types of neutral, aprotic Lewis bases, such as 4-(dimethylamino)-pyridine (DMAP), 4-pyrrolidinopyridine (PPY), 1-methylimidazole (NMI), N-heterocyclic carbenes (NHCs), and P(*n*-Bu)$_3$, are known to catalyze nucleophilic acyl substitution reactions via a mechanism called *acyl transfer*.[1] In this mode of catalysis, a catalyst (**:cat**) attacks an acyl donor, **1**, to generate a reactive ion pair, **2**, which in turn reacts with another nucleophile (Y–H), giving rise to the final product (**3**) and releasing the catalyst (**Scheme 1**, Part (a)).

In a related pathway, the initially formed cationic species, **5**, undergoes deprotonation next to the activated carbonyl to form zwitterionic enolate **7**, which can also be generated from the corresponding ketene (**6**). Intermediate **7** can be thought of as a synthetic ketene equivalent capable of formal cycloadditions (cf. **9**) or Markovnikov addition (cf. **11**) across the enolate double bond.

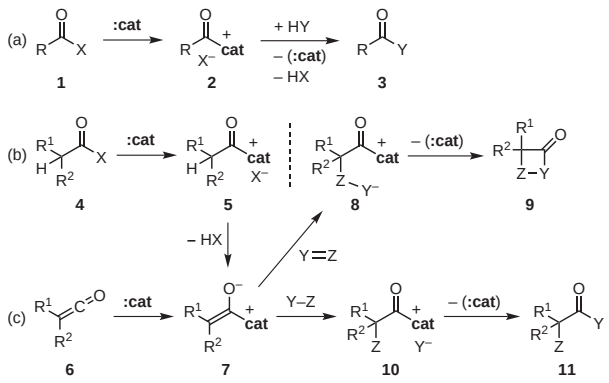
These and conceptually related modes of reactivity of acyl donors (vide infra) present rich opportunities from the point of view of asymmetric catalysis. Consequently, many research groups worldwide have been involved in the design of chiral, Lewis base catalysts that are capable of asymmetric induction in these reactions.[2] Of the many such chiral catalysts reported in the literature to date, relatively few have displayed good enantioselectivity in the reactions tested. The most successful catalysts developed by other groups (**12**–**21**) are illustrated in **Figure 1**.[3–12] Even within this select group, however, some have demonstrated only narrow substrate and/or reaction scopes, while others require multistep syntheses, which restricts their widespread use.

2. Catalyst Development

In 2003, when our group first became interested in this field, we observed the preponderance of chiral catalyst designs based on attaching a chiral element to the structures of DMAP[13] and PPY[14]—the most widely used *achiral* acylation catalysts. This perfectly logical approach, however, proved to be unexpectedly difficult to implement: introducing a chiral tetrahedral carbon atom next to the nucleophilic nitrogen abolished all catalytic activity,[15] while moving it further away produced only limited enantioselectivity.[16] In fact, of all the 4-aminopyridine-based designs described to date, Fu's planar-chiral catalyst **13**[4] stood out as the only truly successful and versatile one. Its only significant drawback was its limited accessibility: its preparation required a 10-step racemic synthesis followed by separation of enantiomers by chiral-stationary-phase HPLC.

We approached the challenge of designing an enantioselective acyl transfer catalyst from the opposite direction: instead of devising new ways of attaching chirality to known achiral catalysts, we sought to identify a new class of Lewis bases, which (i) would be readily

amenable to the introduction of chirality, and (ii) could reasonably be expected to turn over. Thus, we became interested in exploring derivatives of 2,3-dihydroimidazo[1,2-a]pyridine (DHIP, **22** , R = X = H).[17] Although there were no prior reports of its catalytic activity, simple resonance considerations suggested that it should be highly nucleophilic and form stabilized N-acylated derivatives (**24**) (**Scheme 2**, Part (a)).[18] Its electronic properties could easily be tuned by substitution (e.g., group X). Finally, the tetrahedral carbon adjacent to the nucleophilic nitrogen could be easily rendered chiral (R ≠ H), which would translate into effective differentiation of the two diastereotopic faces of the acyl carbonyl. In 2004, we disclosed our first-generation catalyst CF_3-PIP (**22a**), which displayed good enantioselectivity and activity in the KR of benzylic alcohols (vide infra). Its synthesis required only two steps from inexpensive, commercially available starting materials (Scheme 2, Part (b)).[18]



Scheme 1. Basic Catalytic Pathways Involving Acyl Transfer. *(Ref. 1)*

Our group subsequently developed several new generations of asymmetric acylation catalysts (**28a**,[19] **30a**,[20] **31a**,[21a] and **31b**[21b]) that demonstrated superior enantioselectivity, broader substrate scope, and greater versatility than CF_3-PIP (**22a**) (**Figure 2**). This work was guided both by mechanistic speculations and by several unanticipated discoveries. Thus, Cl-PIQ (**28a**) was designed based on the idea that extending the aromatic system of CF_3-PIP (**22a**) will enhance π interactions[22] with alcohol substrates in the transition state (vide infra). In 2005, we found that tetramisole (**29**)—a well-known, commercially available veterinarian drug[23]—was, in fact, a competent enantioselective acylation catalyst.[20] Benzannulation of its structure led to benzotetramisole (BTM, **30a**), which displayed dramatically improved enantioselectivity. We were also surprised to discover that DBN (**32**), long regarded as a strong, non-nucleophilic base, displayed good catalytic activity in acylation reactions. Its sulfur analogue, THTP (**33**), was even more active, which was attributed to the S···O noncovalent interactions with the acyl carbonyl.[24] Interestingly enough, bicyclic amidines and isothioureas with different ring sizes were much less active than **32** and **33**, respectively.[25] In 2006, Okamoto disclosed DHPB (**34**) that surpassed in catalytic activity not only THTP (**33**) but also the "benchmark catalyst" DMAP.[26] Homobenzotetramisole (HBTM, **31a**) was designed as a hybrid of BTM and Okamoto's catalyst (**34**). Finally, adding a methyl group cis to the phenyl group (e.g., HBTM-2, **31b**) led to enhanced catalytic activity and simplified the synthesis.

It soon became clear that the emerging new class of Lewis bases, which we dubbed "Amidine-Based Catalysts", or ABCs, had great

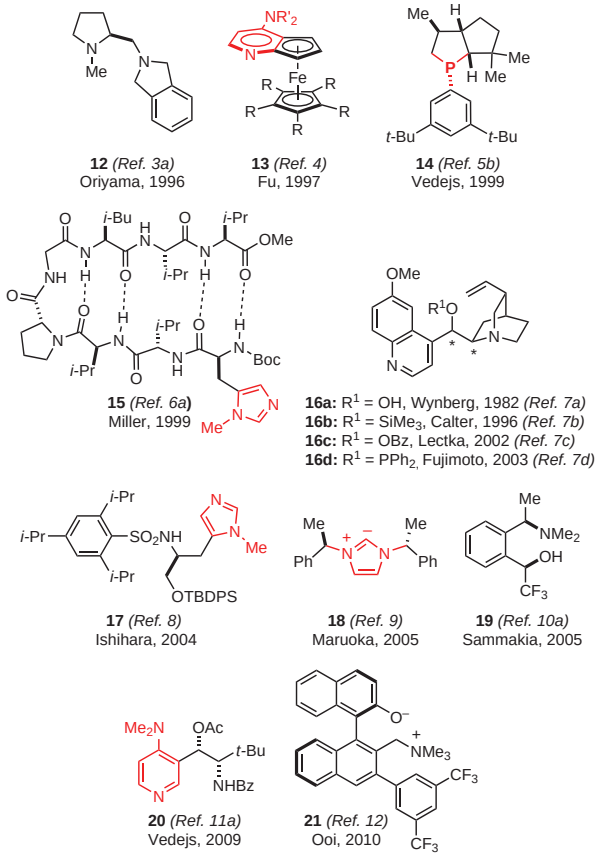
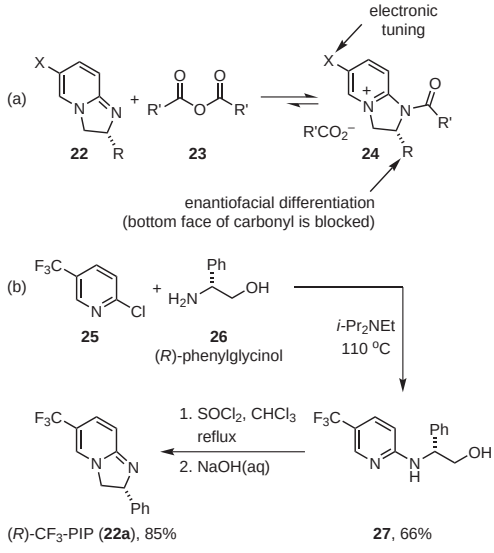


Figure 1. Best Enantioselective Acyl-Transfer Catalysts Developed by Other Groups. *(Ref. 3–12)*



Scheme 2. Design and Synthesis of the First-Generation DHIP-Based Acyl-Transfer Catalyst. *(Ref. 18)*

potential. In addition to our efforts, several research groups, attracted by the synthetic accessibility of chiral ABCs, became involved in the design of their analogues. Many structural variations described in the literature resulted in competent catalysts, and, although there are too many of them to illustrate, it is instructive to discuss several of them. Further elaboration of the quinoline core of Cl-PIQ (**28a**) by Fossey and Deng led to catalysts (e.g., **28b–d**) displaying improved enantioselectivity in some reactions.[27] However, the extra effort involved in making these analogues will likely limit their widespread application. (*R*)-(+)-*N*-Methylbenzoguanidine ((*R*)-NMBG, **30b**), developed by Nakata and Shiina[28] is less effective than its prototype BTM (**30a**); nevertheless, it is interesting because it demonstrates that substituting the sulfur with a methylamino moiety is compatible with good catalytic activity and enantioselectivity. HBTM-2.1 (**31c**), reported by Smith and co-workers,[29] displays enhanced catalytic activity, which is consistent with the larger steric bulk of the isopropyl group relative to the methyl in HBTM-2 (**31b**). Okamoto's group reported 4-Mes-DHPB (**35**), which is notable for being the only effective chiral ABC lacking a stereogenic center next to the nucleophilic nitrogen.[30] In addition to the chiral organocatalysts discussed so far, Fossey and Deng designed a series of chiral ligands, **36** and **37**, with structures related to that of Cl-PIQ.[31] Catalysts **28a**, **30a**, **31a**, and **31c** are now commercially available, and an improved procedure for the synthesis of BTM (**30a**)[32] as well as alternative strategies for the synthesis of HBTM-type catalysts have been published.[33] This should further facilitate their production on an industrial scale.

3. Applications

ABCs are increasingly employed in asymmetric catalysis because of their broad reaction scope, generally high enantioselectivity, and easy accessibility. In this section, we summarize their applications reported to date. It should be noted that many of the reactions described below have been catalyzed successfully by only one structural type of ABC, while others proved to be less effective. Whenever several ABCs have displayed acceptable performance in a particular transformation, we have included all suitable catalysts in the description of the reaction conditions. The reader interested in finding the optimal catalyst and conditions for a given reaction is encouraged to consult the references provided for additional details. Unless noted otherwise, the absolute stereochemistry shown for the reaction product was obtained by utilizing the enantiomers of ABCs featured in Figure 2.

3.1. Acyl Transfer

Enantioselective reactions that proceed via the general mechanism outlined in Scheme 1**,** Part (a) (vide supra) can be subdivided into two basic categories, depending on which reactant is chiral or prochiral: (i) enantioselective solvolysis (chirality present in the acyl donor: in R and/or the leaving group X), and (ii) enantioselective acylation (chirality present in the acyl acceptor HY). All of these possibilities have been realized with ABCs. In most cases, the acylation itself does not generate any new stereocenters, but manifests its enantioselectivity in the form of KR,[34] DKR,[35] or desymmetrization.[36]

3.1.1. Acylative Kinetic Resolution (KR) of Alcohols

The KR of secondary alcohols served as a model process during the development of ABCs **22a**, **28a**, **30a**, and **31a**,**b** in our laboratory.[18–21,37] Good-to-excellent selectivity factors[34e] (up to s = 355) were obtained for most substrates tested using the inexpensive propionic and isobutyric anhydrides. Later, this research direction was significantly expanded upon by the groups of Shiina,[28,38] Smith,[29] Chen,[39] Deng and Fossey,[27,40] and other researchers, and remains to date one of the most thoroughly studied applications of this family of catalysts (**Scheme 3**).[18–21] The structures of the alcohol substrates shown suggest that the presence of a π system adjacent to the hydroxyl group is crucial to the success of KR. Indeed, experimentally observed structure–selectivity trends and computational studies point to π–π and cation–π interactions

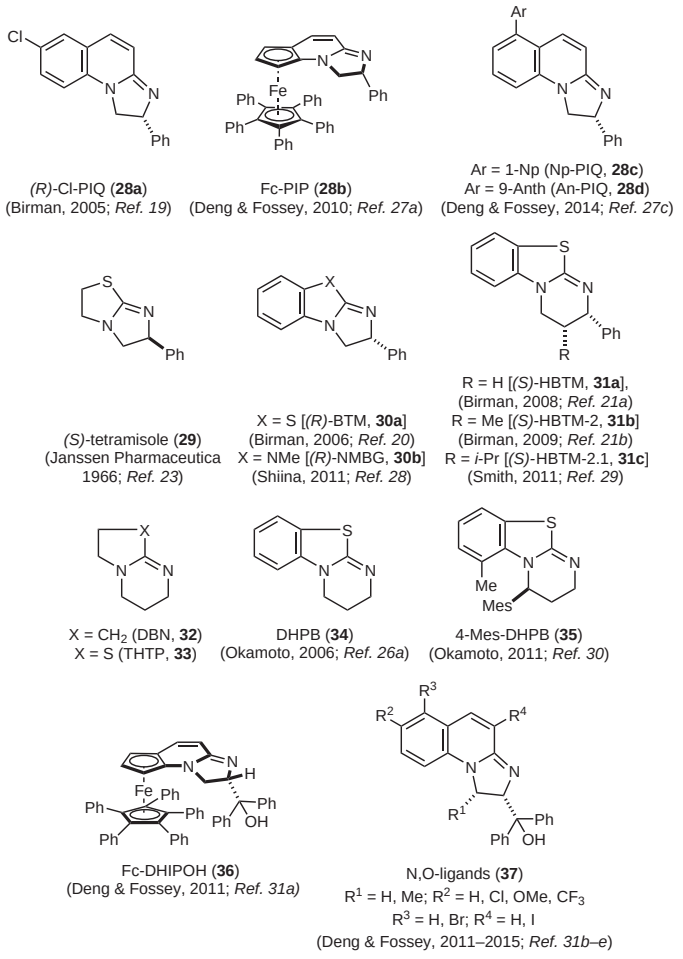
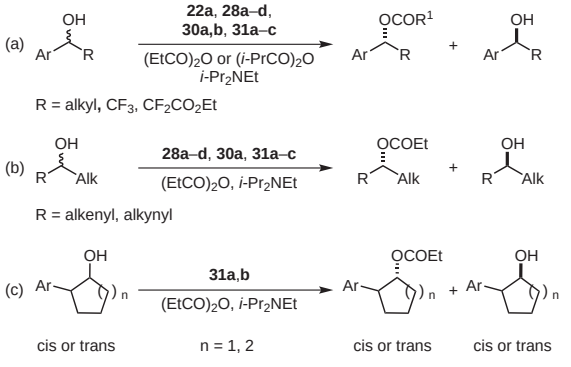


Figure 2. Representative Amidine-Based Catalysts (ABCs) and Related Ligands.



Scheme 3. Alcohol Classes Resolved via Acylation with Propionic and Isobutyric Anhydrides. *(Ref. 18–21,37)*

being responsible for the chiral recognition of substrates in the KR of benzylic alcohols (**Figure 3**).[41] The same or similar interactions are likely involved in the KR of the other classes of alcohols presented here. Typically, propionic and isobutyric anhydrides have been employed as acylating agents. However, Shiina and co-workers have demonstrated in a number of cases that superior enantioselectivities may be realized by utilizing the mixed diphenylacetic–pivalic anhydride generated in situ (**Scheme 4**).[38b–f]

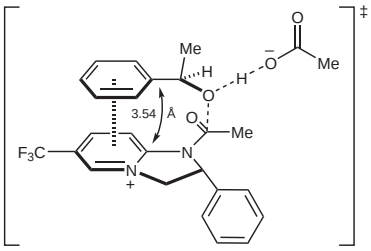
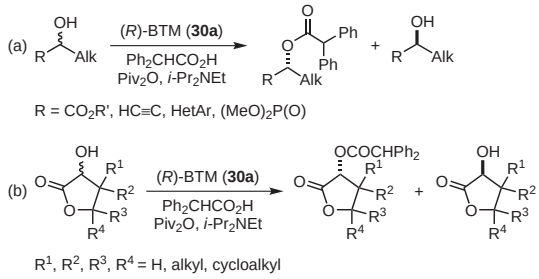
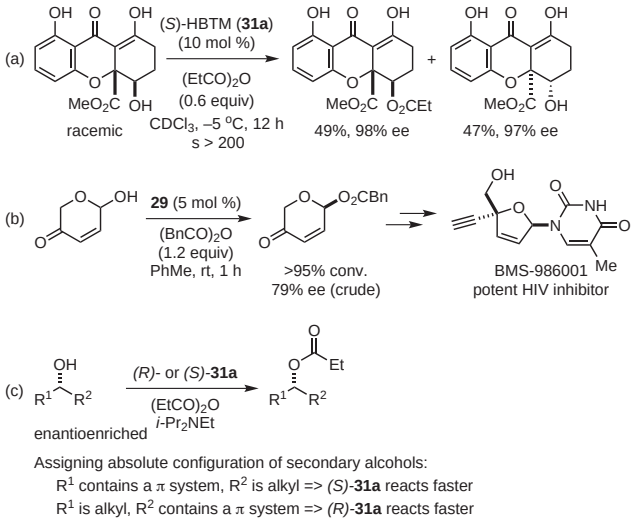


Figure 3. Transition-State Model for the Asymmetric Acylation of 1-Phenylethanol Promoted by **22a**. *(Ref. 41)*



Scheme 4. The Diphenylacetic–Pivalic Anhydride Combination Leads to Superior Enantioselectivities in the Resolution of Alcohols by ABCs. *(Ref. 38b–f)*



Scheme 5. ABCs in the KR and DKR of Key Synthetic Intermediates and the Stereochemical Assignment for Alcohols. *(Ref. 42–45)*

Apart from the above examples that focused on the systematic investigation of relatively simple substrates, Porco's research group reported the highly enantioselective KR of late-stage intermediates in the total synthesis of tetrahydroxanthone natural products (e.g., **Scheme 5**, Part (a))[42] Ortiz et al., at Bristol-Myers Squibb, achieved a remarkably efficient, multigram-scale DKR of an inexpensive lactol en route to the potent HIV inhibitor BMS-986001 (Scheme 5, Part (b)).[43,44]

Rychnovsky's team developed a convenient method for the absolute stereochemical assignment of secondary alcohols via TLC analysis of the acylations of an enantioenriched alcohol that are catalyzed by opposite enantiomers of HBTM.[45] The faster reaction reveals which catalyst is a better match and, therefore, which substituent, R^1 or R^2, contains a π system that is recognized by the catalyst (Scheme 5, Part (c)).

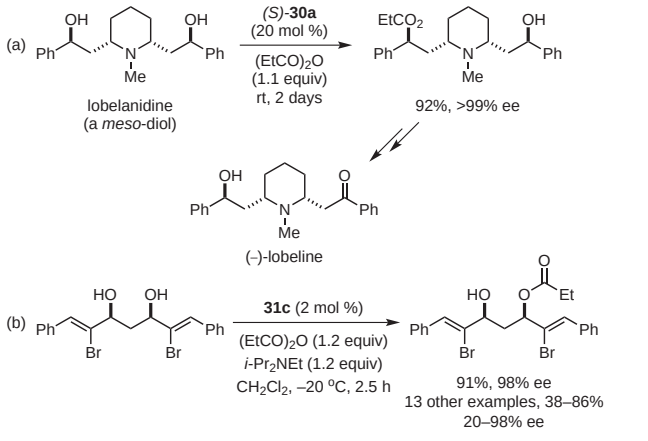
3.1.2. Desymmetrization of Diols

In 2007, we reported a concise asymmetric synthesis of the alkaloid lobeline that involved as a key step the BTM-catalyzed desymmetrization of the *meso*-diol lobelanidine (**Scheme 6** Part (a)).[46] Recently, Chuzel, Bressy and co-workers[47] applied HBTM-2.1 (**31c**) to the desymmetrization of allylic and benzylic 1,3-diols (Scheme 6, Part (b)).[47]

3.1.3. KR of Lactams and Thiolactams through N-Acylation

Catalysts **28a** and **30a** are highly effective in the acylative KR of several classes of lactams and thiolactams containing a π system or an ester next to the nucleophilic nitrogen (**Scheme 7**). The available data indicate that BTM (**30a**) is more enantioselective, while Cl-PIQ (**28a**) works with a broader range of substrates. DFT calculations indicate that the transition state geometries in these processes are qualitatively similar to those described in Figure 3, and are likewise governed by π interactions.[48]

Interestingly, the reverse process, enantioselective N-deacylation, has also been realized (Scheme 7, Part (e)): Methanolysis of *N*-isobutyrylthiazolidine-2-thiones and *N*-isobutyryloxazolidine-2-thiones is effectively promoted by **30a**.[49] By analogy with the stereochemical assignment of secondary alcohols (Scheme 5, Part (c)), Rychnovsky's group developed a method for the rapid determination of the absolute configuration of lactams and thiolactams.[50]



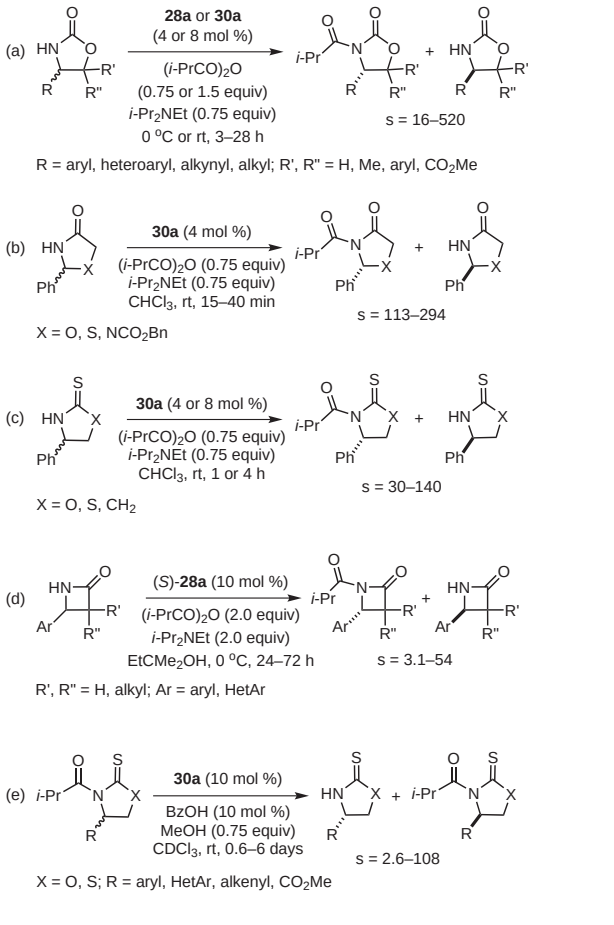
Scheme 6. (a) BTM-Catalyzed Desymmetrization of a *meso*-Diol as a Key Step in the Concise Synthesis of the Alkaloid Lobeline. (b) HBTM-2.1 Catalyzed Desymmetrization of Allylic and Benzylic 1,3-Diols. *(Ref. 46, 47)*

3.1.4. C-Acylations

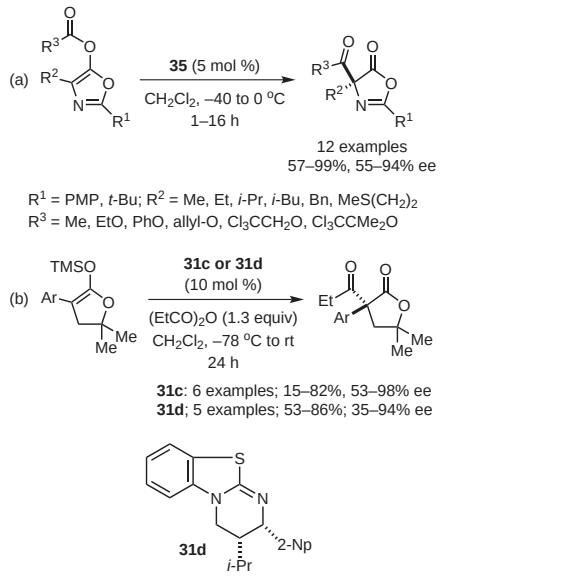
An enantioselective Steglich rearrangement has been achieved using three types of isothiourea-based catalysts. Dietz and Gröger achieved the first acetyl migration (Z = Me) with moderate enantioselectivity using tetramisole (**29**) and BTM (**30a**).[51] Smith and co-workers employed HBTM-2.1 (**31c**) to obtain ester derivatives with excellent ee's.[52] Okamoto and co-workers demonstrated that their catalyst 4-Mes-DHPB (**35**), with a remote chiral center, is effective in both variants of this transformation (**Scheme 8**, Part (a)).[30] The analogous rearrangement of dihydrofuryl carbonates has been accomplished by Smith's group.[53] Alternatively, the same product can be obtained by an intermolecular C-acylation of silyl ketene acetals using catalysts **31c** or **31d** (with a 2-naphthyl substituent instead of phenyl) (**Scheme 8**, Part (b)).[54]

3.1.5. KR of 2-Arylalkanoic Acids

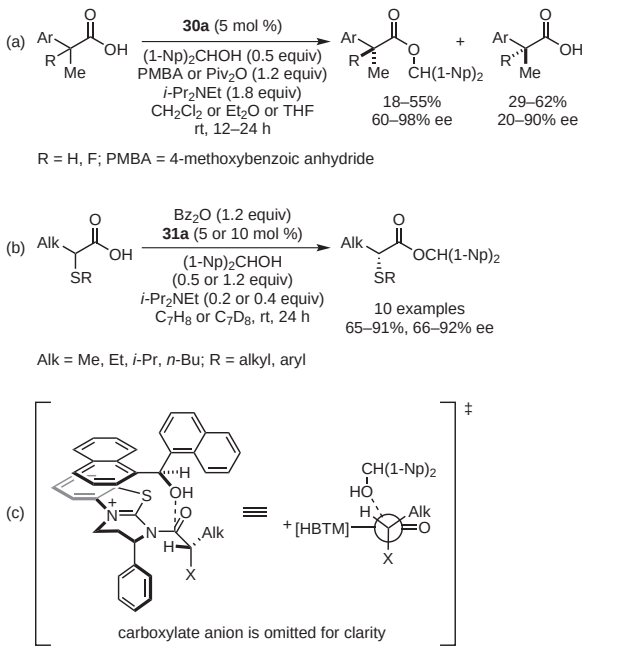
Alkanoic acids bearing an aryl or electron-withdrawing group at the α position have been resolved via enantioselective esterification with di(1-naphthyl)methanol. Shiina's group utilized BTM (**30a**) and its naphth-2-yl analogue, **30c**, to promote this transformation, and activated the racemic substrates in situ using the mixed-anhydride method (**Scheme 9**, Part (a)).[55,56] This method proved suitable for the KR of 2-aryl-2-fluoropropionic acids as well.[57] Interestingly, changing the solvent to DMF allowed them to achieve the DKR of 2-arylpropionic acids.[58] Our group developed an alternative activation protocol using DCC, and achieved higher enantioselectivities and broader substrate scope with HBTM **(31a)**.[59] We also found that **31a** promotes the DKR of α-(arylthio)- and α-(alkylthio)alkanoic acids under similar conditions (Scheme 9, Part (b)).[60] Our group, in collaboration with Houk's group, proposed a Felkin–Anh-like transition-state model to explain the origin of enantioselectivity in these processes (Scheme 9, Part (c)).[61]



Scheme 7. KR of Lactams and Thiolactams through N-Acylation or N-Deacylation. *(Ref. 48–49)*



Scheme 8. C-Acylations. *(Ref. 30,54)*



Scheme 9. KR and DKR of α-Substituted Alkanoic Acids through Enantioselective Esterification and the Proposed Transition-State Model for the Reaction. *(Ref. 55–61)*

3.1.6. Dynamic Kinetic Resolution (DKR) of Azlactones

We have also achieved the DKR of azlactones through enantioselective alcoholysis with di(1-naphthyl)methanol in the presence of (*S*)-**30a** and benzoic acid as a co-catalyst (**eq 1**).[62]

3.1.7. KR of *N*-Aroyl-β-lactams

We have extended our studies of the DKR of azlactones, to the KR of *N*-aroyl-β-lactams through a highly enantioselective ring opening with methanol (**eq 2**).[63] In contrast to the previously mentioned examples of enantioselective alcoholysis (Scheme 9 and eq 1), wherein the use of the bulky dinaphthylmethanol is crucial for asymmetric induction, this transformation proceeds via a different enantioselectivity-determining step, which renders the nature of the alcohol relatively unimportant.

3.2. Zwitterionic Enolate Mediated Reactions

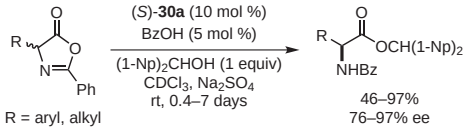
Most ABC reactions in this category are formal cycloadditions, as illustrated by Scheme 1, Part (b).[64] Asymmetric induction observed in these processes can usually be rationalized in a straightforward manner by invoking a zwitterionic enolate formed from the ABC and the substrate (**Figure 4**).

3.2.1. Formal [2 + 2] Cycloadditions

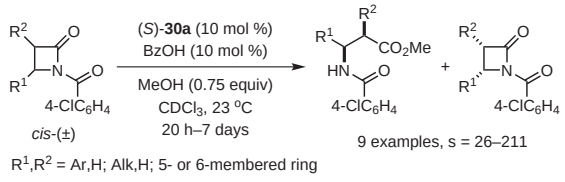
Romo's group has pioneered the use of ABCs in formal cycloadditions of zwitterionic enolates. They first demonstrated the utility of tetramisole (**29**) in a stoichiometric, enantioselective, aldol-lactonization (NCAL) reaction featuring *double* enantioselection (**Scheme 10**, Part (a)).[65] They subsequently developed a catalytic variant of the same and related transformations (Scheme 10, Part (b)) by utilizing HBTM (**31a**).[66] Recently, the same group achieved impressive tandem processes wherein the chiral catalyst controls both the Michael addition to a conjugated acyl chloride and the ensuing NCAL (Scheme 10, Part (c))[67] Smith and co-workers developed a convenient synthesis of trans β-lactams by the in situ activation of arylacetic[68] or alkenylacetic acids[69] and their subsequent coupling with *N*-sulfonylimines (Scheme 10, Part (d)).

3.2.2. Formal [4 + 2] Cycloadditions

Smith and co-workers have developed several asymmetric catalytic variants of the formal hetero-Diels–Alder reaction of C1 ammonium enolates generated by in situ activation of carboxylic acids with α,β-unsaturated carbonyl compounds. The intramolecular version of this process (**Scheme 11**, Part (a))[70–72] works well with regular enones using tetramisole (**29**) while the intermolecular variant apparently requires the more electron-deficient unsaturated keto esters,[70] keto phosphonates,[73] or trihalomethyl ketones[74,75] (Scheme 11, Part (b)). Deng's group demonstrated that their planar-chiral Fc-PIP catalyst (**28b**) also works in the intramolecular process (Scheme 11, Part (a), X = O).[76] Smith's team achieved analogous cycloadditions with α,β-unsaturated *N*-sulfonylimines (Scheme 11, Part (c))[77] and aroyldiazenes promoted by BTM (**30a**).[78] Izquierdo and Pericas demonstrated that the solid-phase-supported derivative of BTM, **30d**, is also competent in the former process (Scheme 11, Part (c)).[79]



eq 1 *(Ref. 62a)*



eq 2 *(Ref. 63)*

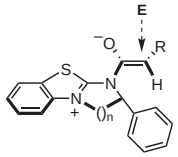
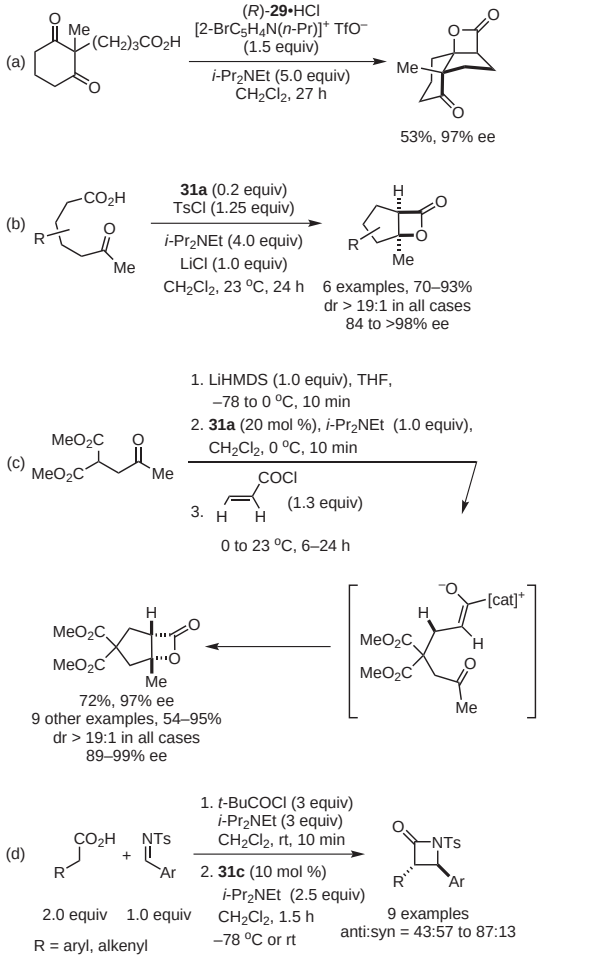


Figure 4. Predictive Model for ABC-Derived Zwitterionic Enolates.



Scheme 10. Formal [2 + 2] Cycloadditions Enabled by Amidine-Based Catalysts. *(Ref. 65–69)*

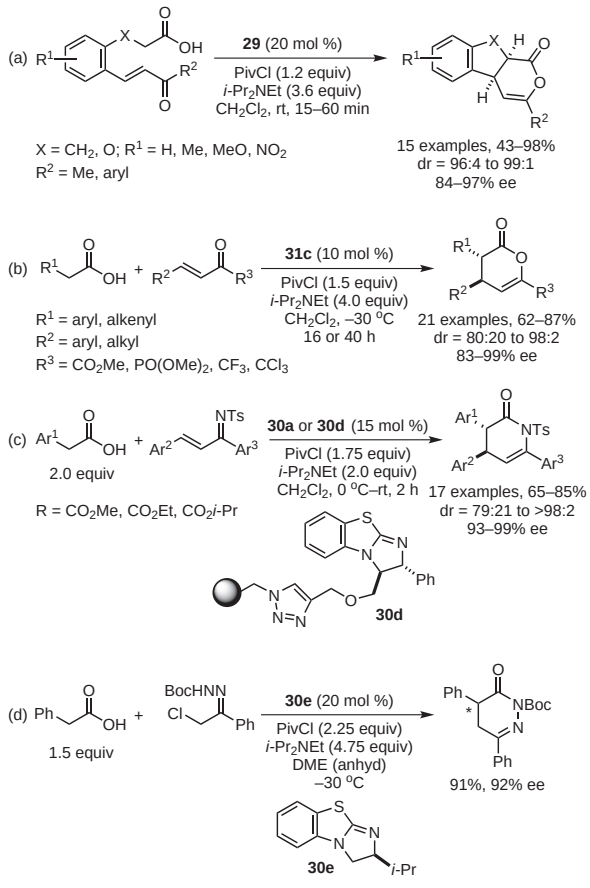
Most of the cycloadducts featured in Scheme 11, Parts (a)–(c) undergo facile alcoholysis, which renders the overall transformation equivalent to an enantioselective Michael addition. Lin, Yao, and collaborators recently developed a DHPB-catalyzed racemic synthesis of dihydropyridazinones via alkenyldiazenes generated in situ from α-chloro-*N*-Boc-hydrazones. A single example in their study performed with (*S*)-BTM-like chiral catalyst **30e** proceeded with high enantioselectivity (Scheme 11, Part (d)).[80] Okamoto's achiral catalyst DHPB (**34**) was the logical choice in Smith's approach to achiral heterocycles (**Scheme 12**).[81]

3.2.3. Asymmetric [3 + 2] Cycloadditions

Studer, Mück-Lichtenfeld, and co-workers achieved the cycloaddition of azomethine ylides with carboxylic acids activated in situ as mixed anhydrides (**Scheme 13**, Part (a)).[82] Chi's team developed a similar process using 4-chlorocyclobutenones as vinylketene equivalents.[83] Smith's group prepared diastereomeric oxazolidinones with high enantioselectivity by the stereodivergent KR of racemic oxaziridines (Scheme 13, Part (b)).[84]

3.2.4. Rearrangement of Ammonium Ylides

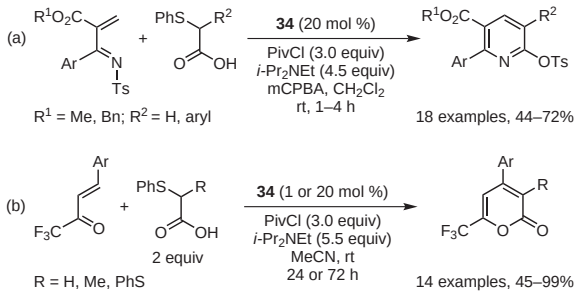
Apart from their extensive use in formal cycloaddition reactions (Schemes 10–13), C1-ammonium enolates generated from chiral ABCs have been utilized by Smith and co-workers in a highly enantio- and diastereoselective [2,3]-rearrangement of quaternary allylic ammonium salts (**eq 3**). The resulting reactive *p*-nitrophenyl ester intermediates were converted into stable esters or amides.[85]



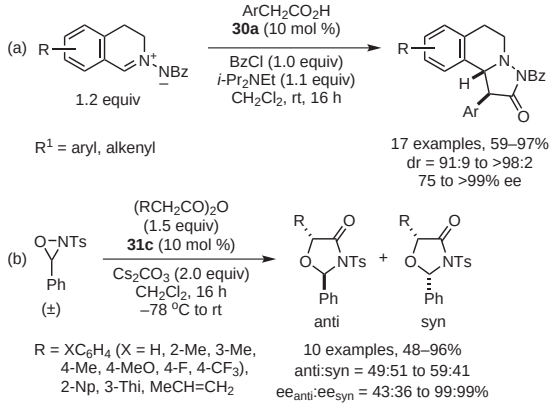
Scheme 11. Formal [4 + 2] Cycloadditions Enabled by Amidine-Based Catalysts. *(Ref. 70–80)*

3.3. Activation of α,β-Unsaturated Acyl Donors

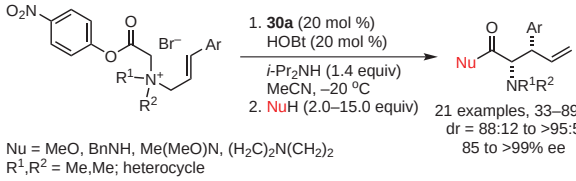
Reactions in this category take advantage of the fact that nucleophilic acyl substitution at the acyl carbonyl lowers the LUMO of the entire conjugated system and thus enhances the reactivity of the double bond towards conjugate additions and cycloadditions. The enantioselectivity observed in these processes was consistent with the incoming nucleophiles (or dienes) approaching from the unhindered face of the N-acylated intermediate (**Figure 5**).



Scheme 12. Isothiourea-Catalyzed One-Pot Syntheses of Functionalized Heterocycles. *(Ref. 81)*



Scheme 13. ABC-Enabled Asymmetric [3 + 2] Cycloadditions. *(Ref. 82,84)*



eq 3 *(Ref. 85)*

3.3.1. Michael Addition

Smith's team described the isothiourea-catalyzed asymmetric Michael addition of 1,3-dicarbonyl compounds to cinnamic anhydrides followed by acylation of the intermediate enolates (**Scheme 14**, Part (a)).[86] A similar transformation was achieved with 2-benzothiazolyl ketone giving a mixture of regioisomers. Fukata, Asano, and Matsubara disclosed a BTM-catalyzed cascade sequence proceeding via enantioselective thiolate conjugate addition and subsequent intramolecular N-acylation to give rise to highly enantioenriched 1,5-benzothiazepines (Scheme 14, Part (b)).[87a] Romo's cascade reaction proceeding through an enantioselective Michael addition of a malonate anion has already been mentioned (see Scheme 10, Part (c)). Our group demonstrated recently that HBTM-2 (**31b**) initiates a cascade transformation of S-cinnamoyl derivatives of 2-mercaptobenzaldehydes into chiral thiochromones with excellent yields and ee's, giving off carbon dioxide as the only byproduct (Scheme 14, Part (c)).[87b]

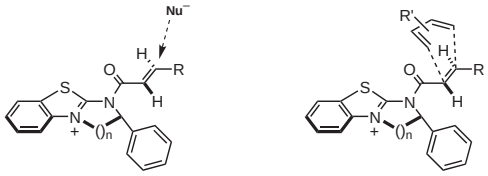
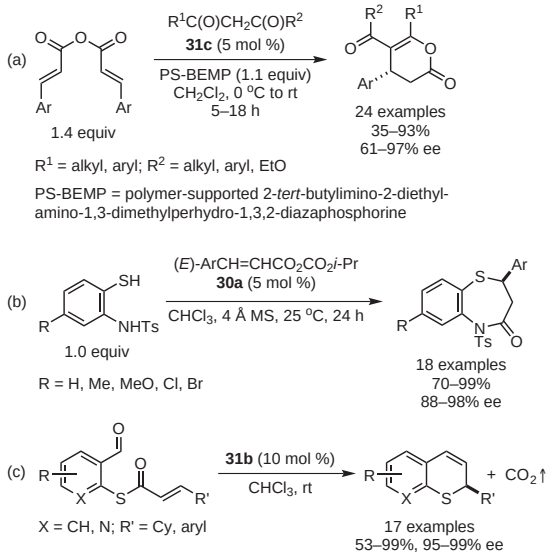
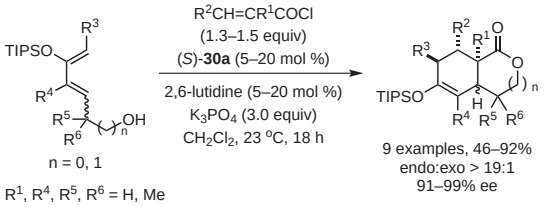


Figure 5. Predictive Models for ABC-Catalyzed Conjugate Additions and Cycloadditions.



Scheme 14. HBTM- and BTM-Catalyzed Asymmetric Michael Addition. *(Ref. 86,87)*



eq 4 *(Ref. 88)*

2-mercaptobenzaldehydes into chiral thiochromones with excellent yields and ee's, giving off carbon dioxide as the only byproduct (Scheme 14, Part (c)).[87b]

3.3.2. Asymmetric Diels–Alder Reaction and 1,3-Dipolar Cycloaddition

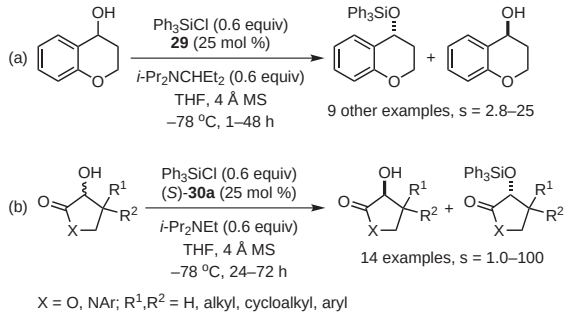
A BTM-enabled, highly diastereo- and enantioselective intermolecular Diels–Alder reaction and lactonization organocascade has recently been disclosed by Romo and co-workers. In this sequence, activated α,β-unsaturated acyl chlorides, acting as dienophiles, lead to cis- and trans-fused bicyclic 5- and 6-membered-ring lactones with up to four contiguous stereocenters (**eq 4**).[88] Lupton's group reported an example of a tetramisole (**29**) and HBTM-2.1 (**31c**) catalyzed cycloaddition between cinnamoyl fluoride and a precursor to an unstabilized azomethine ylide; however, only low yields and enantioselectivities were obtained.[89]

3.4. Silylative Kinetic Resolution of Alcohols

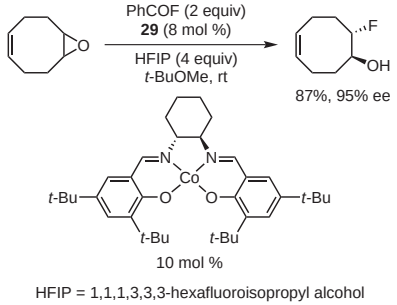
Apart from their widely recognized utility as enantioselective acylation catalysts, ABCs also promote enantioselective O-silylations. Using this approach, Wiskur and co-workers achieved the KR of several classes of cyclic alcohols (**Scheme 15**).[90]

3.5. Enantioselective Ring-Opening of Epoxides

Tetramisole (**29**) and DBN (**32**) have been employed by Kalow and Doyle as a cooperative dual-catalyst system, together with a chiral (salen)Co complex, for the effective enantioselective ring-opening of meso epoxides with fluoride ion (**eq 5**).[91]



Scheme 15. Kinetic Resolution of Secondary Alcohols and α-Hydroxy Lactones and Lactams through Enantioselective Silylation. *(Ref. 90a,c)*



eq 5 *(Ref. 91)*

4. Conclusion and Outlook

As is evident from the many examples presented above, over the 12 years since our first report, ABCs have become one of the most widely used classes of Lewis base catalysts in enantioselective acyl transfer and related transformations. In hindsight, it is surprising that these applications had not been discovered earlier. Tetramisole (**29**) had been available in chemical catalogues for decades and had occasionally found other applications; DBN (**32**) had been widely utilized as a strong base; while THTP (**33**), DHPB (**34**), racemic BTM (**30a**), and HBTM (**31a**) analogues had been described, albeit in relatively obscure journals and patents. The high nucleophilicity of ABCs could have been reasonably anticipated from simple resonance considerations. The fact remains, however, that their potential as acylation catalysts had remained completely unexplored.

The steady increase in the number of publications utilizing ABCs in recent years can be explained, at least in part, by their easy synthetic (and commercial) availability and demonstrated efficacy in a growing number of diverse transformations. We believe, however, that there is an additional factor underlying their popularity: many aspects of their reactivity and enantioselectivity lend themselves easily to rational explanations and predictions, as illustrated by the transition state models shown above (cf. Figures 3–5 and Scheme 9). We hope that this combination of attractive features will continue to stimulate the discovery of new creative applications of ABCs for years to come.

5. Acknowledgment

The author thanks his students, postdocs, and external collaborators who have contributed to the development of ABCs, including catalyst design, discovery of their new applications, and understanding of the origin of enantioselectivity in reactions they promote. Financial support for our group's research in this area has been provided by the National Institute of General Medical Sciences (R01 GM072682), National Science Foundation (CHE-1012979, CHE-1566588), and Washington University in Saint Louis.

6. References

(1) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(2) (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (b) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570. (c) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (d) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(3) (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.

(4) (a) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (b) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, *412*.

(5) (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(6) (a) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601.

(7) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006. (c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626. (d) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 3383.

(8) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212.

(9) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.

(10) (a) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13502. **(b)** Notte, G. T.; Sammakia, T. *J. Am. Chem. Soc.* **2006**, *128*, 4230.

(11) (a) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14. (b) See also Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, *925*.

(12) Uraguchi, D.; Koshimoto, K.; Miyake, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 5567.

(13) (a) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21. (b) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR* **1967**, *176*, 197. (c) Steglich, W.; Hoefle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

(14) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

(15) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

(16) For early examples, see: (a) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169. (b) Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71.

(17) (a) Bremer, O. *Justus Liebigs Ann. Chem.* **1936**, *521*, 286. (b) For general reviews of DHIP derivatives, see: Sulojeva, E.; Yure, M.; Gudriniece, E. *Chem. Heterocycl. Compd.* **1999**, *35*, 1121. (c) Sulojeva, E.; Yure, M.; Gudriniece, E. *Chem. Heterocycl. Compd.* **2000**, *36*, 885.

(18) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226.

(19) (a) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (b) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285.

(20) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351.

(21) (a) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. (b) Zhang, Y.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2525.

(22) (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (b) Hunter, C. A.; Lawson, K. R.; Perkins, J.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 651. (c) Wei, Y.; Held, I.; Zipse, H. *Org. Biomol. Chem.* **2006**, *4*, 4223.

(23) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 15th ed.; O'Neil, M. J., Ed.; RSC Publishing: Cambridge, U.K., 2013.

(24) (a) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104. (b) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 4383.

(25) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.

(26) (a) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347. (b) For a study of DHPB derivatives with even higher activity, see Okamoto, S.; Sakai, Y.; Watanabe, S.; Nishi, S.; Yoneyama, A.; Katsumata, H.; Kosaki, Y.; Sato, R.; Shiratori, M.; Shibuno, M.; Shishido, T. *Tetrahedron Lett.* **2014**, *55*, 1909.

(27) (a) Hu, B.; Meng, M.; Wang, Z.; Du, W.; Fossey, J. S.; Hu, X.; Deng, W.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17041. (b) Jiang, S.-S.; Gu, B.-Q.; Zhu, M.-Y.; Yu, X.; Deng, W.-P. *Tetrahedron* **2015**, *71*, 1187. (c) Wang, Z.; Ye, J.; Wu, R.; Liu, Y.-Z.; Fossey, J. S.; Cheng, J.; Deng, W.-P. *Catal. Sci. Technol.* **2014**, *4*, 1909. (d) Jiang, S.-S.; Xu, Q.-C.; Zhu, M.-Y.; Yu, X.; Deng, W.-P. *J. Org. Chem.* **2015**, *80*, 3159.

(28) Nakata, K.; Shiina, I. *Org. Biomol. Chem.* **2011**, *9*, 7092.

(29) Belmessieri, D.; Joannesse, C.; Woods, P. A.; MacGregor, C.; Jones, C.; Campbell, C. D.; Johnston, C. P.; Duguet, N.; Concellón, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559.

(30) Viswambharan, B.; Okimura, T.; Suzuki, S.; Okamoto, S. *J. Org. Chem.* **2011**, *76*, 6678.

(31) (a) Shi, Y.-H.; Wang, Z.; Hu, B.; Wang, M.; Fossey, J. S.; Deng, W.-P. *Org. Lett.* **2011**, *13*, 6010. (b) Wang, M.; Wang, Z.; Shi, Y.-H.; Shi, X.-X.; Fossey, J. S.; Deng, W.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 4897. (c) Wang, Z.; Yu, X.; Tian, B.-X.; Payne, D. T.; Yang, W.-L.; Liu, Y.-Z.; Fossey, J. S.; Deng, W.-P. *Chem.—Eur. J.* **2015**, *21*, 10457. (d) He, F.-S.; Zhu, H.; Wang, Z.; Gao, M.; Yu, X.; Deng, W.-P. *Org. Lett.* **2015**, *17*,

4988. (e) Li, C.-Y.; Yang, W.-L.; Luo, X.; Deng, W.-P. *Chem.—Eur. J.* **2015**, *21*, 19048.
(32) Daniels, D. S. B.; Smith, S. R.; Lebl, T.; Shapland, P.; Smith, A. D. *Synthesis* **2015**, *47*, 34.
(33) (a) Ranieri, B.; Robles, O.; Romo, D. *J. Org. Chem.* **2013**, *78*, 6291. (b) Ni, Q.; Song, X.; Xiong, J.; Raabe, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 1263.
(34) (a) General principles: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (c) Pellissier, H. *Adv. Synth. Catal.* **2011,** *353*, 1613. (d) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011,** *50*, 6012. (e) Enantioselectivity in KR is expressed in terms of the selectivity factor, s, defined as the ratio of the reaction rates of the fast- and slow-reacting enantiomers of a substrate: s = k(fast)/k(slow). Selectivity factors equal to, or greater than, 20 are considered synthetically useful (see reference 34b).
(35) (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563. (b) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659.
(36) (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (c) Díaz-de-Villegas, M. D.; Gálvez, J. A.; Badorrey, R.; López-Ram-de-Víu, M. P. *Chem.—Eur. J.* **2012**, *18*, 13920.
(37) (a) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722. (b) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859.
(38) (a) Shiina, I.; Nakata, K. *Tetrahedron Lett.* **2007**, *48*, 8314. (b) Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem.—Eur. J.* **2010**, *16*, 167. (c) Shiina, I.; Ono, K.; Nakata, K. *Chem. Lett.* **2011**, *40*, 147. (d) Shiina, I.; Umezaki, Y.; Kuroda, N.; Iizumi, T.; Nagai, S.; Katoh, T. *J. Org. Chem.* **2012**, *77*, 4885. (e) Shiina, I.; Ono, K.; Nakahara, T. *Chem. Commun.* **2013**, *49*, 10700. (f) Nakata, K.; Gotoh, K.; Ono, K.; Futami, K.; Shiina, I. *Org. Lett.* **2013**, *15*, 1170.
(39) (a) Xu, Q.; Zhou, H.; Geng, X.; Chen, P. *Tetrahedron* **2009**, *65*, 2232. (b) Zhou, H.; Xu, Q.; Chen, P. *Tetrahedron* **2008**, *64*, 6494.
(40) Hu, B.; Meng, M.; Fossey, J. S.; Mo, W.; Hu, X.; Deng, W.-P. *Chem. Commun.* **2011**, *47*, 10632.
(41) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836.
(42) (a) Qin, T.; Iwata, T.; Ransom, T. T.; Beutler, J. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2015**, *137*, 15225. (b) Qin, T.; Skraba-Joiner, S. L.; Khalil, Z. G.; Johnson, R. P.; Capon, R. J.; Porco, J. A., Jr. *Nat. Chem.* **2015**, *7*, 234.
(43) Ortiz, A.; Benkovics, T.; Beutner, G. L.; Shi, Z.; Bultman, M.; Nye, J.; Sfouggatakis, C.; Kronenthal, D. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 7185.
(44) See also Wang, H.-Y.; Yang, K.; Yin, D.; Liu, C.; Glazier, D. A.; Tang, W. *Org. Lett.* **2015**, *17*, 5272.
(45) (a) Wagner, A. J.; David, J. G.; Rychnovsky, S. D. *Org. Lett.* **2011**, *13*, 4470. (b) Wagner, A. J.; Rychnovsky, S. D. *J. Org. Chem.* **2013**, *78*, 4594.
(46) Birman, V. B.; Jiang, H.; Li, X. *Org. Lett.* **2007**, *9*, 3237.
(47) Merad, J.; Borkar, P.; Bouyon Yenda, T.; Roux, C.; Pons, J.-M.; Parrain, J.-L.; Chuzel, O.; Bressy, C. *Org. Lett.* **2015**, *17*, 2118.
(48) (a) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (b) Yang, X.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2011**, *13*, 4755. (c) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605.
(49) Bumbu, V. D.; Yang, X.; Birman, V. B. *Org. Lett.* **2013**, *15*, 2790.
(50) Perry, M. A.; Trinidad, J. V.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 472.
(51) (a) Dietz, F. R.; Gröger, H. *Synlett* **2008**, 663. (b) Dietz, F. R.; Gröger, H. *Synthesis* **2009**, 4208.
(52) (a) Joannesse, C.; Johnston, C. P.; Concellon, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914. (b) Joannesse, C.; Johnston, C. P.; Morrill, L. C.; Woods, P. A.; Kieffer, M.; Nigst, T. A.; Mayr, H.; Lebl, T.; Philp, D.; Bragg, R. A.; Smith, A. D. *Chem.—Eur. J.* **2012**, *18*, 2398.
(53) Joannesse, C.; Morrill, L. C.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2011**, 1865.
(54) Woods, P. A.; Morrill, L. C.; Bragg, R. A.; Smith, A. D. *Chem.—Eur. J.* **2011,** *17*, 11060.
(55) (a) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887.
(56) (a) Shiina, I.; Nakata, K.; Ono, K.; Onda, Y.; Itagaki, M. *J. Am. Chem. Soc.* **2010,** *132*, 11629. (b) Tengeiji, A.; Nakata, K.; Ono, K.; Shiina, I. *Heterocycles* **2012**, *86*, 1227.
(57) Tengeiji, A.; Shiina, I. *Molecules* **2012**, *17*, 7356.
(58) (a) Shiina, I.; Ono, K.; Nakata, K. *Catal. Sci. Technol.* **2012**, *2*, 2200. (b) Tokumaru, E.; Tengeiji, A.; Nakahara, T.; Shiina, I. *Chem. Lett.* **2015**, *44*, 1768.
(59) (a) Yang, X.; Birman, V. B. *Adv. Synth. Catal.* **2009**, *351*, 2301. (b) Yang, X.; Birman, V. B. *Chem.—Eur. J.* **2011**, *17*, 11296.
(60) Yang, X.; Birman, V. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 5553.
(61) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem., Int. Ed.* **2012**, *51*, 9638.
(62) (a) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892. (b) For a computational study, see Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288.
(63) Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902.
(64) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596.
(65) Purohit, V. C.; Matla, A. S.; Romo, D. *J. Am. Chem. Soc.* **2008**, *130*, 10478.
(66) (a) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010,** *49*, 9479. (b) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 13348.
(67) Liu, G.; Shirley, M. E.; Van, K. N.; McFarlin, R. L.; Romo, D. *Nat. Chem.* **2013**, *5*, 1049.
(68) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, *79*, 1626.
(69) Morrill, L. C.; Smith, S. M.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2014**, *79*, 1640.
(70) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714.
(71) Belmessieri, D.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2013**, *15*, 3472.
(72) Belmessieri, D.; de la Houpliere, A.; Calder, E. D. D.; Taylor, J. E.; Smith, A. D. *Chem.—Eur. J.* **2014**, *20*, 9762.
(73) Smith, S. R.; Leckie, S. M.; Holmes, R.; Douglas, J.; Fallan, C.; Shapland, P.; Pryde, D.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 2506.
(74) (a) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146. (b) Morrill, L. C.; Ledingham, L. A.; Couturier, J.-P.; Bickel, J.; Harper, A. D.; Fallan, C.; Smith, A. D. *Org. Biomol. Chem.* **2014**, *12*, 624.
(75) Morrill, L. C.; Stark, D. G.; Taylor, J. E.; Smith, S. R.; Squires, J. A.; D'Hollander, A. C. A.; Simal, C.; Shapland, P.; O'Riordan, T. J. C.; Smith, A. D. *Org. Biomol. Chem.* **2014**, *12*, 9016.
(76) Jiang, S.; Hu, B.; Yu, X.; Deng, W. *Chin. J. Chem.* **2014**, *32*, 694.
(77) (a) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653. (b) Yeh, P.-P.; Daniels, D. S. B.; Fallan, C.; Gould, E.; Simal, C.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2015**, *13*, 2177.

(78) Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088.
(79) Izquierdo, J.; Pericàs, M. A. *ACS Catal.* **2016**, *6*, 348.
(80) Li, X.; Gai, K.; Yuan, Z.; Wu, J.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2015**, *357*, 3479.
(81) (a) Stark, D. G.; Morrill, L. C.; Yeh, P.-P.; Slawin, A. M. Z.; O'Riordan, T. J. C.; Smith, A. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 11642. (b) Stark, D. G.; O'Riordan, T. J. C.; Smith, A. D. *Org. Lett.* **2014**, *16*, 6496. (c) Yeh, P.-P.; Daniels, D. S. B.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 964.
(82) Hesping, L.; Biswas, A.; Daniliuc, C. G.; Mück-Lichtenfeld, C.; Studer, A. *Chem. Sci.* **2015**, *6*, 1252.
(83) Li, B.-S.; Wang, Y.; Jin, Z.; Chi, Y. R. *Chem. Sci.* **2015**, *6*, 6008.
(84) Smith, S. R.; Fallan, C.; Taylor, J. E.; McLennan, R.; Daniels, D. S. B.; Morrill, L. C.; Slawin, A. M. Z.; Smith, A. D. *Chem.—Eur. J.* **2015**, *21*, 10530.
(85) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476.
(86) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 2193.
(87) (a) Fukata, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2015**, *137*, 5320. (b) Ahlemeyer, N. A.; Birman, V. B. *Org. Lett.* **2016**, *18*, ASAP, DOI: http://dx.doi.org/10.1021/acs.orglett.6b01639.
(88) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, *136*, 4492.
(89) Pandiancherri, S.; Ryan, S. J.; Lupton, D. W. *Org. Biomol. Chem.* **2012**, *10*, 7903.
(90) (a) Clark, R. W.; Deaton, T. M.; Zhang, Y.; Moore, M. I.; Wiskur, S. L. *Org. Lett.* **2013**, *15*, 6132. (b) Wang, L.; Akhani, R. K.; Wiskur, S. L. *Org. Lett.* **2015**, *17*, 2408.
(91) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.

About the Author

Vladimir Birman was born in Kharkov, Ukraine. He began his undergraduate study of chemistry in Moscow, but completed his B.S. degree at the University of North Carolina at Charlotte. His Ph.D. (University of Chicago, with Professor V. H. Rawal) and postdoctoral studies (Columbia University, with Professor S. J. Danishefsky) focused on the total synthesis of natural products. Upon joining the faculty at Washington University in Saint Louis, MO, in 2003, he became interested in asymmetric organocatalysis, primarily in the development of amidine-based catalysts that are described in this review.

A Green Chemistry Pioneer

Dr. Rajender S. Varma

Thank you, Dr. Varma, for your continued significant contributions to green chemistry and sustainability.

"I have a passion for exploratory research, especially one that involves learning from Nature to address environmental problems in a sustainable and green chemistry way. Long-term goals are to contribute wide-ranging chemical expertise to develop and evaluate novel and environmentally safer procedures in industrial chemistry in order to minimize the detrimental impact of human activity on human health and the environment."

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Advancing Sustainable Catalysis with Magnetite. Surface Modification and Synthetic Applications


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Abstract. This article surveys the recent developments in the synthesis, surface modification, and synthetic applications of magnetite nanoparticles. The emergence of iron(II,III) oxide (triiron tetraoxide or magnetite; Fe_3O_4, or $FeO•Fe_2O_3$) nanoparticles as a sustainable support in heterogeneous catalysis is highlighted.

Outline

1. Introduction

The development in organic chemistry of practical and sustainable methods that satisfy the green chemistry principles is an ongoing challenge.[1] Green chemistry strives to safeguard the natural environment and its systems by reducing both the use of harmful chemicals and the generation of chemical waste while promoting recyclability.[2,3] Catalysis has been an integral part of this effort, and homogeneous catalysis has been the primary choice[4] for chemists due to the accessibility of all possible catalytic sites of the metal catalyst and its solubility in the reaction medium. Moreover, it is relatively easier to tune homogeneous catalysts in order to have better control of the regio-, chemo-, and enantioselectivity of the reaction and to obtain improved yields.[5] Industry generally employs homogeneous catalysts for the large-scale synthesis of many commercial products; separating the catalyst from the final product is, however, a major challenge, thereby hampering the use of such catalysts despite their many advantages.[6,7]

Metal contamination is highly regulated in industry and is even more so in the pharmaceutical industry.[7] The use of traditional laboratory techniques such as distillation, extraction, or chromatographic separation has often not been effective in removing traces of metal catalysts from the desired products.[6,7] To address the challenges associated with metal contamination and recovery of homogeneous catalysts, chemists have developed a wide range of strategies that have resulted in the heterogenization of homogeneous catalyst systems.[8,9] Most of the heterogenized catalysts are based on silica supports due to silica's excellent stability, porosity, accessibility, and to the straightforward ability to anchor organic ligands onto its surface.[10,11] Anchoring onto silica can be achieved by covalent bonding or by simple noncovalent interaction.[12,13] In heterogeneous systems, the active sites that are available for reaction are located on the surface of the heterogeneous support, resulting in an overall decrease in activity of these catalytic systems as compared to their homogeneous counterparts. Therefore, the development of novel, heterogenized catalysts having an increased surface area, reactivity, and selectivity, and resulting in better yields—coupled with ease of separation and effective recovery—is highly desirable for sustainable chemical synthesis.

With the growing environmental consciousness, there has been a paradigm shift toward employing metal nanoparticles in order to utilize all of the active sites in the catalysts and minimize the generation of

chemical waste.[14,15] To this end, the heterogeneous nature of nanoparticles enables recovery and reuse; however, aggregation and deactivation are a serious problem that has been associated with bare nanoparticles. Thus, the search for new catalytic systems with benign alternatives to homogenous catalysis is an important, ongoing area of research.

In this survey, we present and discuss the use of magnetic nanoparticles as a support in metal-catalyzed reactions. We have limited the discussion to the dispersibility and functionalization of nanoparticles, their applications in catalysis, and their use as scavengers of silver nanoparticles.

2. Exploiting Magnetic Attraction in Catalyst Recovery

Nanoparticles increase the available surface area of the active catalyst, thereby increasing the contact frequency between the catalyst and the substrate, and making such catalyst systems resemble their homogeneous counterparts. Moreover, the heterogeneous nature of the nano-support facilitates the recovery of the catalyst from the reaction mixture; however, the separation of tiny particles is challenging under ordinary circumstances, and efficient recovery requires high-speed centrifugation along with longer sedimentation times. Although centrifugation is a simple process, it becomes difficult to separate tiny particles of catalyst from large volumes of solvent and, thus, separation and recovery become very tedious on an industrial scale. The most important attributes associated with nanocatalysts are directly related to their physical and chemical properties, which can be tailored to particular tasks by manipulating the shape, size, and morphology of the nanocatalysts. Since the biggest challenge lies in the efficient recovery of the nanocatalyst at the end of the reaction (most heterogeneous systems require filtration or centrifugation to separate and recover the catalyst), making the nanoparticle support *magnetic* would facilitate recovery by using an external magnet, thus eliminating the catalyst filtration step (**Figure 1**).[16] Since reusability after recovery is a primary driving force for employing heterogeneous catalysts, this offers a promising approach that can meet the requirements of high accessibility and recyclability.[17]

3. Synthesis and Surface Modification of Magnetic Supports

The synthesis of magnetic nanoparticles and their surface modification have been very well studied.[17] Numerous magnetic nanoparticles are derived from metals such as Ni, Co, and Fe. The magnetic property of the nanoparticles is not limited to the pure metals; their oxides (e.g., Fe_3O_4), alloys, and bimetallic combinations such as iron ferrites (e.g., $CuFe_2O_4$) have been well documented.[18] Rather than a comprehensive review on magnetic nanoparticles, which is beyond the limit of this account, we describe herein the progress made by us and others in developing magnetic nanocatalysts and their varied applications, including the recovery of trace metal nanoparticles from wastewater. Our main focus has been on the use of magnetite and its bimetallic combinations as magnetically separable supports. These supports measure well vis-à-vis such important benchmarks as facile accessibility, ease of large-scale production, tolerance of moderately high temperatures and pressures, high magnetization with small particles size, low toxicity, receptivity to surface modification and functionalization, and cost. Advances in synthesis provide access to monodispersed nanoparticles, with control over both size and morphology. Additionally, magnetite particles show negligible remnant magnetization and trifling agglomeration. Despite their inherent stability, a protective layer of a coating can improve the stability of magnetic nanomaterials and improve their performance under demanding conditions. A plethora of methods exist for surface modification and derivatization and for anchoring of organic surfactants and acids, including the generation of a thin shell of carbon and silica.[18] The choice of anchoring ligand and coating material depends on the specific application, with silica often being considered a suitable coating since it can eliminate unwanted interactions with the magnetic core. The controlled coating of the magnetic core with silica can be achieved using Stober's method by hydrolyzing a sol-gel precursor such as tetraethoxysilane (TEOS).[18] Coating with a thin layer of carbon is another option to ameliorate the thermal and chemical stability, leading to nanoparticles that are considered superior to their inorganic and organic counterparts, and allowing them to withstand extreme conditions.[19] The carbon coating can be easily achieved using flame-spray pyrolysis and could be performed on an industrial scale.[20] Although some of these methods are known, we sought to develop experimentally simpler methods for the synthesis and surface modification of magnetite, including coating with carbon and silica. Glutathione and dopamine could be anchored by sonication of the solution of iron oxide with glutathione or dopamine, which provides surface-modified nano-FGT (Fe_3O_4–Glutathione) and nano-DOPA (Fe_3O_4–Dopamine), respectively. The dopamine- and glutathione-coated magnetic nanoparticles were converted into active catalysts by immobilizing different metals on the outer coatings (**Scheme 1**).[21,22] Although, these catalysts have proven very useful, their preparation entails three tedious steps: (i) synthesis of nano-ferrite, (ii) post-synthetic modification via anchoring of ligand, and (iii) immobilization of a metal. To overcome these drawbacks and avoid the use of toxic ligand and/or reagents, the synthetic procedures were further simplified. Silica-coated magnetite could serve as an alternative for ligand anchoring in the development of magnetic active catalysts. We have developed a simple, one-pot procedure for the synthesis of such catalysts by generating Fe_3O_4 in situ, followed by coating with silica and immobilization of the active metal (**Scheme 2**, Part (a)).[23] A similar approach has been employed for the synthesis of carbon-coated magnetite.[24] In this case, the procedure involves the in situ generation of magnetite and immobilization of biodegradable and naturally abundant cellulose on its surface followed by controlled calcination. This work is presently in its infancy and requires further research to optimize the thickness of the carbon layer, which should help make inroads into wider applications in organic synthesis (Scheme 2, Part (b)).[24]

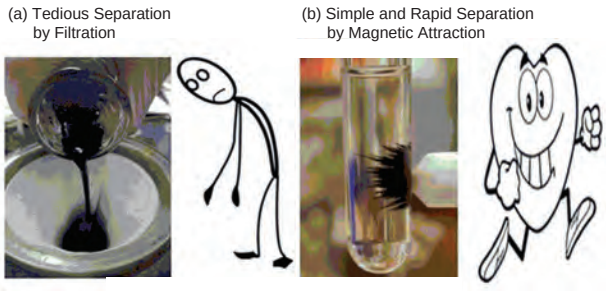


Figure 1. Catalyst Separation by Magnetic Attraction vs Filtration.

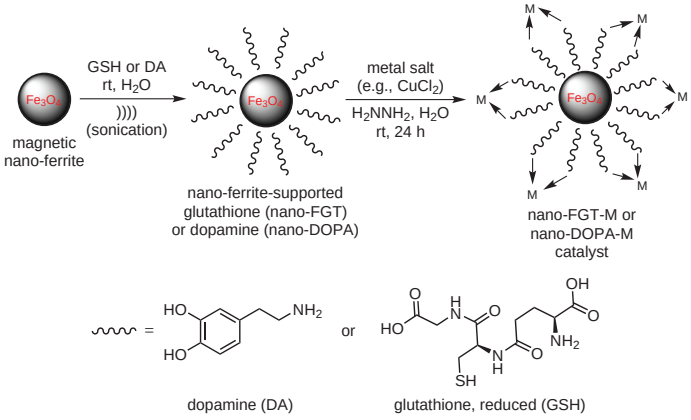
4. Attaching Organic Ligands to Magnetite

The last decade has seen an exponential growth in organocatalysis and its applications in the synthesis of small molecules. A wide range of reactions have benefited from these applications, and these reactions have been rendered sustainable by the heterogenization of the organocatalysts

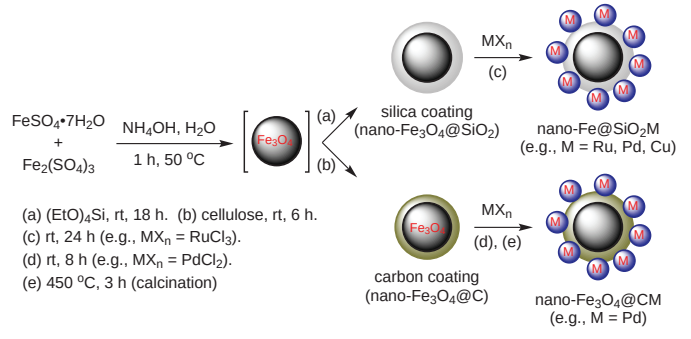
employed and the use of unconventional energy sources such as microwave irradiation. Most of the time, the reactions are carried out in volatile organic solvents over longer periods of time. We envisaged the use of glutathione, a tripeptide and an essential component of plant and human cells, as an organocatalyst, and developed a heterogenized, magnetically separable nano-FGT system. The presence of a highly reactive thiol group at the center of the molecule is ideally suited as a linker to the surface of magnetite by keeping the two active amino acid flanks available for reaction. Magnetically separable nano-FGT displayed high activity in Paal–Knorr-type reactions between amines and 2,5-dimethoxytetrahydrofuran, allowing a wide range of pyrrole derivatives to be prepared in good yields (**eq 1**).[25] The most important advantages of the reaction were the use of benign aqueous media and the magnetic recoverability of the catalyst.[25]

Having established the use of nano-FGT as a magnetically separable organocatalyst, we then demonstrated the immobilization of copper nanoparticles on nano-FGT surfaces, and applied the resulting catalyst in the Huisgen 1,3-dipolar cycloaddition to generate 1,2,3-triazoles through one-pot click reactions. Several 1,2,3-triazoles have displayed interesting biological properties, such as antibacterial, antiallergic, and anti-HIV activities in addition to their use as fungicides and herbicides. The simplicity and efficiency of the 1,3-dipolar cycloaddition, as well as the molecular architectures it gives rise to, have made it one of the most useful reactions in synthesis. Recent discoveries relating to the catalysis and rate enhancement of this reaction have enabled many novel applications. To further improve the utility and user-friendliness of this process, we have developed a practical, multicomponent variant by immobilizing copper on the surface of nano-FGT and demonstrated its power in the azide–alkyne dipolar cycloaddition (**eq 2**).[26] The choice of the cycloaddition reaction was based on the premise that the redox property of glutathione would help in the generation of the active copper species. When it became apparent in later studies that this catalyst was not useful for the coupling of aryl thiols,[26] we changed the anchoring ligand in order to develop a more active catalyst for such coupling reactions.

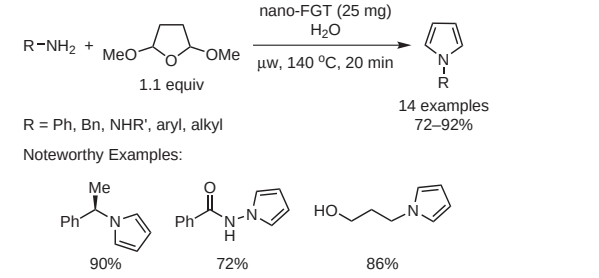
Cross-coupling reactions play an important role in organic synthesis, and are key steps in the synthesis of many molecules that are of interest in biology and materials science. A variety of applications of organosulfur compounds are known in diverse fields such as in the treatment of diabetes, cancer, inflammation, and Alzheimer's disease. Traditionally, cross-coupling reactions have been conducted under drastic conditions such as high reaction temperatures in toxic and high-boiling solvents. Although organosulfur chemistry has benefited from advances in transition-metal catalysis, C–S cross-coupling reactions were scarcely studied due to deactivation of the transition-metal catalyst and sulfur poisoning. The success of the reaction has been highly predicated on the use of ligands under inert conditions. Thus, the development of ligand-free, inexpensive, moisture–insensitive, and recyclable catalysts for this reaction has been highly desirable as it can contribute to reducing the use of toxic chemicals. The copper catalyst nano-FGT-Cu was found to be inactive in this transformation. However, this catalyst showed promising activity when the anchor was replaced with dopamine. Thus, nano-DOPA was modified using $CuCl_2$ with particle size of 10–25 nm, and the resulting catalyst, nano-α-Fe_3O_4–



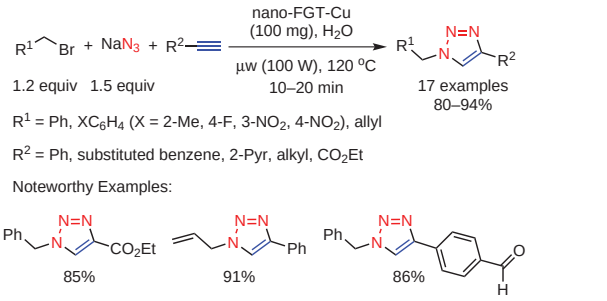
Scheme 1. Synthesis of Glutathione- and Dopamine-Coated Magnetite Followed by Immobilization of the Active Metal. *(Ref. 21,22)*



Scheme 2. Simple, One-Pot Synthesis of (a) Silica- and (b) Carbon-Coated Magnetic Nanoparticles Bearing an Active Metal. *(Ref. 23,24)*



eq 1 *(Ref. 25)*



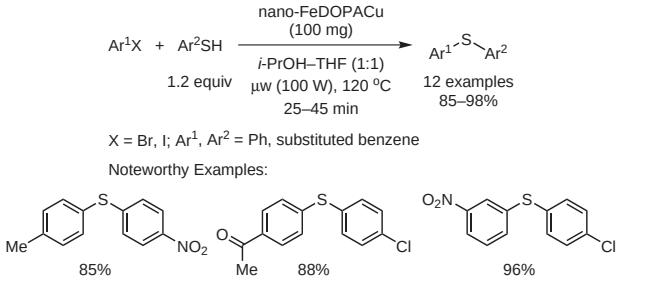
eq 2 *(Ref. 26)*

dopamine–copper (nano-FeDOPACu), was employed for the coupling of thiophenols with 1-bromo-4-nitrobenzene at 120 °C under microwave (μw) irradiation to selectively form the corresponding sulfides in quantitative yields.[22] Moreover, the cross-coupling of commercially available aryl halides with thiophenols proceeded efficiently, forming the corresponding diaryl sulfides in good-to-excellent yields (**eq 3**).[22] The magnetic nature of the catalyst facilitates easy recovery, and avoids the use of excess solvent in the workup.

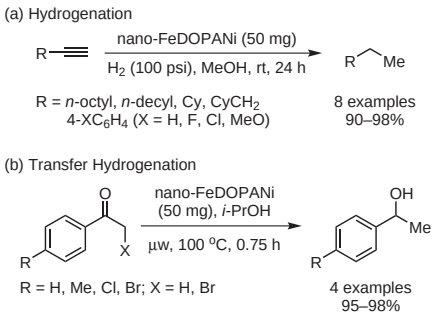
Nano-DOPA was used for the immobilization of Ni, Pd, and Ru metals. This immobilization resulted in the formation of nano-ferrite-Ni (nano-DOPANi),[27] nano-ferrite-Ru (nano-DOPARu),[28] and nano-ferrite-Pd (nano-DOPAPd)[29] catalysts. Nano-DOPANi was explored for the hydrogenation of a variety of alkynes in methanol and dichloromethane under a hydrogen atmosphere: most of the substrates, except heterocyclic alkynes and the nitro group, were smoothly hydrogenated at room temperature to give the corresponding alkanes in very good yields (**Scheme 3**, Part (a)).[27] The conversion of carbonyl compounds to the corresponding alcohols is one of the most important transformations in organic synthesis, where a catalytic hydrogen-transfer protocol is often used. In general, precious Pd or Au are employed for this transformation. In contrast, we have demonstrated the suitability of inexpensive nano-DOPANi catalyst for the transfer hydrogenation of a variety of ketones under microwave irradiation (Scheme 3, Part (b)).[27]

Nano-DOPAPd is a very active catalyst, with a very impressive turnover number, for the oxidation of primary aliphatic and benzylic alcohols to the corresponding aldehydes (**Scheme 4**, Part (a)).[29a] This catalyst has also been employed in the oxidation of alkenes to the corresponding alcohols, with loss of a terminal carbon, and in the Heck coupling of aryl halides with alkenes (Scheme 4, Part (b)).[29b] The latter reaction is carried out in pyridine–DMF and tolerates a wide range of functional groups. Interestingly, we have demonstrated that this catalyst can be effectively utilized for the Heck-type arylation of alkenes with diaryliodonium salts in H_2O–PEG-400 (1:1) under sonication, to give the corresponding products in 5 min or less and moderate to high yields (Scheme 4, Part (c)).[29c] The reaction was equally efficient with inactivated alkenes such as styrene, allyl alcohol, and allyl acetate. The most important attribute of this method is that it proceeds under neutral conditions, whereas the reported methods require a base for completion of the reaction. In the course of our studies, we discovered that this catalyst is also active in the O-allylation of phenols with allylic acetates in aqueous media. Traditionally, allyl ethers have been prepared by the Williamson method, which involves the use of strongly basic metal alkoxide anions and highly active allyl halides. The addition of oxygen nucleophiles to η^3-allyl metal complexes of transition metals provides a mild alternative approach for their synthesis from allyl alcohols. However, most of the existing methods for transition-metal-catalyzed O-allylation via η^3-allyl metal intermediates are accomplished using a non-recyclable homogeneous catalyst and toxic organic solvents. Allyl ethers have now been synthesized in the presence of nano-DOPAPd and mild base in aqueous media, with ease of recovery and recycling of the catalyst, which had not been possible using traditional metal catalysts (Scheme 4, Part (d)).[30]

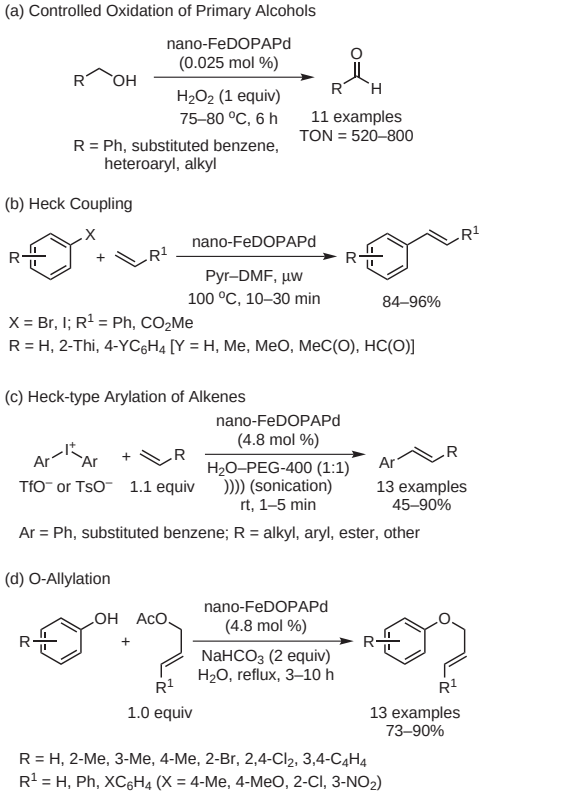
Traditionally, amides have been synthesized by the oxidative hydration of nitriles in acidic or basic media, wherein byproducts are formed due to hydrolysis of the nitriles and/or amides. In addition,



eq 3 *(Ref. 22)*



Scheme 3. Nano-FeDOPA-Supported Nickel and Its Application in (a) Hydrogenation and (b) Transfer-Hydrogenation Reactions. *(Ref. 27)*



Scheme 4. Nano-FeDOPA-Supported Palladium and Its Application in Cross-Coupling and Other Reactions. *(Ref. 29,30)*

many functional groups do not tolerate such harsh conditions, resulting in decreased selectivity for the reaction. The development of efficient procedures for the synthesis of amides that circumvent the extravagant use of stoichiometric reagents and/or acidic and basic media is highly desirable. The ruthenium hydroxide coated nanomaterial catalyst, nano-DOPARu, has proven very effective for the hydration of nitriles in aqueous medium under MW irradiation (**eq 4**).[28] Activated, inactivated, and heterocyclic nitriles, as well as a variety of benzonitriles and aliphatic nitriles were smoothly hydrated to the corresponding amides in good yields.

5. Silica-Coated Magnetite and Its Application in Organic Synthesis

Magnetic nanoparticles have been established as a high-surface-area heterogeneous support for the development of heterogeneous catalysis. To render this system even greener and avoid the use of toxic ligands and reagents, a one-pot procedure for the synthesis of magnetic, silica-supported ruthenium, palladium, and copper as magnetically retrievable catalysts has been developed, and the applications of these catalysts in organic synthesis have been demonstrated. Magnetic nanoferrite (Fe_3O_4) was generated in situ by hydrolysis of $FeSO_4$•$7H_2O$ and $Fe_2(SO_4)_3$ in water at pH 10 (adjusted by utilizing 25% ammonium hydroxide), followed by heating at 50 °C for 1 h. The reaction solution was cooled down to room temperature, tetraethyl orthosilicate (TEOS) added, and the mixture vigorously stirred for 18 h. The metal salt, $RuCl_3$, $PdCl_2$, or $CuCl_2$, was then added, the pH of the solution adjusted again to ~10 with 25% NH_4OH, and stirring continued for 24 h. The magnetic, silica-supported metal nanoparticles (nano-Fe@SiO_2Ru, nano-Fe@SiO_2Pd, and nano-Fe@SiO_2Cu) were separated using an external magnet, washed with water and acetone, and dried under reduced pressure at 50 °C for 8 h. The formation of single-phase, silica-coated Fe_3O_4 nanoparticles was confirmed by X-ray diffraction (XRD) and transmission electron microscopy (TEM), which indicated a spherical morphology and a size range of 15–30 nm for the nanoparticles.[23]

The palladium-catalyzed Buchwald–Hartwig amination has been well explored; but, the reported methods require the use of toxic N-heterocyclic carbenes, phosphines, or other complex ligands. The main problems with these aminations are that they often require long reaction times, and the ligands are air-sensitive and expensive. Moreover, while there have been significant discoveries and progress in the *copper*-catalyzed coupling reaction of aryl halides with amines, the success of these newer methodologies is highly dependent on the nature of the organic ligands used. Although, these ligands have been very important for accelerating the copper-catalyzed coupling of aryl halides with amines, none of them has displayed a general efficiency in the reaction. Our group has succeeded in overcoming these drawbacks and the use of toxic ligands and reagents by employing magnetic silica as a heterogeneous support in the development of nano-Fe@SiO_2Cu.[31] The application of magnetic, silica-supported copper was demonstrated in the heterogeneously catalyzed amination of aryl halides in aqueous medium as a benign solvent under microwave irradiation conditions. Nano-Fe@SiO_2Cu displayed high catalytic activity in the amination of aryl bromides and iodides with primary, secondary, cyclic, and acyclic amines in pure water (**eq 5**).[32] It is worth noting that 1-bromo-4-iodobenzene was selectively converted into corresponding 4-bromoarylamine with 1 equivalent of pyrrolidine after exposure to MW irradiation at 100 °C for 1 h. The reaction of amines with aryl halides bearing boronic acid derived functional groups leads to the formation of the corresponding arylamines accompanied by removal of the boronic acid moiety.

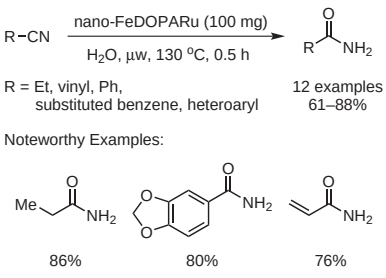
The wider applicability of nano-Fe@SiO_2Ru was demonstrated in the aqueous hydration of nitriles to the corresponding amides and the transfer-hydrogenation reaction of carbonyl compounds using isopropanol. Nano-Fe@SiO_2Pd has proven to be a robust high-surface-area heterogeneous catalyst for the synthesis of allylic ethers in aqueous media.[32]

6. Catalysis with Palladium Supported on Carbon-Coated Magnetite

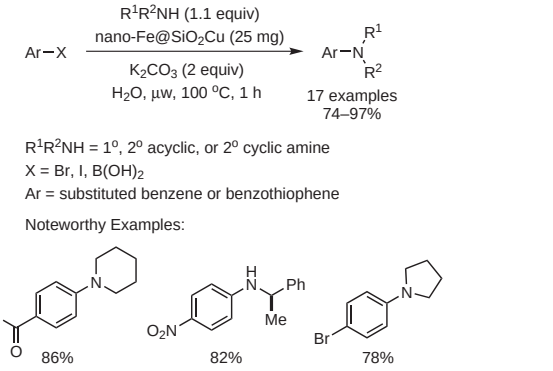
The carbon coating of magnetite is accomplished in one pot by the sequence of nanoparticle synthesis, coating with cellulose, and calcination. Magnetite (Fe_3O_4) was generated in situ by stirring a solution of 1:1 $FeSO_4$•$7H_2O$ and $Fe_2(SO_4)_3$ in water at pH 10, followed by digestion at 50 °C. The resulting solution was added to an aqueous suspension of cellulose, followed by addition of $PdCl_2$ and stirring for 8 h. The magnetite–cellulose-supported Pd material was separated, washed with water, and calcined to give the magnetic, carbon-supported palladium (nano-Fe_3O_4@CPd).[33] The application of this metal has been successfully demonstrated in the catalytic hydrogenation of alkenes and alkynes and in the reduction of the nitro group (**Scheme 5**).[33]

7. Magnetite Sulfonic Acid

Magnetite sulfonic acid was synthesized by treating Fe_3O_4 with neat chlorosulfonic acid, and the resulting nano-Fe_3O_4@SO_3H was characterized using XRD, SEM, and FTIR spectroscopy. The percent loading of –SO_3H per gram of catalyst was calculated using pH analysis. This material catalyzed a Ritter-type reaction, wherein a wide range of alcohols and nitriles react efficiently under solvent-free conditions to generate valuable amides (**eq 6**).[34] Earlier variants, performed with homogeneous catalysts, had a limited scope.



eq 4 *(Ref. 28)*



eq 5 *(Ref. 32)*

8. Magnetically Recoverable Metathesis Catalysts

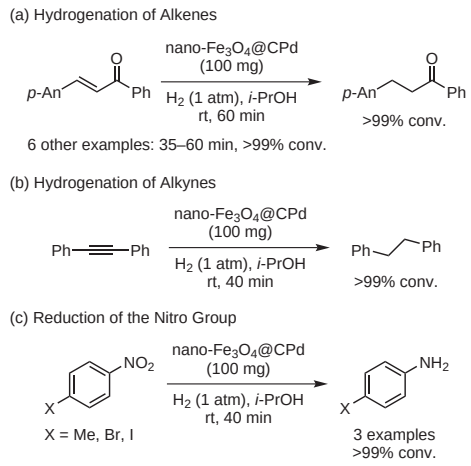
Hoveyda–Grubbs-type metathesis catalysts can be loaded onto magnetic iron oxide supports either by modification of the surface of magnetic nanoparticles (MNP) or by coprecipitation during the synthesis of MNPs. Zhu and co-workers have heterogenized a second-generation Hoveyda–Grubbs catalyst over iron oxide via a surface-modification approach.[35] In this synthesis, commercially available MNPs were coated with *ortho*-isopropoxystyrene ligands by covalent bonds. The reaction of supported ligands with the second-generation Grubbs catalyst formed the magnetically retrievable Hoveyda–Grubbs catalyst, which displayed high activity in metathesis reactions (**Scheme 6**).[35]

9. C–H Activation with Magnetic, Graphitic Carbon Nitride

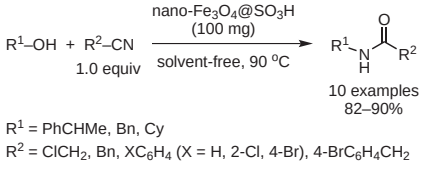
Our group has immobilized magnetic nano-ferrite over a graphitic carbon nitride surface (g-C_3N_4), and demonstrated the applicability of the resulting catalyst (Fe@g-C_3N_4) to the C–H activation of amines (**eq 7**).[36] The resulting α-aminonitriles can be utilized for the synthesis of natural products and pharmaceutically important scaffolds.

10. Separation and Measurement of Silver Nanoparticles in Wastewater

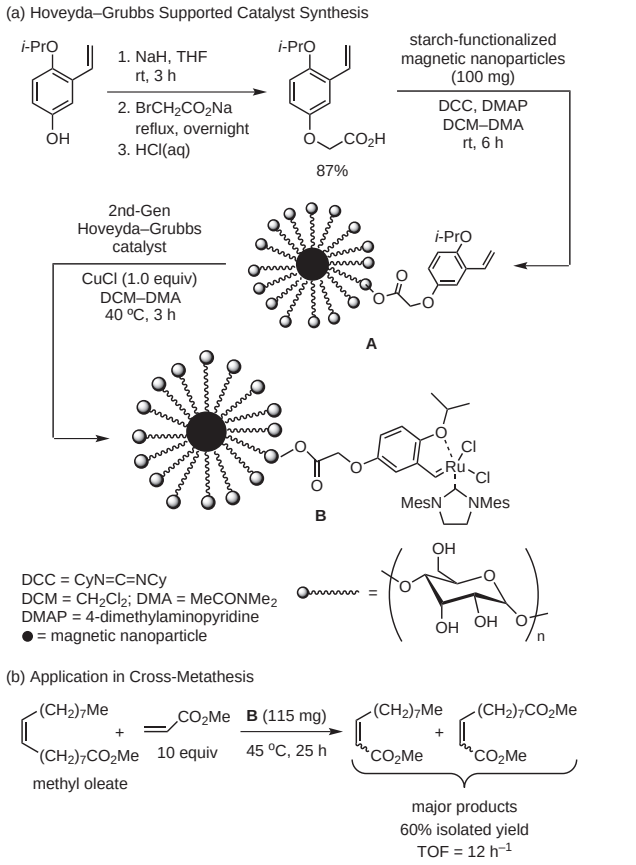
Magnetic particles as sorbents can provide a simple method for the separation and isolation of trace amounts of nanoparticles. Magnetic nano-ferrites are superparamagnetic, but do not remain permanently magnetized after the field is removed, and can be easily tuned by surface modification to develop robust adsorbent materials. We have demonstrated the use of magnetic nanoparticles for the capturing of silver nanoparticles (AgNPs) from aqueous media: AgNPs were thus captured, concentrated, and quantified by ICP-AES analysis. Physical characterization by SEM/EDX confirmed the presence of AgNPs captured by the magnetic particles. Experiments with environmental samples revealed that AgNPs can be recovered almost quantitatively from complex matrices. Hence, this method has potential as an analytical tool for concentrating and recovering nanoparticles from the environment. The main advantage of this method over commonly employed techniques is that AgNPs can be retrieved and separated using an external magnet.[37]



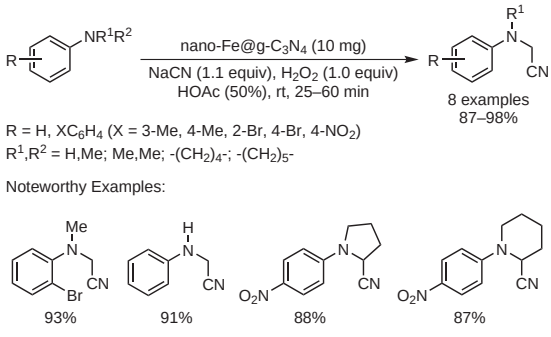
Scheme 5. Nano-Fe_3O_4@C-Supported Palladium Effectively Catalyzes Hydrogenations and Reductions. *(Ref. 33)*



eq 6 *(Ref. 34)*



Scheme 6. Synthesis and Application of Magnetically Retrievable Hoveyda–Grubbs Metathesis Catalyst. *(Ref. 35)*



eq 7 *(Ref. 36)*

11. Conclusion and Outlook

Magnetite has emerged as a sustainable and versatile support for the development of heterogeneous catalysts. A wide range of heterogeneous catalysts have been developed for C–C, C–S, C–N, and C–O bond formations, oxidations, reductions, and metathesis reactions. The most important aspect of the development of magnetite-supported catalysis is the design and synthesis of a reaction-specific, stable, and benign catalyst. The recyclability, stability, and magnetic attraction are some of the salient features of the magnetite-supported catalysts. These catalysts also have great potential in emerging areas of research involving continuous flow and microreactor synthesis. Due to the powerful interaction between magnetite and active metals, the deterioration of the metal in the reaction solution can be minimized to a large extent. The magnetite-supported catalysts provide a strong foundation for the development of heterogeneous catalysis and environmental remediation.

12. Acknowledgment

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13. References

(1) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.
(2) *Designing Safer Chemicals*; Boethling, R., Voutchkova, A., Eds.; Handbook of Green Chemistry – Green Processes, Vol. 9; Anastas, P. T., Series Ed.; Wiley-VCH: Weinheim, Germany, 2012.
(3) Gilbertson, L. M.; Zimmerman, J. B.; Plata, D. L.; Hutchison, J. E.; Anastas, P. T. *Chem. Soc. Rev.* **2015**, *44*, 5758.
(4) Schafer, L. L.; Mountford, P.; Piers, W. E. *Dalton Trans*. **2015**, *44*, 12027.
(5) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127.
(6) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.
(7) Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530.
(8) Zhao, M.; Ou, S.; Wu, C.-D. *Acc. Chem. Res.* **2014**, *47*, 1199.
(9) Yoon, M.; Srirambalaji, R.; Kim, K. *Chem. Rev.* **2012**, *112*, 1196.
(10) Zhu, Z.; Yang, W. *J. Phys. Chem. C* **2009**, *113*, 17025.
(11) Rostamnia, S.; Doustkhah, E. *RSC Adv.* **2014**, *4*, 28238.
(12) Zaera, F. *Chem. Soc. Rev*. **2013**, *42*, 2746.
(13) Sun, L.-B.; Liu, X.-Q.; Zhou, H.-C. *Chem. Soc. Rev.* **2015**, *44*, 5092.
(14) Xia, Y.; Yang, H.; Campbell, C. T. *Acc. Chem. Res.* **2013**, *46*, 1671.
(15) Stratakis, M.; Garcia, H. *Chem. Rev.* **2012**, *112*, 4469.
(16) Nasir Baig, R. B.; Varma, R. S. *Chem. Commun.* **2013**, *49*, 752.
(17) Gawande, M. B.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev*. **2013**, *42*, 3371.
(18) Wang, D.; Astruc, D. *Chem. Rev.* **2014**, *114*, 6949.
(19) Schätz, A.; Grass, R. N.; Kainz, Q.; Stark, W. J.; Reiser, O. *Chem. Mater*. **2010**, *22*, 305.
(20) Grass, R. N.; Athanassiou, E. K.; Stark, W. J. *Angew. Chem., Int. Ed*. **2007**, *46*, 4909.
(21) Nasir Baig, R. B.; Varma, R. S. *Green Chem*. **2012**, *14*, 625.
(22) Nasir Baig, R. B.; Varma, R. S. *Chem. Commun*. **2012**, *48*, 2582.
(23) Nasir Baig, R. B.; Varma, R. S. *Chem. Commun*. **2012**, *48*, 6220.
(24) Nasir Baig, R. B.; Nadagouda, M. N.; Varma, R. S. *Green Chem.* **2014**, *16*, 4333.
(25) Polshettiwar, V.; Baruwati, B.; Varma, R. S. *Chem. Commun.* **2009**, 1837.
(26) Nasir Baig, R. B.; Varma, R. S. *Curr. Org. Chem*. **2013**, *17*, 2227.
(27) Polshettiwar, V.; Baruwati, B.; Varma, R. S. *Green Chem.* **2009**, *11*, 127.
(28) Polshettiwar, V.; Varma, R. S. *Chem.—Eur. J*. **2009**, *15*, 1582.
(29) (a) Polshettiwar, V.; Varma, R. S. *Org. Biomol. Chem*. **2009**, *7*, 37. (b) Polshettiwar, V.; Nadagouda, M. N.; Varma, R. S. *Chem. Commun*. **2008**, 6318. (c) Vaddula, B. R.; Saha, A.; Leazer, J.; Varma, R. S. *Green Chem.* **2012**, *14*, 2133.
(30) Saha, A.; Leazer, J.; Varma, R. S. *Green Chem.* **2012**, *14*, 67.
(31) Nasir Baig, R. B.; Varma, R. S. *Ind. Eng. Chem. Res.* **2014**, *53*, 18625.
(32) Nasir Baig, R. B.; Varma, R. S. *RSC Adv.* **2014**, *4*, 6568.
(33) Nasir Baig, R. B.; Varma, R. S. *ACS Sustainable Chem. Eng*. **2014**, *2*, 2155.
(34) Gawande, M. B.; Rathi, A. K.; Nogueira, I. D.; Varma, R. S.; Branco, P. S. *Green Chem*. **2013**, *15*, 1895.
(35) Yinghuai, Z.; Kuijin, L.; Huimin, N.; Chuanzhao, L.; Stubbs, L. P.; Siong, C. F.; Muihua, T.; Peng, S. C. *Adv. Synth. Catal.* **2009**, *351*, 2650.
(36) Verma, S.; Nasir Baig, R. B.; Han, C.; Nadagouda, M. N.; Varma, R. S. *Chem. Commun.* **2015**, *51*, 15554.
(37) Mwilu, S. K.; Siska, E.; Nasir Baig, R. B.; Varma, R. S.; Heithmar, E.; Rogers, K. R. *Sci. Total Environ.* **2014**, *472*, 316.

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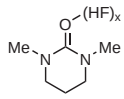
(1) Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem.* Soc. **2014**, *136*, 14381. (2) Okoromoba, O. E.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, *17*, 3975.



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ABOUT OUR COVER

Detail from ***Young Woman with Peonies***. Photo courtesy National Gallery of Art, Washington, DC.

Young Woman with Peonies (oil on canvas, 60 × 75 cm) was painted in 1870 by Frédéric Bazille (1841–1870). Born into a wealthy Montpellier family, his interest in art started early, and, because of his parents' insistence on him studying medicine, he moved to Paris in 1862 to study both. There, he quickly became a close friend of Monet, Renoir, and Sisley, who were fellow students in Charles Gleyre's art studio, and, together with them and with Pissarro, pioneered the Impressionist style of painting. Having failed his medical exams in 1864, Bazille then devoted his energy to painting fulltime.

The Impressionist movement aimed to capture on canvas fleeting moments in particular landscapes or in the lives of ordinary people in their natural settings (outside the artist's studio), to capture a generally realistic "impression" of the scene by highlighting the effects of light and shadows. This depiction, possibly of a flower vendor, is one of Bazille's last* and beautifully exemplifies this style. It was perhaps inspired by a famous painting, *Olympia* (at the Musée d'Orsay, Paris), executed and exhibited just a few years earlier by Édouard Manet, another of Bazille's friends and one of his influences.

This painting is part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

One of a pair of similar paintings executed by Bazille just a few months before he died. To find out more, visit* ***sigma-aldrich.com/acta493*

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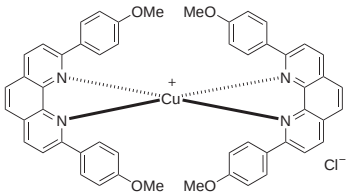

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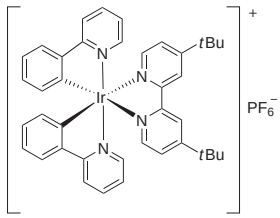

L511838
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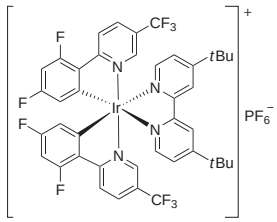
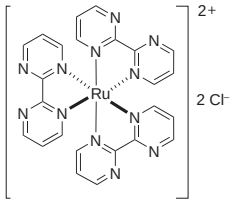


L511765
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$



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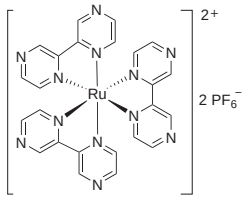

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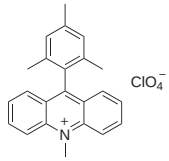
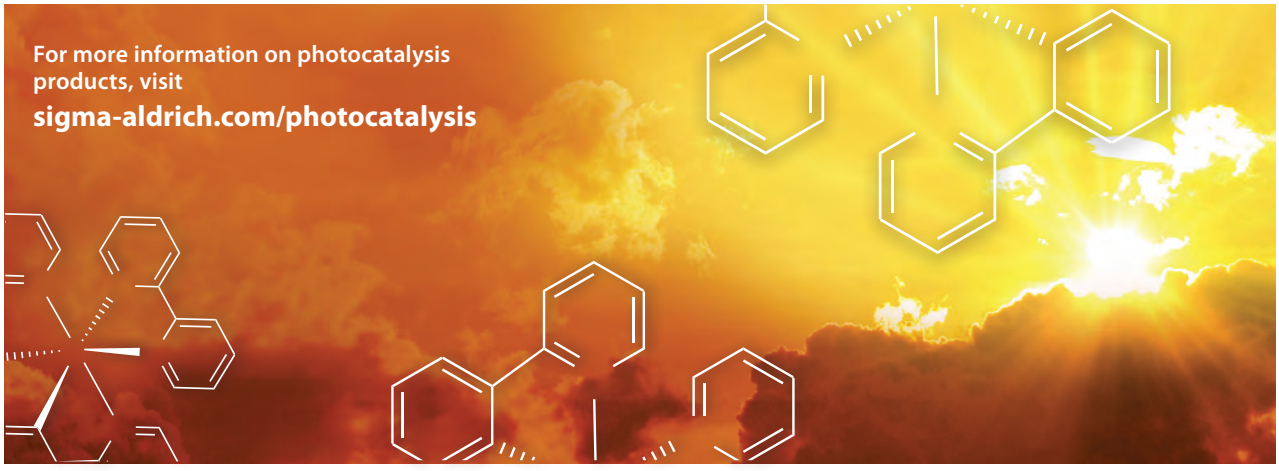


L511811
9-Mesityl-10-methylacridinium perchlorate

Reference:
Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Stephenson, C. R. J. *Aldrichimica Acta* **2014**, *47*, 15.



Photocatalytic C–F Reduction and Functionalization

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Keywords. hydrodefluorination; C–F functionalization; photocatalysis; partially fluorinated aromatics.

Abstract. Functionalized polyfluorinated aromatics have become an important group of molecules for pharmaceutical and industrial applications. However, facile access to such valuable molecules remains an unmet challenge. In this review, we present and discuss photocatalytic C–F functionalization, which is emerging as a straightforward and operationally simple path to access partially fluorinated aromatics.

Outline

1. Introduction

Fluorinated organic compounds have become an extremely important and valued class of molecules with amplified use as pharmaceuticals[1] and agrochemicals,[2] and with a number of industrial applications such as organic photovoltaics (i.e., OLEDs)[3] and liquid crystal molecules.[4] Following the invention in the 1950s of the first fluorine-containing pharmaceutical, fludrocortisone,[1a] the field has grown rapidly. In the last few decades, the frequency of fluorine incorporation within drugs has risen sharply. Starting from 2% of drugs that contained fluorine in 1970, this proportion has grown to about 25% of the total number of drugs available today.[1b] Furthermore, among the small-molecule drugs that have been approved by the U.S. Food and Drug Administration (FDA) in 2013, 33% contained a C–F bond and several of them (i.e., Adempas®, Gilotrif®, Tafinlar®, Tivicay®) contain a fluoroarene moiety in their structure. Within the crop sciences, the percentage of molecules containing organofluorine is at least 30%.[5]

Upon close inspection of the structures of medicinally and industrially important fluoroaromatics, some common features can be identified (**Figure 1**). Almost all of them are (i) considerably functionalized in order to perform a desired role, (ii) partially fluorinated not perfluorinated, and (iii) the fluoroaromatic moiety in each serves as a terminating unit except in very few cases. This latter observation is perhaps due to the unavailability of complex polyfluorinated arenes that can serve to elaborate the molecules further. Recently, more efforts have been devoted to the development of selective fluorination strategies that can be employed to access polyfluorinated arenes. These strategies include C–H fluorination[6] (**Scheme 1**, Part (a)) and cross-coupling reactions using both nucleophilic[7] and electrophilic[8] fluorine sources (Scheme 1, Part (b)). While these methods have significantly expanded the number of accessible fluorinated arenes, the need for arenes that contain either strategically prefunctionalized or specific directing groups in the starting arene limits the use of such methods. This limitation is most clear when polyfluorinated arenes are desired, which would require highly elaborated starting materials, or simply may not be accessible with directed fluorination.[6b,9] An alternate approach would be to start with a simple perfluoroarene in which C–F bonds already exist in all of the desired locations, and develop selective C–F functionalization reactions that utilize the undesired C–F bonds to construct the molecule. If successful, the perfluoroarene would serve as a synthetic lynchpin of polyfluorinated arenes. For instance, current syntheses of fluorinated azole fungicides share a common synthetic intermediate, **2a**,[1a] which is accessible in six steps from 1,3-dichlorobenzene (**2j**), a nonfluorinated commercially available starting material (**Scheme 2**).[10] Conceivably, direct C–F functionalization of the corresponding perfluoroarene, **2k**, followed by C–F reduction could significantly shorten the synthetic sequence. In this review, we present and discuss recent advances in the field of photocatalytic C–F reduction and functionalization of polyfluoroarenes, whereby new reactions are developed that can provide facile and rapid synthesis of functionalized polyfluorinated aromatics.

2. Hydrodefluorination

As an alternative to selective fluorination, hydrodefluorination (HDF) (Scheme 1, Part (c))[5,11] has emerged as one way to access polyfluorinated arenes. While the potential advantages of the HDF approach as compared to existing selective fluorinations make it attractive, a number

of challenges make its future less clear. Although the reduction of aryl iodides, bromides, and even chlorides is feasible,[11] cleavage of short and strong C_{aryl}–F bonds (**Figure 2**) has been a challenge. The extreme properties associated with C–F bonds make the design of efficient HDF catalysts quite challenging.

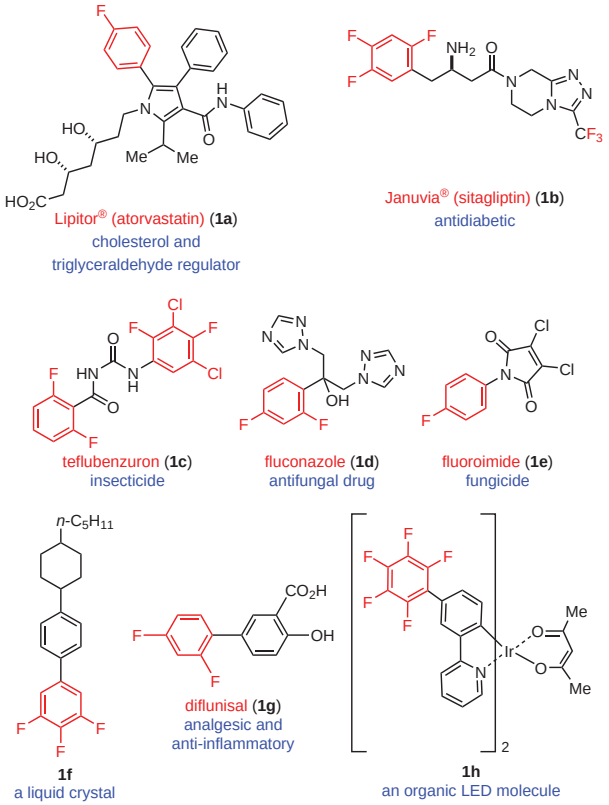
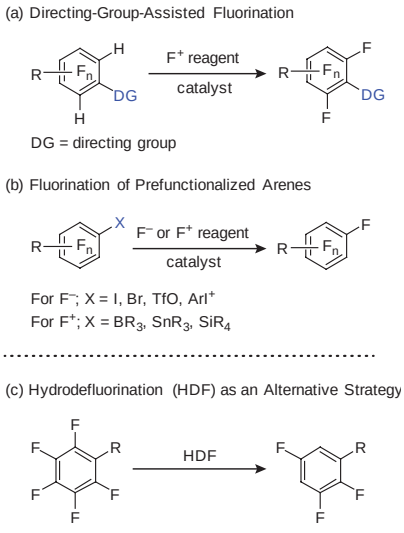


Figure 1. Pharmaceutically and Industrially Important Fluorinated Aromatics.

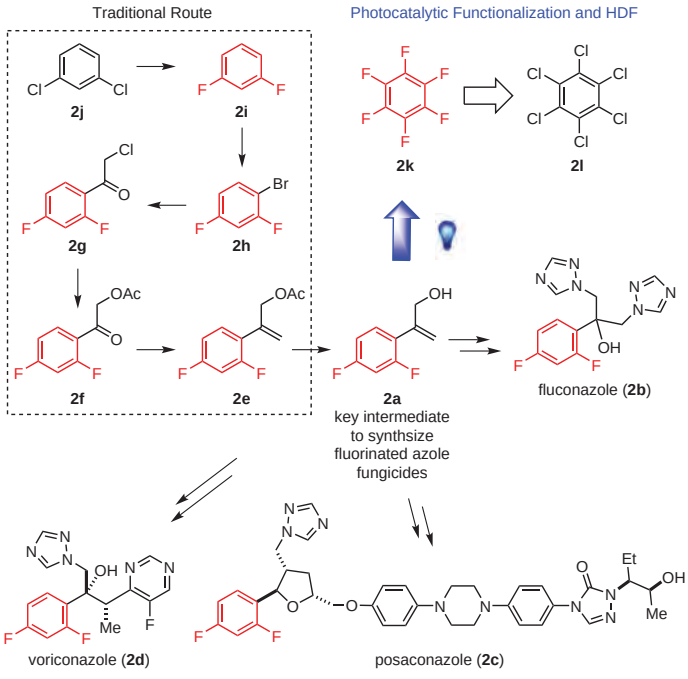


Scheme 1. Selective Fluorination Strategies and Hydrodefluorination (HDF).

Existing catalysts for HDF reactions often suffer from low turnover numbers (TONs) due to the formation of strong metal–fluorine bonds during the catalytic cycle. In their attempts to develop more robust HDF systems, chemists have utilized a number of strategies to deal with this dilemma. One solution is to use "fluorophilic" silyl[12] or aluminum[13] hydrides, in which the hydride-bearing atom itself can form a strong fluorine bond, liberating the catalyst from the thermodynamic well and increasing the overall exergonicity of the reaction. Nonetheless, most HDF systems still suffer from low TONs.[14]

2.1. Photocatalytic Hydrodefluorination

In recent years, photoredox catalysis[15] has become popular as a way to introduce a single electron into a molecule. The beauty of photocatalyzed single-electron chemistry is the ability to make reactive species catalytically and in a controlled manner in situ. Given this and indirect evidence from Stephenson's photocatalytic C_{aryl}–I reduction,[16] investigations have been undertaken to selectively reduce C–F bonds using visible light photocatalysis. The prediction was that *fac*-tris[2-phenylpyridinato-C^2,*N*]iridium(III) [*fac*–Ir(ppy)$_3$], which is a coordinatively saturated 18-electron complex and a potent reductant



Scheme 2. Actual and Potential Expedient Syntheses of Key Intermediate for Fluorinated Azole Fungicides. *(Ref. 1a,10)*

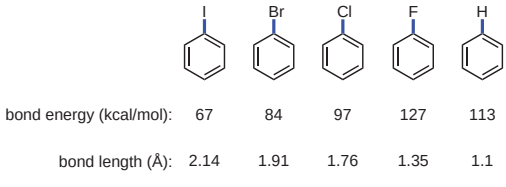


Figure 2. Comparison of Aryl–X Bond Lengths and Strengths.

[Ir(III)/(II), –2.19 V vs SCE][15a,17a] would be capable of transferring an electron to the perfluoroarene. This was expected to lead to fragmentation of the C–F bond to give a fluoride, perfluoroaryl radical, and ultimately the desired C–F reduced products after a hydrogen-atom transfer.[17b,c] Furthermore, the outer sphere nature of the electron transfer might avoid the problematic catalyst–fluoride intermediates and lead to higher TONs.

Pentafluoropyridine (**3b**) was chosen as the model substrate, because electron transfer was expected to be slightly exothermic between the reduced photocatalyst [Ir(III)/(II)] and **3b** (**3b**, V = –2.12 vs SCE) (**Figure 3**).[18] When the photocatalyst, **4a**, absorbs a photon in the visible region (**Scheme 3**), it is promoted to an excited state (**4b**).[15a] From this excited state, the photocatalyst can act as either a reductant or an oxidant.[15a] It was proposed that a single-electron transfer from the tertiary aliphatic amine (**4c**) to the excited state of the catalyst (i.e., reductive quenching) results in an amine radical cation (**4d**) and the reduced photocatalyst (**4e**). Intermediate **4e** engages in an outer-sphere electron transfer to the fluoroarene substrate, **3b**, to generate a perfluoroaryl radical anion, **4f**. Subsequent fluoride extrusion forms a perfluoroaryl radical (**4g**) which then abstracts a hydrogen atom from either the amine, **4c**, or amine radical cation, **4d**, leading to the desired reduced product, **4k**. The other results discussed in this review arise from the interception of the versatile key radical intermediate **4g** with π bonds of alkenes, arenes, and alkynes. The interception with alkynes has been employed to understand the underlying controlling factors of energy vs electron transfer, by which *E*- or *Z*-alkene products can be obtained by the judicious choice of photocatalyst. The use of the inexpensive and easy-to-handle *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) as the reductant alleviates the need for fluorophilic metal hydrides, and makes this methodology operationally simple.

2.2. Mono(hydrodefluorination)

Under the optimized conditions, both electron-deficient perfluoro-heteroarenes and electron-rich fluorinated heterocycles underwent smooth mono-HDF to form **5a**, **5f**, and **5h**, respectively (**eq 1**).[19] The

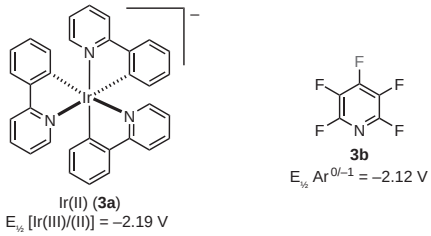
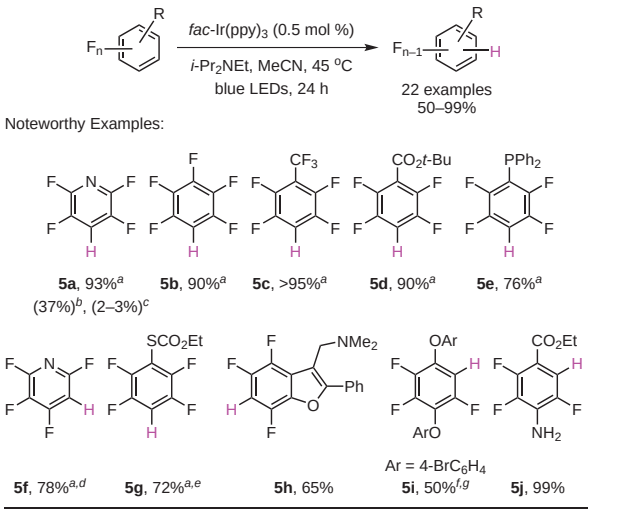
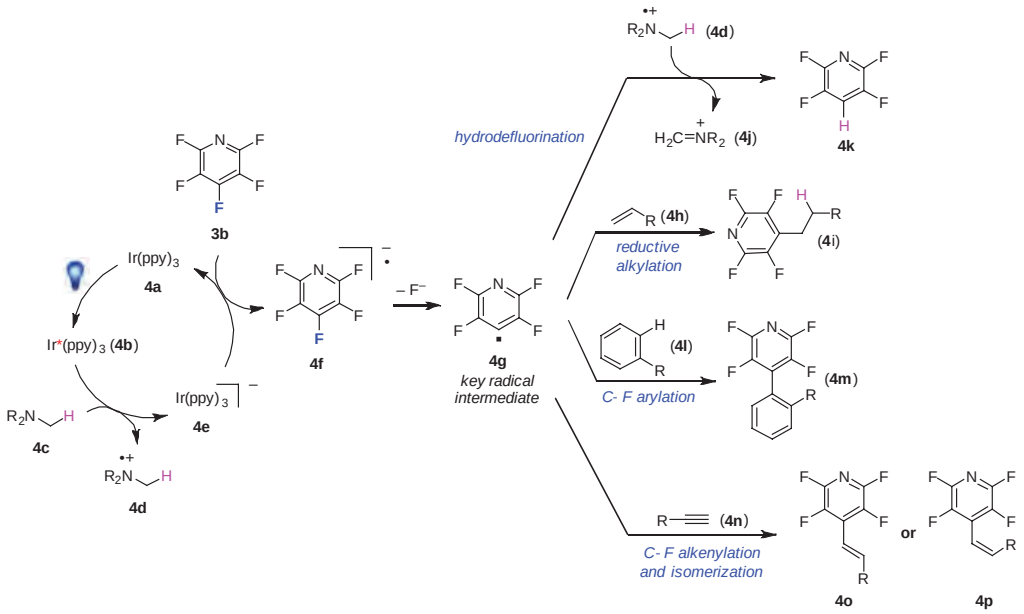


Figure 3. Comparison of Catalyst and Substrate Reduction Potentials. *(Ref. 18)*



[a] ^{19}F NMR yield. [b] Obtained with $Ru(bpy)_3Cl_2$. [c] Obtained with $Ru(bpm)_3Cl_2$. [d] From 3-chlorotetrafluoropyridine. [e] Contains 10% di-HDF product. [f] 65 °C, 72 h. [g] At 70% conversion.

eq 1 *(Ref. 19)*



Scheme 3. Plausible Mechanistic Pathways to HDF and Reductive Alkylation, Arylation, and Alkenylation.

reaction demonstrated remarkable functional group tolerance, and had a broad substrate scope. It is worth noting that the chlorine atom in 3-chlorotetrafluoropyridine was preferentially fragmented leading to **5f**, while the distant bromines in the precursor to **5i** survived the HDF with only a trace amount of bromine loss. Tertiary aliphatic amines (**5h**) and even phosphines (**5e**) also survived the hydrodefluorination reaction. During the optimization trials, it was found that the two other, significantly less reducing photocatalysts—$Ru(bpy)_3Cl_2$ (V = −1.33 vs SCE) and $Ru(bpm)_3Cl_2$ (V = −0.91 vs SCE)[20] (bpy = 2,2'-bipyridine, bpm = 2,2'-bipyrimidine)—also facilitated HDF (leading to **5a**), albeit at a much slower rate. This phenomenon suggests that there are other unexplored factors governing these electron transfers apart from the reduction potentials alone.

2.3. Di- and Tri(hydrodefluorination)

Often, the rates between the first and second reductions were substantially different such that one could obtain either *mono*-, or *di*-HDF products by simply varying the amount of the amine reductant and reaction time (**eq 2**).[19] The regiochemistry of HDF is primarily dictated by the electronics of the aromatic system in the starting material, though it is worth noting that there can be a steric contribution, as seen by comparing the rate difference between the di-HDF of the methyl (**6d**) and *tert*-butyl (**6e**) esters of perfluorobenzoic acid.

Our group also investigated the robustness of the catalytic system. Repeated additions of pentafluoropyridine and diisopropylethylamine to the photocatalytic system achieved an unprecedented TON of 22,550—the highest among the TONs for all of the HDF systems reported to date. In addition, by utilizing pentafluoropyridine and octafluoronaphthalene, we have demonstrated that the kinetics of the reaction could be further enhanced by utilizing a flow system.[19] Collectively, the ability to perform the photocatalytic reaction in flow and at very low loading of a commercially available catalyst might allow the process to be scaled.

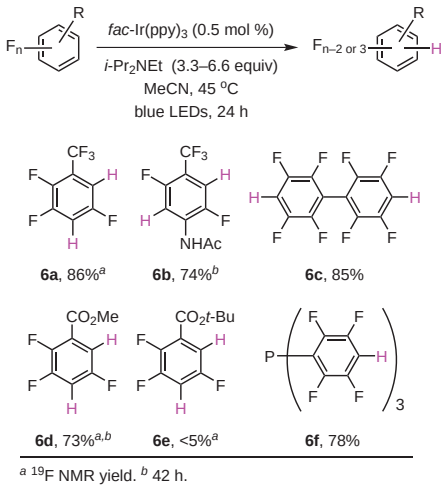
3. Alkylation of Fluoroarenes

Having demonstrated that photoredox catalysis can be employed to break the robust C–F bond and access the relatively unexplored perfluoroaryl radical, we attempted to exploit this understanding to develop more elaborate C–F functionalization reactions. To this end, the first photocatalytic C–F alkylation was published in 2015.[21] Carbon-centered radicals possess a remarkable bond-forming capability[22] with unactivated π bonds that are sterically congested and are generally considered inert under most reaction conditions. Key to utilizing radicals in this manner is their controlled generation. In general, the idea was to intercept with alkenes the perfluoroaryl radical as it is formed. This would result in a more stable, longer-lived alkyl radical, which would then undergo the subsequent H-atom abstraction to afford a net hydroperfluoroarylation of the alkene. Given the vast number of alkenes available, this approach was expected to lead to a large variety of alkylated polyfluoroarenes.

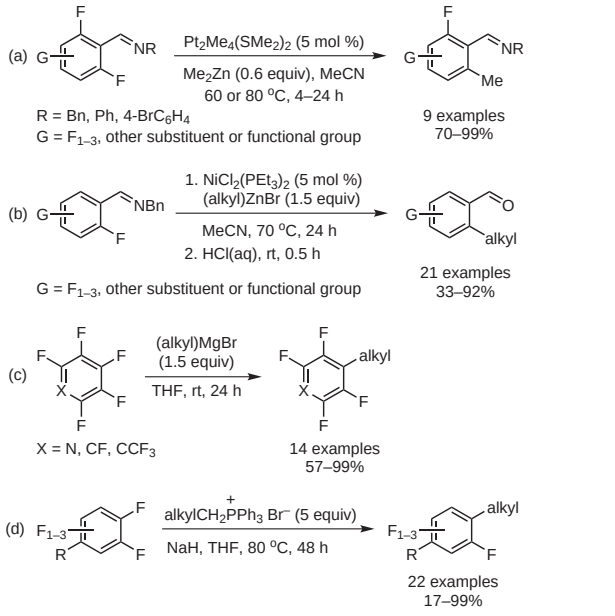
In the last few years, several groups have successfully alkylated highly fluorinated arenes. Love and co-workers have demonstrated the directing-group-assisted ortho alkylation of polyfluoroarenes with Pt[23] and later with Ni[24] based catalysts in the presence of a benzyl imine directing group (**Scheme 4**, Parts (a) and (b)). In 2014, Li's group showed that the direct addition of alkyl Grignard reagents to perfluoroarenes was also possible (Scheme 4, Part (c)).[25] More recently, Wu's team developed a regioselective alkyl transfer from phosphonium ylides to perfluoroarenes (Scheme 4, Part (d)).[26] While these approaches are making inroads toward selective C–F alkylation, there is still an urgent need to develop new synthetic methods that provide access to complex alkylated fluoroarenes.

3.1. Photocatalytic C–F Alkylation of Fluoroarenes

With the goal of developing selective C–F alkylations, our group found that a variety of perfluoroarenes engaged unactivated alkenes to give alkylated products.[21] In general, since the perfluoroaryl radical was anticipated to be extremely unstable and consequently highly reactive,[27] one might have expected that the reaction would be poorly regioselective with respect to the alkene. The addition, however, takes place with excellent selectivity when there are differences in the substitution patterns of the alkene, with addition occurring at the less



eq 2 *(Ref. 19)*



Scheme 4. Previous Alkylation Strategies of Fluoroaromatics. *(Ref. 23–26)*

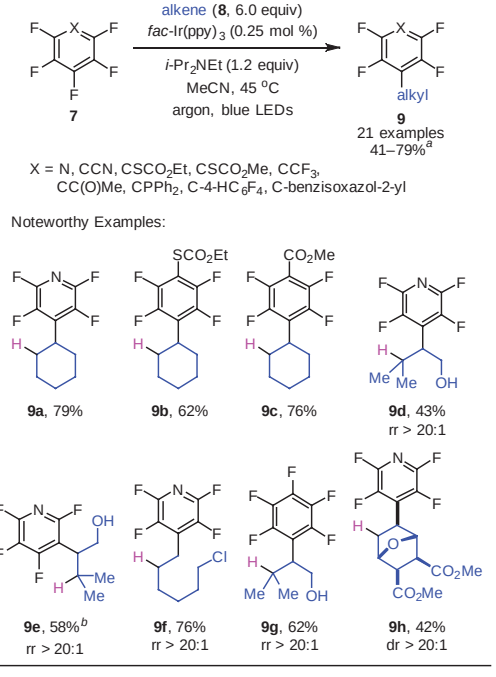
substituted carbon (**9d–f**) of the alkene (**eq 3**). The complementary reactivity of S_NAr chemistry and photocatalysis was demonstrated by subjecting 3-chlorotetrafluoropyridine to the photocatalytic reductive alkylation reaction, which results in the functionalization of the 3-chloro position while keeping the 4-fluoro intact (**9e**). In contrast, S_NAr substitution on this same precursor would be expected to occur at the C-4 position.[28] Survival of the remote alkyl chloride of **9f** is also noteworthy, and speaks to the functional group compatibility of the photocatalytic reaction.

A common disadvantage of previous C–F alkylation reactions was the incremental increase in complexity of the final products, which arises as a result of alkylating reagents that are of low complexity. In this regard, the use of unmodified alkenes presents enormous opportunity to access coupled products that are stereochemically dense in a single step, since sophisticated alkenes are ubiquitous. This feature makes the photocatalytic reductive alkylation reaction extraordinarily versatile. For instance, a [4 + 2] adduct derived from furan has been satisfactorily coupled with pentafluoropyridine, yielding the product, **9h**, which contains five stereocenters—two of them base-labile—three cycles, and a bridging oxygen.

The S_NAr reaction takes advantage of the highly fluorinated nature of perfluoroarenes to simultaneously elaborate the molecules and reduce their fluorine content to access sophisticated fluoroarenes with just 2–3 fluorines. It was initially suspected that the fluorines on the arene ring activate the substrate towards reduction and that the removal of fluorine would deactivate the substrate towards reduction, and thus it was not clear that subsequent photochemical C–F functionalizations would take place with sufficient rates to be useful on substrates with fewer fluorine atoms. A series of substrates containing rings with three fluorine atoms were synthesized and subjected to the reaction. After substitution of the most electronically activated 4 position, photocatalytic functionalization moved to the C–F bond adjacent to the electron-withdrawing group or atom (**eq 4**).[21] The ability to perform photocatalytic C–F functionalizations on previously elaborated substrates would thus allow rapid access to structurally complex, polyfluorinated arenes with diverse functionality.

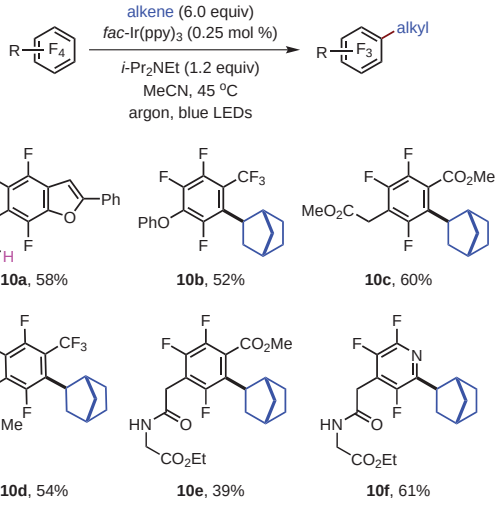
The photochemical functionalization and S_NAr reactions of perfluoroarenes exhibit complementary selectivities (**Scheme 5**).[21,28,29] This phenomenon was demonstrated by subjecting substituted fluoroarenes **11a** and **11b**, which are themselves products of S_NAr chemistry,[28] to the photochemical alkylation conditions (**Scheme 6**).[21]

Densely functionalized arenes with a reduced number of fluorines are a challenging target in drug discovery.[1c] Subsequent photocatalytic HDF of the products could provide access to additional valuable partially fluorinated arenes. Thus, commercially available perfluoroarenes (**13a–d**) were subjected to the S_NAr reaction, giving rise to elaborated perfluoroarenes (**Scheme 7**).[21,28] Next, the elaborated substrates were photocatalytically functionalized to obtain alkylated arenes. Finally, they were subjected to photocatalytic HDF to further reduce the fluorine content, supplying structurally complex difluorinated arenes (**13e–j**).

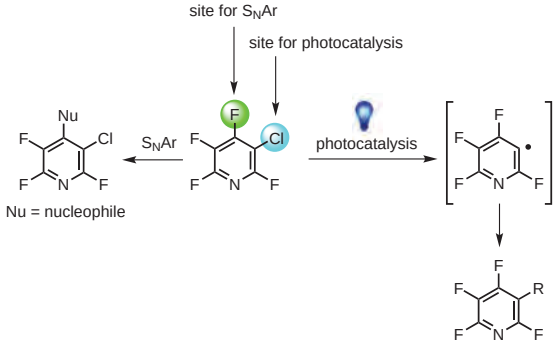


[a] The regioisomeric (rr) and diastereomeric ratios (dr) were determined with respect to the alkene by ^{1}H NMR of the crude reaction mixture after workup. [b] From 3-chlorotetrafluoropyridine.

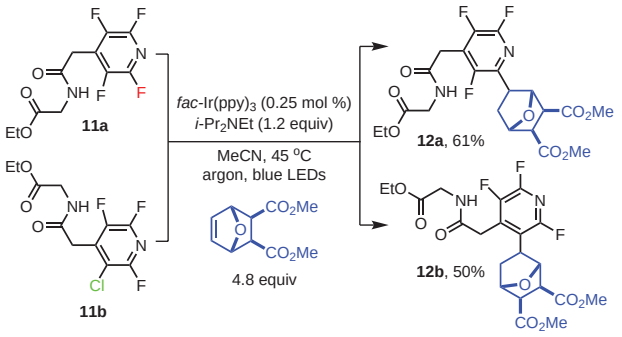
eq 3 *(Ref. 21)*



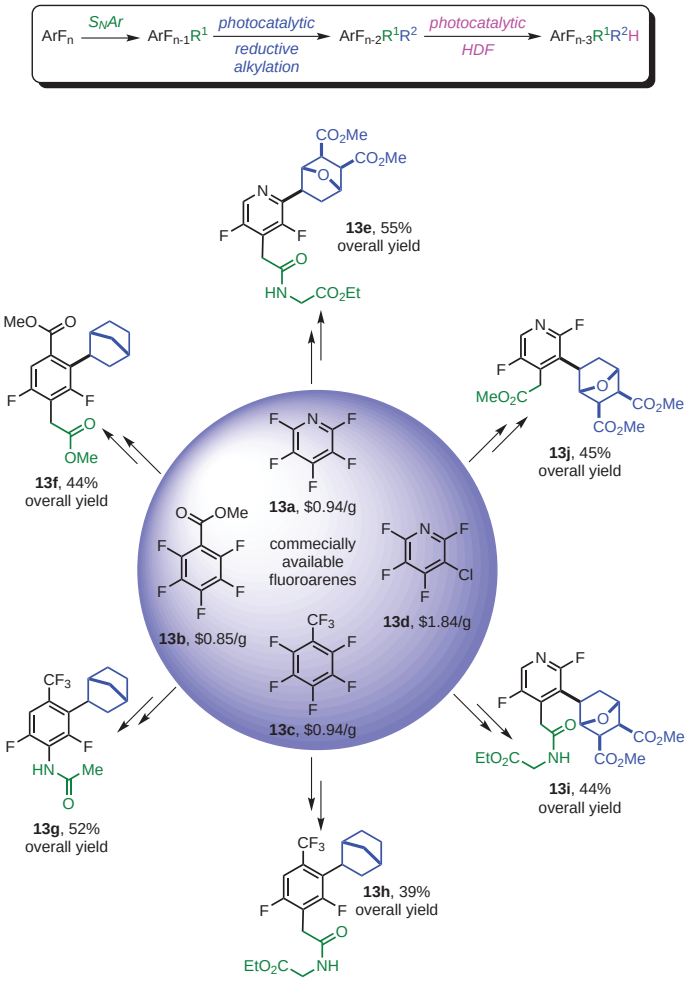
eq 4 *(Ref. 21)*



Scheme 5. Complementary Nature of S_NAr and Photocatalysis. *(Ref. 21,28,29)*



Scheme 6. Accessing Complementary Regioisomers by Using Differential Reactivities of C–X Bonds. *(Ref. 21)*



Scheme 7. Sequential S_NAr and Photocatalysis as a Succinct and Versatile Way to Access Complex, Partially Fluorinated Arenes. *(Ref. 21,28)*

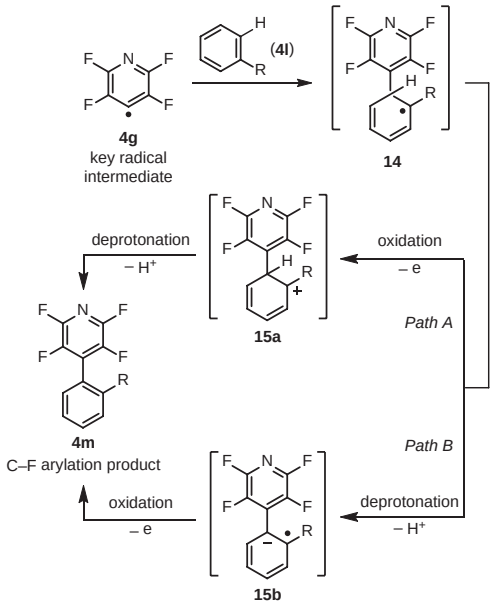
The sequence took place with acceptable yields and with excellent regio- and diastereoselectivities, and demonstrated how structurally complex difluoro aromatics can be obtained in a straightforward manner from commercially available perfluoroarenes.

4. Arylation of Fluoroarenes

Having demonstrated the ability to perform the reductive alkylation of a C–F bond, our group investigated next the possibility of performing an oxidation of the incipient alkyl radical rather than the hydrogen-atom transfer that takes place in the alkylation reaction. It was expected that accomplishing an oxidation might be difficult, since the conditions used to accomplish the C–F fragmentation must produce a strong reductant, at least transiently. As a starting point, hydrogen arenes were chosen, and were anticipated to re-aromatize after temporary loss of aromaticity, which was expected to serve as a driving force for the oxidation. Careful consideration of electronic factors suggested that oxidation of intermediate **14** could happen either before (*Path A*) or after (*Path B*) the deprotonation step (**Scheme 8**).[29] The actual path taken would depend on the nature of the two arene partners. Starting with the HDF conditions, the reaction was optimized to produce appreciable amounts of the C–F arylation product, demonstrating the first catalytic dual C–F, C–H functionalization to obtain polyfluorinated biaryls,[29] though other less direct methods exist (**eq 5**).[30]

4.1. Photocatalytic Arylation

Unlike reductive alkylation, the desired arylation of fluoroarenes is expected to end with oxidative re-aromatization. Since there is no hydrogen-atom abstraction during the generation of the desired product, it was speculated that the amine might simply serve as a transient electron donor and a base. Consequently, substoichiometric amounts of amine base would be sufficient for the reduction of the catalyst, *fac*-Ir(ppy)$_3$, if it were liberated from the HF salt. Given that the free amine, *i*-Pr$_2$NEt, can act as a hydrogen atom source as well, the amount of the HDF product could be controlled by keeping the amine



Scheme 8. Proposed Mechanism for C–F Arylation. *(Ref. 29)*

content low and lowering the temperature. An inorganic base, $KHCO_3$, was found to be optimal for scavenging the HF byproduct. Good-to-modest yields were obtained for a variety of fluoroarenes and electron-rich and electron-poor H-arenes that were coupled together (**eq 6**).[29] The ability of the perfluoroaryl radical to form highly sterically congested C–C bonds (**16d**) is particularly noteworthy and is rivaled by few methods. Consistent with that observed in the photocatalytic HDF (**5f**) and photochemical C–F alkylation chemistry (**9e**), C–Cl fragmentation (**16h**) takes place selectively over C–F fragmentation. Interestingly, some basic heterocycles showed *anti*-Minisci selectivity (**16f**,**g**) demonstrating a divergence from typical radical addition to basic heterocycles (**Figure 4**).[29] This difference may be due to the differences in pH between the photocatalytic C–F, C–H arylation and typical Minisci conditions, which are strongly acidic. The acidic matrix protonates the basic heterocycles and causes a polarity reversal.

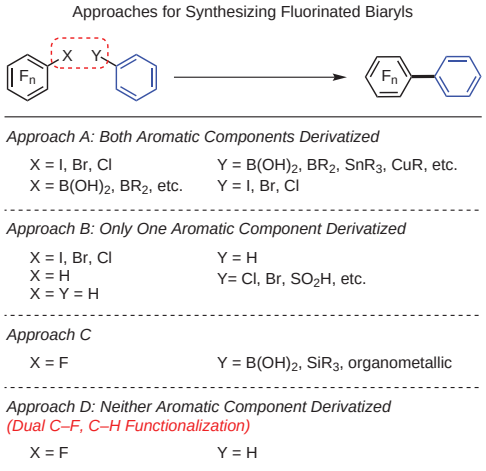
Given the mildness of the reaction and the ability to construct sterically congested biaryls, it was envisioned that the reaction would be ideal for late-stage functionalization. This could ease the difficult fluoroarene installation and offer an alternative route to some of the lengthy procedures to access fluorinated biaryls. In the case of heavily functionalized H-arenes, which would likely be the more valuable component of the reaction mixture, it is logical to use the perfluoroarene as the excess reagent (**eq 7**).[29]

Recall that the further photocatalytic alkylations and reductions were possible on the substrates with a reduced number of fluorines (see Scheme 7). Similarly, we wanted to demonstrate the ability to access *di*-fluorinated biaryls. The commercially available fluoroarenes were subjected to sequential substitution, arylation, and HDF. Electronically determined regioselectivity was observed during the HDF reaction, while some other competing phenomena gave rise to minor regioisomers (**Scheme 9**).[29]

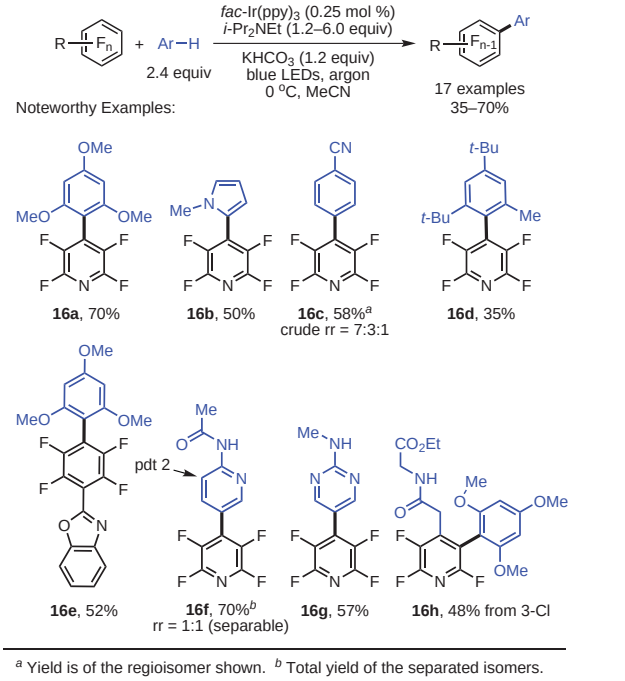
5. Photocatalytic Alkenylation and Energy Transfer

The work described so far in this review is a consequence of photocatalyst-induced electron transfer that results in either C–F reductions or C–F functionalizations, leading to new C–C bonds. However, it has been shown that the excited state of the Ir-based photocatalysts can also be quenched via an energy-transfer process rather than electron transfer in cases where a styrenyl-like system is present.[31] However, the reactions employing both electron transfer and energy transfer are rather rare, presumably due to a diminutive understanding of the factors that govern these two fundamentally different processes. Among the very few examples of sequential electron and energy transfers,[32] chemists have utilized strategies such as a solvent change to favor electron transfer or a switch to photocatalysts of insufficient energy to prevent energy transfer.[32,33] In order to gain a better insight into how to switch between these two mechanistically distinct photoquenching processes, a novel hydrofluoroarylation reaction of alkynes was conceived. Toward that end, the work on selective energy transfer was integrated with the ability to perform C–F functionalization via photocatalytic electron transfer.[32,34] The proposed reaction was ideal, because the available photocatalysts that were sufficiently reducing to induce C–F fragmentation were also sufficiently energetic to facilitate the isomerization event, effectively removing the known strategies for separating these two mechanistic processes.

Additionally, we were interested in investigating an underexplored facet of photocatalytic energy transfer, specifically, the rate of energy transfer as a function of intermolecular distance between the substrate



eq 5 *(Ref. 30)*



eq 6 *(Ref. 29)*

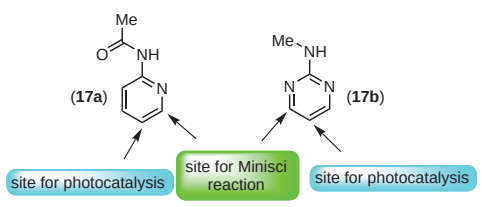
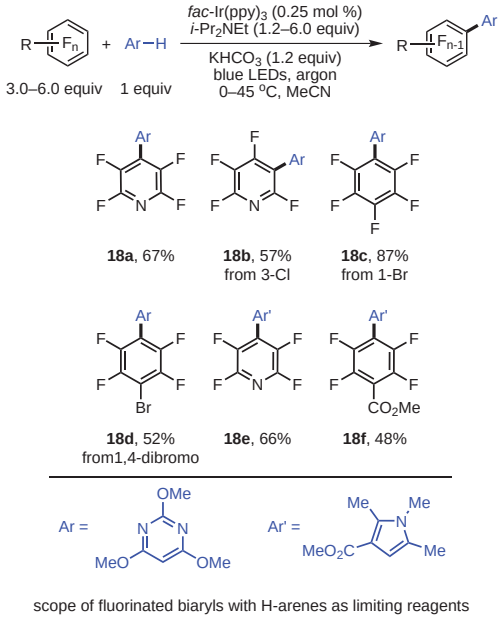


Figure 4. Observed *anti*-Minisci Selectivity. *(Ref. 29)*



scope of fluorinated biaryls with H-arenes as limiting reagents

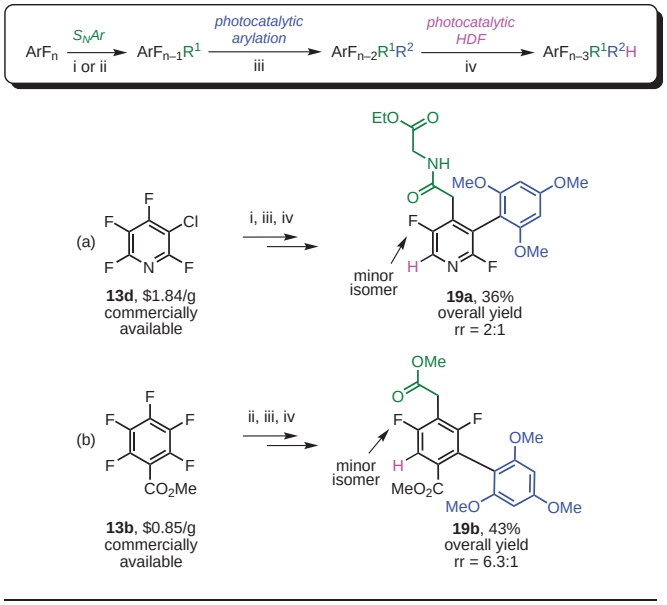
eq 7 *(Ref. 29)*

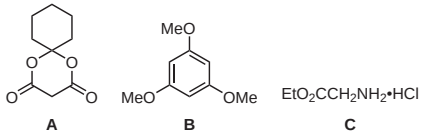
and photocatalyst.[35] Given that both Förster's[36] and Dexter's[37] energy-transfer processes are known to be highly dependent on internuclear distance, we anticipated that the steric volume of the photocatalyst could potentially serve as a handle that would allow us to turn energy transfer on or off. The key radical intermediate, **4g**, generated via electron transfer would add to the alkyne to give a vinyl radical, **20a**, followed by H-atom abstraction to give the alkenylated product, **20b** (**Scheme 10**).[35] An energy-transfer process could then lead to a selective double-bond isomerization to obtain the *Z* isomer, **4p**, preferentially.

First, we carried out optimizations that focused on achieving high yields of the alkenylated product, regardless of *E* or *Z* geometry. Incremental addition of amine and reduced temperature suppressed the formation of the undesired (HDF) product.

Next, to probe the mechanistic details, a bulky alkyne, *tert*-butylacetylene (**21**, **Scheme 11**) was used because of its strong kinetic preference for the *E* isomer (**22a**) and large preference for the *Z* isomer (**22b**) at the photostationary state.

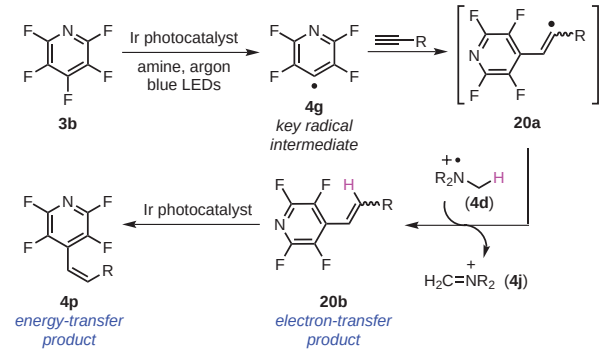
The observation of sensitized isomerization of stilbenes with planar sensitizers, such as benzophenone and xanthone, had revealed a strong correlation between the emissive energy of the sensitizer and the *Z*:*E* ratio.[38] In contrast to such planar sensitizers, Ir-based photocatalysts with three bidentate ligands are approximately spherical, and a plot of log(*Z*:*E*) vs the photocatalyst's emissive energy revealed no correlation.[38] The plot of log(*Z*:*E*) as a function of the radius of the catalyst approximated as a sphere shows a linear correlation, suggesting



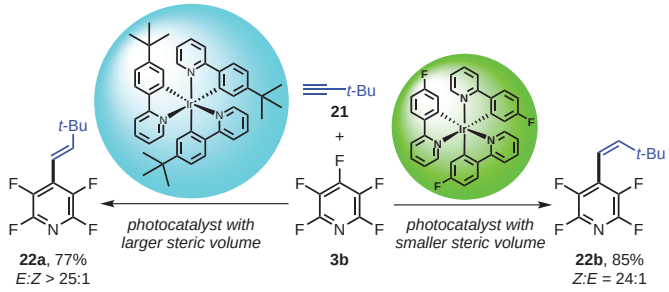


i. (a) **A**, *i*-Pr_2NEt; (b) **C** (93%). ii. (a) **A**, *i*-Pr_2NEt; (b) HCl, **MeOH** (>99%)
iii. **B**, *fac*-Ir(ppy)$_3$ (0.25 mol %), *i*-Pr_2NEt, MeCN, blue LEDs, argon, 0 °C (48 or 52%)
iv. *fac*-Ir(ppy)$_3$ (0.25 mol %), *i*-Pr_2NEt, MeCN, blue LEDs, argon, 45 °C (81 or 83%)

Scheme 9. Elaboration via Synergistic S_NAr and Photocatalysis. *(Ref. 29)*



Scheme 10. Photocatalytic Alkenylation and Isomerization via Subsequent Electron- and Energy-Transfer Processes. *(Ref. 35)*



Scheme 11. Observed Alkenylation *E* or *Z* Switch by Switching Photocatalysts with Different Steric Volumes. *(Ref. 35)*

that the propensity to undergo energy transfer diminishes as the volume of the catalyst increases. This valuable observation should lead chemists to consider the size of photocatalysts as a sensitive parameter that can be employed to switch between photocatalyzed processes regardless of emissive energy.

6. Conclusions and Outlook

In summary, photocatalysis is becoming a powerful tool to help solve the central problem of C–F functionalization as it pertains to accessing polyfluorinated arenes. It has been shown that photocatalysis provides access to the reactive perfluoroaryl radical, and we have demonstrated several strategies for intercepting the radical with a variety of coupling partners. The use of a commercially available photocatalyst and a tertiary aliphatic amine furnished the highest reported TON for an HDF reaction without any need for metal hydrides. The photocatalytic reactions discussed in this review take place under mild conditions and display excellent functional group compatibility and broad substrate scope. The reactions open a new avenue to synthesize complex polyfluorinated arenes. While some yields of the C–F functionalization products are modest, they are offset by the fact that the reagents need no prefunctionalization and come directly from commercial sources, allowing an unprecedented level of complexity to be achieved in just a few synthetic steps, and creating many opportunities for chemists who are involved in lead discovery programs.

7. References

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(2) (a) Selby, T. P.; Bereznak, J. F.; Bisaha, J. J.; Ding, A. X.; Gopalsamuthiram, V.; Hanagan, M. A.; Long, J. K.; Taggi, A. E. Fungicidal Substituted Azoles. World Pat. Appl. WO 2009137651 A8, March 18, 2010. (b) Gregory, V.; Taggi, A. E. Fungicidal Mixtures. World Pat. Appl. WO 2011056463 A2, May 12, 2011.

(3) (a) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. *Adv. Mater.* **2003**, *15*, 1455. (b) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1832.

(4) Hird, M. *Chem. Soc. Rev.* **2007**, *36*, 2070.

(5) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

(6) (a) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956. (b) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081.

(7) (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134. (c) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292.

(8) (a) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150.

(9) Weaver, J.; Senaweera, S. *Tetrahedron* **2014**, *70*, 7413.

(10) (a) Blundell, P.; Ganguly, A. K.; Girijavallabhan, V. M. *Synlett* **1994**, 263. (b) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Desai, J. A.; Ganguly, A. K.; Hare, R. S.; Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2023.

(11) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

(12) Aizenberg, M.; Milstein, D. *Science* **1994**, *265*, 359.

(13) Arndt, P.; Spannenberg, A.; Baumann, W.; Burlakov, V. V.; Rosenthal, U.; Becke, S.; Weiss, T. *Organometallics* **2004**, *23*, 4792.

(14) Kuehnel, M. F.; Lentz, D.; Braun, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328.

(15) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Ischay, M. A.; Yoon, T. P. *Eur. J. Org. Chem.* **2012**, 3359. (d) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

(16) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854.

(17) (a) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143. (b) Konovalov, V. V.; Laev, S. S.; Beregovaya, I. V.; Shchegoleva, L. N.; Shteingarts, V. D.; Tsvetkov, Y. D.; Bilkis, I. *J. Phys. Chem. A* **2000**, *104*, 352. (c) Shteingarts, V. D. *J. Fluorine Chem.* **2007**, *128*, 797.

(18) Beletskaya, I. P.; Artamkina, G. A.; Mil'chenko, A. Y.; Sazonov, P. K.; Shtern, M. M. *J. Phys. Org. Chem.* **1996**, *9*, 319.

(19) Senaweera, S. M.; Singh, A.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 3002.

(20) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.

(21) Singh, A.; Kubik, J. J.; Weaver, J. D. *Chem. Sci.* **2015**, *6*, 7206.

(22) Lalevée, J.; Allonas, X.; Fouassier, J.-P. *J. Org. Chem.* **2005**, *70*, 814.

(23) (a) Wang, T.; Alfonso, B. J.; Love, J. A. *Org. Lett.* **2007**, *9*, 5629. (b) Sun, A. D.; Love, J. A. *J. Fluorine Chem.* **2010**, *131*, 1237.

(24) Sun, A. D.; Leung, K.; Restivo, A. D.; LaBerge, N. A.; Takasaki, H.; Love, J. A. *Chem.—Eur. J.* **2014**, *20*, 3162.

(25) Sun, Y.; Sun, H.; Jia, J.; Du, A.; Li, X. *Organometallics* **2014**, *33*, 1079.

(26) Lu, W.; Gao, J.; Yang, J.-K.; Liu, L.; Zhao, Y.; Wu, H.-C. *Chem. Sci.* **2014**, *5*, 1934.

(27) Birchall, J. M.; Hazard, R.; Haszeldine, R. N.; Wakalski, A. W. *J. Chem. Soc. (C)* **1967**, 47.

(28) Senaweera, S. M.; Weaver, J. D. *J. Org. Chem.* **2014**, *79*, 10466.

(29) Senaweera, S.; Weaver, J. D. *J. Am. Chem. Soc.* **2016**, *138*, 2520.

(30) (a) DePasquale, R. J.; Tamborski, C. *J. Org. Chem.* **1969**, *34*, 1736. (b) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350. (c) Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1000. (d) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *J. Fluorine Chem.* **2002**, *117*, 115. (e) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073. (f) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915. (g) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346. (h) Lindner, S.; Bräse, S.; Masters, K.-S. *J. Fluorine Chem.* **2015**, *179*, 102. (i) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276. (j) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377. (k) Meyer, A. U.; Slanina, T.; Yao, C.-J.; König, B. *ACS Catal.* **2016**, *6*, 369. (l) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978. (m) Nakamura, Y.; Yoshikai, N.; Ilies, L.; Nakamura, E. *Org. Lett.* **2012**, *14*, 3316. (n) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Organometallics* **2014**, *33*, 3669. (o) Sun, A. D.; Love, J. A. *Org. Lett.* **2011**, *13*, 2750.

(31) (a) Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2016**, *138*, 1040. (b) Kumarasamy, E.; Raghunathan, R.; Jockusch, S.; Ugrinov, A.; Sivaguru, J. *J. Am. Chem. Soc.* **2014**, *136*, 8729. (c) Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 12064. (d) Farney, E. P.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 793. (e) Zou, Y.-Q.; Duan, S.-W.; Meng, X.-G.; Hu, X.-Q.; Gao, S.; Chen, J.-R.; Xiao, W.-J. *Tetrahedron* **2012**, *68*, 6914. (f) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (g) Chen, Y.; Kamlet, A. S.; Steinman, J. B.; Liu, D. R. *Nat. Chem.* **2011**, *3*, 146.

(32) Lin, Q.-Y.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2014**, *79*, 10434.

(33) Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602.

(34) (a) Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, *136*, 5275. (b) Fabry, D. C.; Ronge, M. A.; Rueping, M. *Chem.—Eur. J.* **2015**, *21*, 5350. (c) Rackl, D.; Kreitmeier, P.; Reiser, O. *Green Chem.* **2016**, *18*, 214.

(35) Singh, A.; Fennell, C. J.; Weaver, J. D. *Chem. Sci*. **2016**, Advance Article, DOI: 10.1039/C6SC02422J.
(36) Förster, T. *Ann. Phys. (Berlin, Ger.)* **1948**, *437*, 55.
(37) Dexter, D. L. *J. Chem. Phys.* **1953**, *21*, 836.
(38) (a) Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. *J. Am. Chem. Soc.* **1964**, *86*, 3197. (b) Klán, P.; Wirz, J. Introduction. In *Photochemistry of Organic Compounds: From Concepts to Practice*; Wiley: Chichester, U.K., 2009; p 1.

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Reference:
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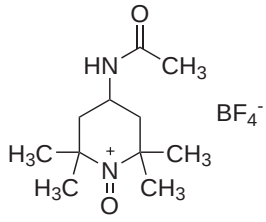

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Reference:
Leadbeater, N. E.; Bobbitt, J. M. *Aldrichimica Acta* **2014**, *47*, 65.

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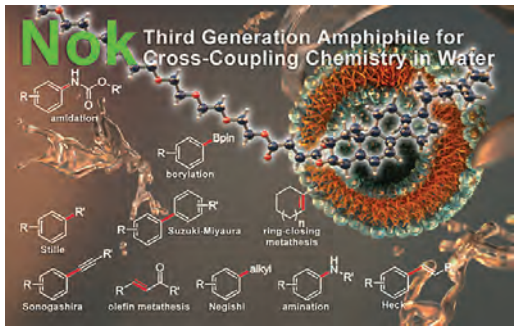

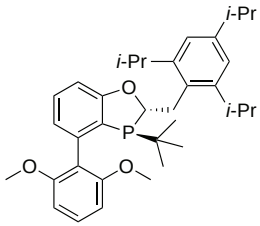

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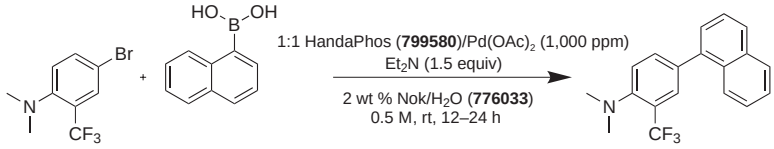

Suzuki–Miyaura cross-coupling reactions run under environmentally friendly conditions.

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Handa, S.; Andersson, M. P.; Gallou, F.; Reilly, J.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4914.

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Recent Enabling Technologies for Diazomethane Generation and Reactions

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Keywords. diazomethane; C1 building block; flow chemistry; hazardous chemistry; membrane reactors.

Abstract. Diazomethane is one of the most versatile reagents in organic synthesis; however, its use is accompanied with certain hazards. To overcome the explosion risk associated with distillation methods employed for the preparation of diazomethane, new techniques for its safe and convenient production and handling are continually being developed. This review highlights the state of the art of diazomethane generation and consumption, in particular by employing flow chemistry principles and techniques.

Outline

1. Introduction

The most time- and atom-efficient synthetic routes frequently require the use of highly reactive, often low-molecular-weight reagents. One such reagent is diazomethane (CH_2N_2), which is an exceptionally powerful and versatile C1 building block in organic synthesis.[1,2] Despite the hazards associated with its generation and utilization, CH_2N_2 is among the most versatile and useful reagents in organic synthesis (**Scheme 1**).[1] Carboxylic acids, as well as various O, N, and S nucleophiles, are directly converted into the corresponding methyl esters or methylated derivatives, respectively. Diazomethane is also used for the synthesis of α-diazoketones, the homologation of ketones and carboxylic acids (Arndt–Eistert reaction), in palladium-catalyzed cyclopropanations, and as a dipole in [3 + 2] cycloadditions to generate N-heterocycles. Reactions with CH_2N_2 are typically fast and clean, and proceed under mild conditions, often producing nitrogen as the sole byproduct.

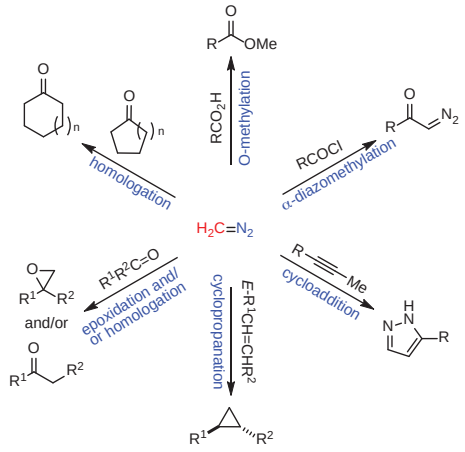
When the synthesis of hazardous reagents is contemplated, the most efficient form of production and use is the in situ approach, where the reagents are generated from benign precursors—preferably inside the closed environment of a flow reactor—and are subsequently directly converted into more advanced, nonhazardous products. In continuous-flow technology, the total volume of material processed at any time is drastically reduced; therefore, the safety of the process is generally significantly increased when compared to that of the batch counterpart. Hence, hazardous chemicals are best synthesized and reacted under flow conditions.[3,4]

Since the last comprehensive review on the preparation and reactions of CH_2N_2 in 1983,[1] substantial efforts have been put into the development of novel techniques for its safe and convenient generation and handling, not only in the research laboratory, but also on a production scale. In this review, we particularly focus on recent literature examples that employ flow chemistry for the synthesis and reactions of CH_2N_2. Batch processes are covered only if CH_2N_2 is generated in situ, or if methods not relying on CH_2N_2 distillation are employed.

2. Safety Considerations

Diazomethane should be treated with extreme caution.[1,5] The hazards associated with the handling of CH_2N_2 and measures for avoiding them are highlighted in **Table 1**.[6,7] As many strong alkylation agents are, CH_2N_2 is a potent carcinogen and is extremely poisonous.[8,9] The severe acute and chronic toxicity is especially problematic because of its high volatility (bp = –23 °C). Diazomethane is highly noxious by inhalation or contact with skin or eyes; therefore, contact with it in any form should be strenuously avoided. Diazomethane is also a sensitizer, and long-term, low-level exposures can lead to asthma-like symptoms. The OSHA PEL (Occupational Safety and Health Administration Permissible Exposure Level) for a time-weighted average concentration (TWA) for CH_2N_2 is 0.2 ppm (0.4 mg/m³).[6,7]

Furthermore, in its pure and undiluted form, it is exceedingly sensitive to explosion, and CH_2N_2 is thus virtually exclusively used as a solution in diethyl ether. Ground-glass joints have to be strictly avoided and flame-polished glassware has to be used when handling CH_2N_2.[5] Excess or spilled CH_2N_2 should be destroyed by adding a scavenger such as acetic acid. It is strongly advised not to store CH_2N_2 solutions.



Scheme 1. Synthetic Versatility of Diazomethane. *(Ref. 1)*

Table 1. Hazards of Diazomethane and Measures to Avoid Them *(Ref. 6,7)*

Type of Hazard or Exposure	Acute Hazards and Symptoms	Avoidance Measures
Explosion	Gas–air mixtures are explosive	• Do NOT expose to friction, shock, heat, bright light, sharp/rough edges, and scratched glassware. • AVOID contact with alkali metals and drying agents (e.g., $CaCl_2$, $MgSO_4$, $CaSO_4$). • Stir by using a PTFE-coated stir bar.
Inhalation	Headache. Labored breathing. Shortness of breath. Sore throat. Vomiting. Symptoms may be delayed (lung edema).	Work in an efficient fume hood with the sash closed.
Skin	Redness. Burning sensation. Pain. Serious frostbite.	Wear gloves and a lab coat.
Eyes	Redness. Pain.	Safety glasses or face shield.

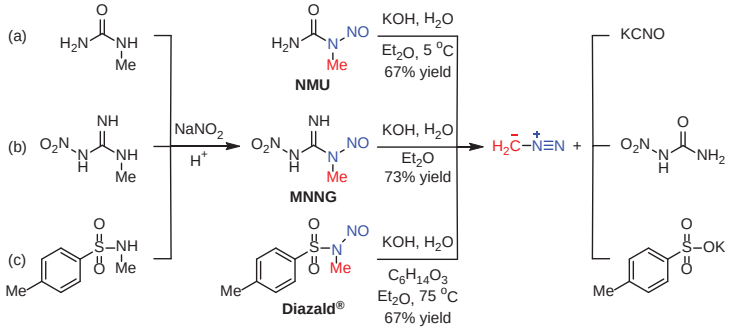
3. Diazomethane Synthesis

Diazomethane is most commonly produced, in the presence of diethyl ether, by base-mediated decomposition of *N*-methyl-*N*-nitrosoamines possessing electron-withdrawing substituents such as sulfonyl or carboxyl groups (**Scheme** 2).[1,4,5,10,11a] The traditional and simplest CH_2N_2 precursor is *N*-nitroso-*N*-methylurea (NMU),[10] which is also a methylating agent and is classified as a carcinogen, mutagen, and teratogen. It is unstable at temperatures above 20 °C and shock-sensitive, and is thus no longer available from chemical suppliers. Similarly, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)[11a]—essentially Aldrich Chemical´s first purchasable reagent[11b]—is no longer for sale due to its mutagenicity and carcinogenicity.[12] Nowadays, *N*-methyl-*N*-nitroso-*para*-toluenesulfonamide (Diazald®) is the preferred precursor;[5] however, it is also a severe irritant. To enhance safety, the synthesis of *N*-methyl-*N*-nitrosoamines via nitrosation of the corresponding *N*-methyl compounds in acidic medium is best incorporated into the overall process. In particular, the otherwise too hazardous NMU could thus be safely generated in situ starting from the harmless and inexpensive *N*-methylurea.[4]

3.1. Batch Methods

Classic distillation techniques have traditionally been employed for the synthesis of anhydrous CH_2N_2 and, therefore, various specialized kits for its generation and purification have been developed and commercialized.[1] In these techniques, diazomethane is co-distilled with anhydrous ether into a dry ice filled cold-finger condenser that is connected to a receiver flask where the ethereal solution of anhydrous CH_2N_2 is collected.[1,13] (For a commercially available version of this setup, see **Figure 1**.) Diazomethane solutions of 1–300 mmol can thus be realized. For smaller scale production (up to ca. 1 mmol), an apparatus, originally developed for generating diazomethane from MNNG without the need for co-distillation, can be used.[1,14] This system consists of an inner and an outer glass tube: diazomethane is generated in the inner tube and can then react with the substrate that is found in the outer tube. For mixing purposes, this setup has to be carefully shaken by hand.

It should be noted that most CH_2N_2 explosions occur during its distillation;[5] hence, new methods and techniques for its safe and convenient preparation and handling are continuously being developed. By employing a biphasic reaction system, CH_2N_2 can be generated in situ in the aqueous layer and is then transferred into the organic layer where the desired reaction takes place.[15,16] Alternatively, in order



Scheme 2. Synthesis of Diazomethane from Different *N*-Methyl-*N*-nitrosoamine Precursors. *(Ref. 1,4,5,10,11a)*

to avoid distillation, several protocols apply a stream of nitrogen to transport CH_2N_2 generated in a batch environment from the solution into the gas phase and further into a substrate-filled receiver flask.[17,18] Both approaches are described in more detail in Section 4 below.

3.2. Continuous-Flow Methods

A further advance toward the safe and convenient in situ generation of CH_2N_2 employs flow chemistry techniques, since the actual reaction volumes in a microreactor or flow device are very small, and safety concerns associated with hazardous reagents are minimized.[19–22] In addition, flow chemistry allows the continuous, on-demand production of potentially toxic, reactive, or explosive intermediates that are consumed in follow-up reactions, thus eliminating the safety risks associated with the accumulation and storage of large quantities of hazardous materials.[3] For these very reasons, it is not surprising that continuous-flow protocols for CH_2N_2 production on a large scale were initially developed in industry.[23,24] It is only very recently that CH_2N_2 generation and consumption under flow conditions have been realized in academia by using either standard (micro)reactors or membrane technology.[19–22]

A simple flow process for the production and in situ conversion of CH_2N_2 comprises a feed containing a suitable *N*-nitrosoamine and a second feed of typically an aqueous solution of potassium hydroxide (KOH). The two feeds are combined in a (micro)reactor to produce CH_2N_2. A third feed with the substrate is subsequently mixed into the reactor to convert the substrate into the CH_2N_2 derivatized product (**Figure 2**). It has to be noted that homogeneity is of utmost importance in continuous-flow chemistry; therefore, solvent systems need to be selected that prevent any precipitation of, for example, potassium *para*-toluenesulfonate (see Scheme 2, Part (c)), and thus avoid system clogging.

An approach for the in situ synthesis of anhydrous CH_2N_2 employs a semipermeable, microporous, but chemically and mechanically resistant, membrane that selectively allows hydrophobic, low-molecular-weight compounds to move across it. By using this approach, a number of different reactor designs can be implemented such as the fully continuous tube-in-tube and the semibatch tube-in-flask reactor technologies. The tube-in-tube reactor design can generally be seen as a versatile tool to saturate gases into a liquid phase.[25,26] Specifically, our group used this reactor to accomplish the generation and purification/separation of anhydrous CH_2N_2 with the goal of developing safe reactions that can be performed in the research laboratory.[27] The inner tube of the device was made of a gas-permeable Teflon® AF-2400 membrane that was enclosed within a thick-walled impermeable outer tubing. Diazald® and aqueous KOH were reacted within the inner tubing, and gaseous CH_2N_2 diffused out through the membrane, and was consumed in the substrate-carrying chamber formed between the outer and inner tubings (**Figure 3**, Part (a)).[27] At the end of the reaction, the content of the inner tube is finally directed into an acetic acid solution to quench excess CH_2N_2. In a further development focusing on operational simplicity and flexibility—in particular with respect to the handling of solids, concentration, and scale—a tube-in-flask reactor was designed, where the membrane tubing was wrapped inside a Duran® or Erlenmeyer flask

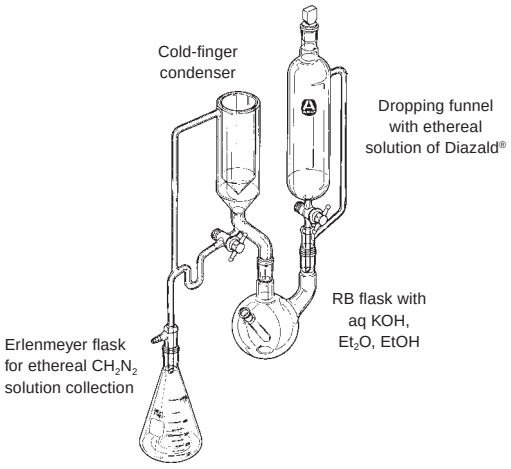


Figure 1. Commercially Available Macro Diazald® Kit for Diazomethane Generation.

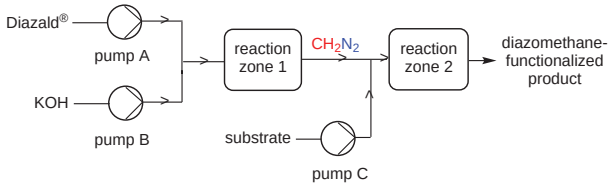


Figure 2. General Setup for the in Situ Generation and Consumption of Diazomethane in a (Micro)reactor.

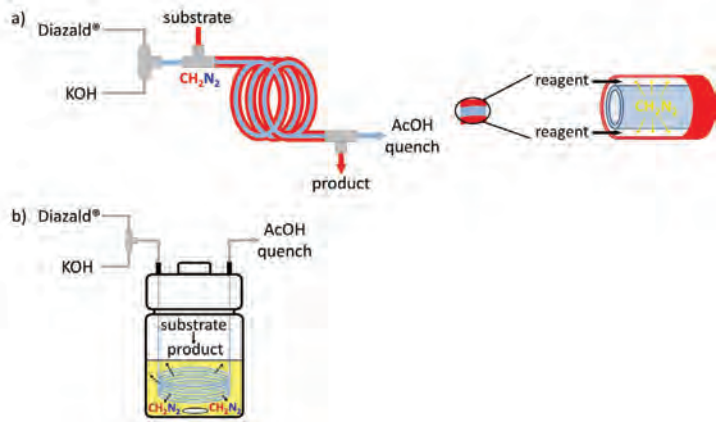


Figure 3. Semipermeable Membrane Technology for Anhydrous Diazomethane Generation. *(Ref. 27,28)*

(Figure 3, Part (b)).[28] Anhydrous diazomethane then diffuses through the membrane into the flask, which is filled with an appropriate solvent and the substrate, and can thus be directly used for reactions in the flask. In this way, anhydrous solutions of CH_2N_2 in any compatible solvent can be generated in a closed system. Similar reactor designs have been previously developed for reactions with ozone[29] and oxygen gas[30]. Whereas anhydrous CH_2N_2 can be obtained straightforwardly within a semipermeable membrane, more effort is required in (micro) reactors, where generally a post-extractive separation is required. A comprehensive coverage of flow protocols will be given in Section 4.

4. Reactions and Reactor Types

Since the generation of CH_2N_2 using flow technology is a comparatively new field of research, the main focus in this Section is to introduce the diverse reactor types and CH_2N_2 generating techniques. Nevertheless, Section 4 is classified according to reaction types.

4.1. O-Methylations

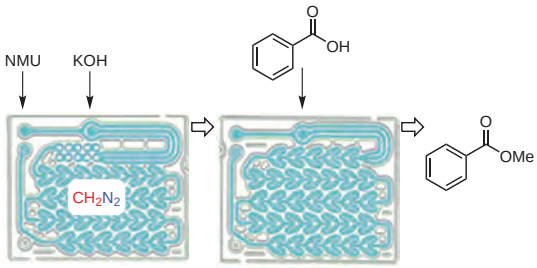
The conversion of carboxylic acids into the corresponding methyl esters is undoubtedly the most popular reaction with CH_2N_2, since it proceeds with high reaction rates, produces only volatile byproducts (N_2), and is highly selective.[1] Other functional groups, such as a phenolic OH or an alkene moiety, remain inactive under the reaction conditions.[1,28] In particular, the methylation of benzoic acid is frequently used for the determination of CH_2N_2 yield, and is thus an indication of the flow reactor performance, since the reaction is generally quantitative and essentially instantaneous.

Employing a microreactor with a setup similar to the one described in Figure 2, CH_2N_2 was generated from Diazald® in Carbitol™ and KOH in isopropyl alcohol. It was subsequently reacted with benzoic acid, which was introduced via a third feed (**Scheme 3**, Part (a)).[31] An excess of benzoic acid was used to additionally neutralize unreacted KOH. Residence times were in the range of seconds for both reaction steps, and a constant yield of 75% of methyl benzoate was achieved over a period of one hour. The key to the success of this process was the 32 mixing elements that were distributed over the length of the reactor. To increase safety, all fluid-containing components were immersed in an acetic acid bath. In a follow-up study, Diazald® was generated continuously in situ starting from *para*-toluenesulfonyl chloride via amidation and nitrosation (Scheme 3, Part (b)) and was then fed into the CH_2N_2 generator after a $NaHCO_3$ wash and dilution with Carbitol™.[32]

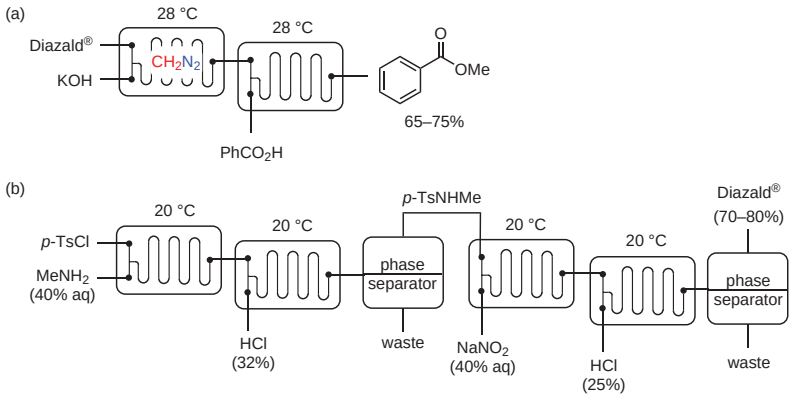
Maggini and co-workers reported an analogous flow format for the synthesis of methyl benzoate, whereby CH_2N_2 was generated from NMU and an aqueous KOH solution (**Scheme 4**).[33] A glass heart-shaped micro-structured fluidic module reactor enabled sufficient mixing of the biphasic mixture, which is crucial for CH_2N_2 production. Up to 19 moles of CH_2N_2 per day could be accomplished, while its amount in the reactor was limited to 6.5 mmol. Finally, a 10-fold scale-up was achieved by increasing the flow reactor dimensions.

Generally, a final separation step would need to be incorporated in the process, if generating pure diazomethane is desired. Thus, CH_2N_2 was produced by flowing a solution of KO*t*-Bu in isopropyl alcohol through a glass cartridge filled with polymer-supported Diazald®.[34] The outlet stream was then directed into a mixing chip, diluted with H_2O, and extracted in a separation membrane where the organic stream contained CH_2N_2. However, due to low benzoic acid conversions and high pressures, this protocol was not pursued further.

A custom-made, small-scale CH_2N_2 generator relying on nitrogen stripping of gaseous CH_2N_2 was designed by Cohen for the derivatization of indole-3-acetic acid.[18] This apparatus cannot be regarded as a flow reactor; however, CH_2N_2 is generated in situ. The device consists of two glass flasks arranged in parallel and fitted with a nitrogen inlet and outlet. Nitrogen is saturated in diethyl ether in the first flask.



Scheme 4. Generation of Diazomethane in a Micro-structured Fluidic Module Reactor. *(Ref. 33)*



Scheme 3. Microreactor Generation of Diazomethane: (a) Directly from Diazald® and (b) from in Situ Generated Diazald®. *(Ref. 31,32)*

CH_2N_2 is generated in the second flask from Diazald® and NaOH, and is subsequently carried by the nitrogen stream into a substrate-filled vial. In a further, more sophisticated modification, the apparatus was employed for a high-throughput quantification of indole-3-acetic acids derived from plant tissue (**Scheme 5**).[35]

4.2. Methylene Insertions

The insertion of methylene by CH_2N_2 into tin tetrachloride ($SnCl_4$) was demonstrated in a device employing a nitrogen stream as carrier for gaseous CH_2N_2.[36] Diazomethane is generated in the first flask in aqueous ethanolic solution from Diazald® and KOH, and is then transported into a tube filled with KOH in toluene to trap side products and water, and finally into a third tube where it is reacted with $SnCl_4$.

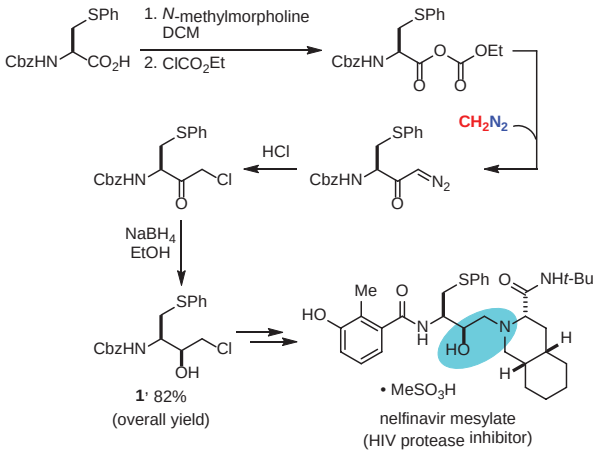
4.2.1. α-Diazoketone and α-Chloroketone Synthesis

α-Diazoketones are generally synthesized from acyl chlorides and CH_2N_2 via a modified Arndt–Eistert homologation. This reaction type is of particular interest because of its use in the synthesis of modern HIV protease inhibitors, such as Atazanavir, which commonly contain a chiral amino alcohol structure in their core. This moiety is typically introduced via an α-chloroketone intermediate, which in turn can be synthesized in a multistep sequence from naturally occurring amino acids in a modified Arndt–Eistert reaction. Since acyl chlorides or activated acids are extremely sensitive to water, strictly anhydrous conditions are required. It is thus essential that purified CH_2N_2 be employed. Diazomethane purification/isolation can either be achieved by extraction, membrane technology, or via nitrogen stripping.

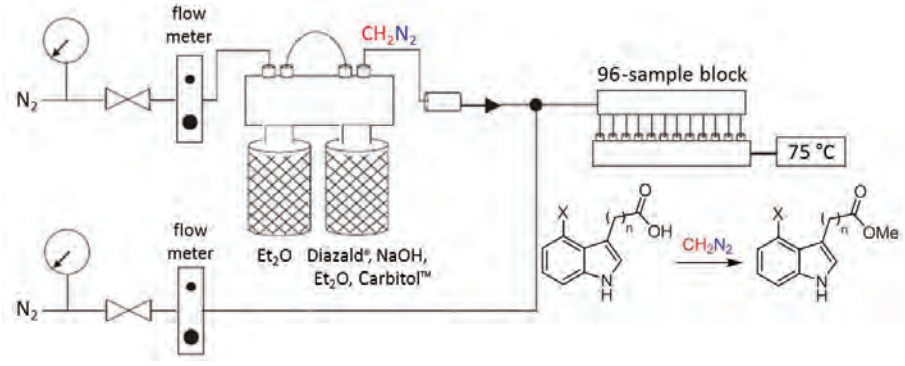
An industrial, continuous-flow process for the generation of organic solutions of anhydrous CH_2N_2 from NMU, which was obtained by nitrosation of *N*-methylurea, was reported by Aerojet (now AMPAC Fine Chemicals) in 1998.[24] Diazomethane, purified by phase separation (extraction), is continuously recovered as an organic solution and can be fed directly to a batch or a further continuous-flow reactor for subsequent reaction. After an aqueous KOH wash of the organic solution, CH_2N_2, with <0.1% water, is obtained. More than 1200 batches of cGMP products using CH_2N_2 at the 3,000 L scale were produced with this setup.[37] A related process based on a continuous membrane separator was reported by DSM.[4,38] The organic phase containing CH_2N_2 passes through a hydrophobic membrane, whereas the aqueous phase of the reaction mixture, including waste salts, is retained by the membrane and is directed into a quench solution.

Proctor and Warr have described a continuous-flow process capable of producing up to 60 tons per year of anhydrous CH_2N_2.[23] Diazomethane was generated from a feed of Diazald® in a high-boiling solvent (DMSO) and a second feed of KOH in water. Anhydrous gaseous CH_2N_2 was separated by a nitrogen stream and further used in a downstream process to produce chiral amino alcohol **1** by a modified Arndt–Eistert homologation (**Scheme 6**).[39]

The membrane technique that merges the generation, separation, and consumption of CH_2N_2 in a continuous-flow, dual-channel microreactor was first applied by Kim and co-workers.[40] A gas-permeable polydimethylsiloxane membrane, which was coated with polyvinylsilazane, allowed pure CH_2N_2 to diffuse from the bottom channel, where it was generated from Diazald® and aqueous KOH, into the upper channel where it reacted with the substrate carried within (**Scheme 7**). Various reactions, including the synthesis of α-diazoketone **2** from benzoyl chloride, were performed in the upper channel. The reactor provided the desired products in excellent yields; however, the throughput was limited to ca. 1 mmol per day.



Scheme 6. The Diazomethane-Enabled, Safe, Cost-Effective, and Direct Industrial-Scale Synthesis of Chiral Amino Alcohol **1**, a Key Intermediate in the Synthesis of Nelfinavir Mesylate, an HIV Protease Inhibitor Drug. *(Ref. 23,39)*



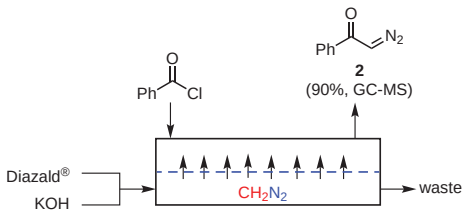
Scheme 5. High-Throughput Quantification of Indole-3-carboxylic Acids Derived from Plant Tissue. *(Ref. 35)*

An analogous approach using a commercial tube-in-tube reactor (see Figure 3, Part (a)) allowed the laboratory-scale generation of anhydrous CH_2N_2 in mmol per hour quantities.[27] Quantitative conversions were obtained for the synthesis of diazoketones (**Scheme 8**), esterifications, cyclopropanations, and [2 + 3] cycloadditions (see Section 4.4). The setup was later extended to achieve the direct transformation of protected α-amino acids, via their mixed anhydrides and α-diazoketones, into the corresponding α-chloroketones in a fully continuous, three-step reaction sequence (**Scheme 9**, Part (a)).[41] The added HCl in the third sequence destroys any excess CH_2N_2 and reacts with the diazoketone to furnish the desired α-chloroketone, **3**. The system was operated continuously for about 4.5 h to produce 1.84 g of the enantiopure α-chloroketone. An enhanced system was employed for the four-step synthesis of β-amino acids from the respective protected α-amino acids via a Wolff rearrangement of the diazoketone intermediates (Scheme 9, Part (b)).[42] The Wolff rearrangement was performed either photochemically (CFL, compact fluorescent lamp) or was catalyzed by Ag_2O packed into a cartridge reactor. In order to remove excess CH_2N_2 and the nitrogen generated during diazoketone formation, additional gas-permeable tubing, which was immersed in a solution of acetic acid, was attached between the second residence coil and the photoreactor.

In addition to α-chloroketone synthesis, methylations, cyclopropanations, and pyrazole synthesis (see Section 4.4) have been performed in the tube-in-flask reactor depicted in Figure 3, Part (b).[28] Higher concentrations (1 M) of Diazald® can be achieved when dissolved in DMF, leading to higher CH_2N_2 concentrations and, ultimately, to a higher product output: several hundred milligrams up to ca. 1 g can be produced within 1 h. Larger scale syntheses can be achieved via parallelization (*numbering up*) by wrapping more membrane tubings into the flask. This way, with four tubings in the flask, 3.65 g of pure α-chloroketone **4** were isolated after ca. 3 h (**Figure 4**). An even more impressive scale could be obtained for the ultrafast methylation of benzoic acid, where 42 g of product were generated within 7 h (6 g/h). With this device, a maximum of 1.8 g of anhydrous CH_2N_2 per hour was safely produced. In addition, the implementation of *in-line* FTIR technology allowed the monitoring of CH_2N_2 generation and consumption.[28] The semi-batch CH_2N_2 generator was additionally employed in a one-pot, three-step synthesis of α-chloroketone **5** starting from *N*-Boc-L-phenylalanine (**Scheme 10**) by following a procedure similar to that described in Scheme 9, Part (a).[43] Diazomethane was produced from NMU as precursor, which in turn was generated in situ by nitrosation of *N*-methylurea in a continuous-flow upstream process.

4.3. Cyclopropanations

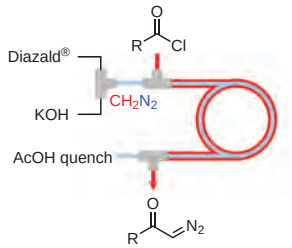
The [2 + 1] cycloaddition reaction of olefins with CH_2N_2 is of major synthetic importance since the resulting cyclopropane subunit is found as a basic structural element in a wide range of naturally occurring



SM	Product	Yield[a]
$MeCO_2H$	$MeCO_2Me$	>99%
PhOH	PhOMe	>99%
PhCHO	PhC(O)Me	81%

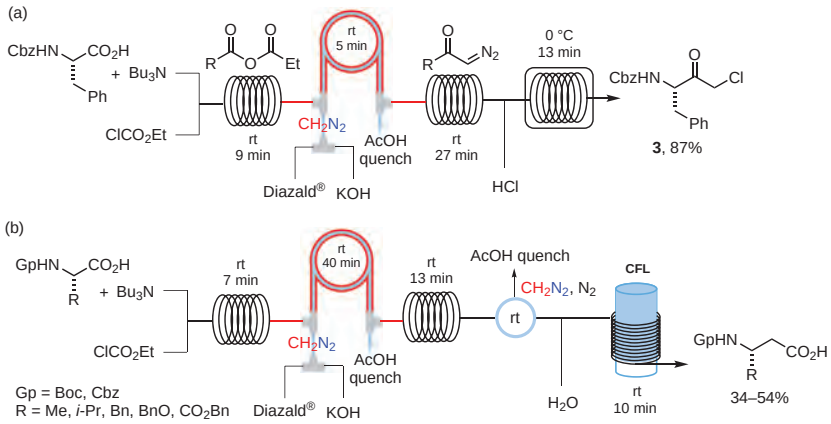
[a] Determined by GC-MS.

Scheme 7. Dual-Channel, Membrane Microreactor for the Generation, Separation, and Reactions of Diazomethane. *(Ref. 40)*



R = Ph (91%, rt), 4-ClC_6H_4 (93%, rt), Bn (78%, –10 °C)

Scheme 8. Continuous-Flow α-Diazoketone Synthesis Using the Tube-in-Tube Reactor System. *(Ref. 27)*



Scheme 9. Multistep, Continuous-Flow Synthesis of (a) α-Chloroketones and (b) β-Amino Acids. *(Ref. 41,42)*

compounds and in several bioactive unnatural analogues.[44] In addition, the cyclopropane ring is a versatile synthetic building block, which can be converted into a range of functionalities.[20] Generally, Pd is the catalyst of choice, but other transition-metal catalysts, including Cu, Ni, and Rh, have also been reported to efficiently catalyze the reaction under mild conditions.[44] The reaction commonly proceeds with excellent stereo- and chemoselectivity, and is compatible with a wide range of functional groups. Whereas the enantioselective cyclopropanation of alkenes by α-diazocarbonyl compounds is one of the most extensively studied transformations in organic chemistry, the efficient and highly enantioselective cyclopropanation employing CH_2N_2 is not that facile.[20,44] Only a few successful examples have been described that employ chiral bidendate copper complexes as catalysts[45] or Oppolzer's sultam[46] as chiral auxiliary.

Biphasic cyclopropanations catalyzed by an iron(III)-porphyrin complex (FeTPPCl) have been developed, where CH_2N_2 is generated in situ in the strongly basic aqueous layer, and is then transferred into an organic layer where the cyclopropanation takes place (**Scheme 11**).[15] Even though this protocol does not require any purification of CH_2N_2, the biphasic reaction necessitates a water-soluble Diazald® derivative, and the protocol is limited to water-insoluble substrates and to reagents that tolerate the strongly basic aqueous conditions. This approach was extended further to cyclopropanations catalyzed by dendrimers possessing the Fe-porphyrin moiety.[47] As in the original procedure by Morandi and Carreira,[15] the Diazald® solution was added slowly (1 equiv/h) via a syringe pump and the cyclopropanation with zero to second generation dendrimer catalysts proceeded with reaction rates that are comparable to that of the original FeTPPCl complex (Scheme 11). Related biphasic cyclopropanations using readily available Pd catalysts, e.g. $Pd(OAc)_2$ or $(PhCN)_2PdCl_2$, were reported by Nefedov and co-workers.[16] Diazomethane was generated from NMU, which was added to the reaction mixture at 50–80 g/h per 0.1 g Pd. Faster addition led to CH_2N_2 decomposition, whereas slower addition promoted Pd precipitation.

An apparatus operated with a continuous argon stream was employed for cyclopropanations of heterobicyclic alkenes (**Scheme 12**).[17,48] Diazomethane was generated in a flask from Diazald® dissolved in EtOH and an aqueous NaOH solution that was added via a dropping funnel. The argon stream carried the gaseous CH_2N_2 into the reaction flask, which contained the alkene in THF and $Pd(OAc)_2$. Excess CH_2N_2 was quenched in a second flask filled with a solution of acetic acid. 7-Oxabicyclic, 2,3-diazabicyclic,[17] and 7-azabicyclic alkenes[48] underwent cyclopropanations in excellent yields within 12–24 h (Scheme 12).

Palladium-catalyzed cyclopropanations of substituted styrenes were successfully performed using a continuous permeable membrane reactor,[38] a tube-in-tube reactor (see Figure 3, Part (a)),[27] a tube-in-flask reactor (see Figure 3, Part (b)),[28] or a glass microreactor containing

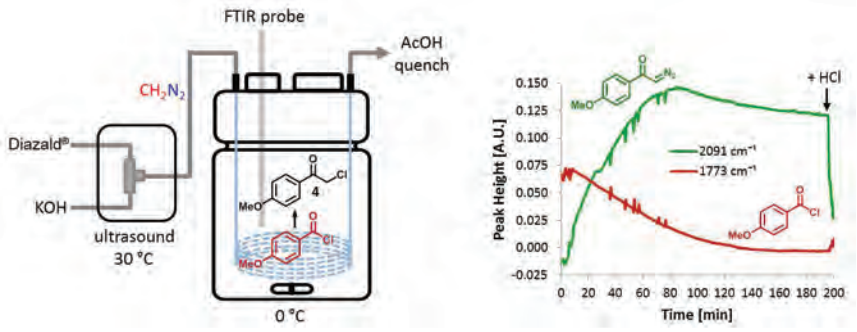
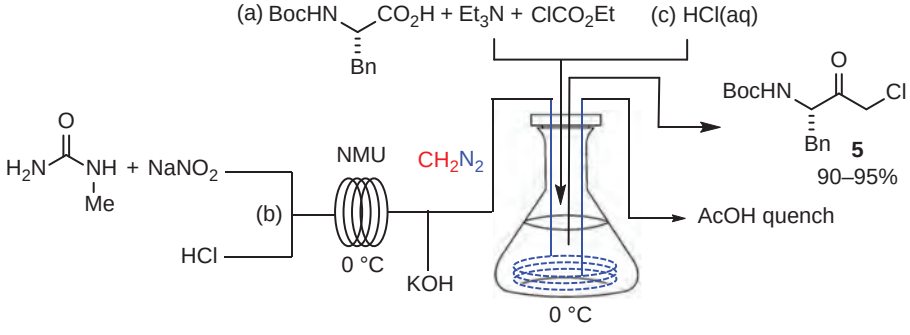


Figure 4. Synthesis of α-Chloroketone **4** in a Tube-in-Flask Reactor (Left) and Reaction Monitoring with FTIR (Right). *(Ref. 28)*



Scheme 10. In Situ Generation of NMU in a Multistep Flow Synthesis of α-Chloroketone **5**. (a) Synthesis of the Mixed Anhydride in the Flask. (b) CH_2N_2 Generation. (c) HCl Quench and Generation of **5**. *(Ref. 43)*

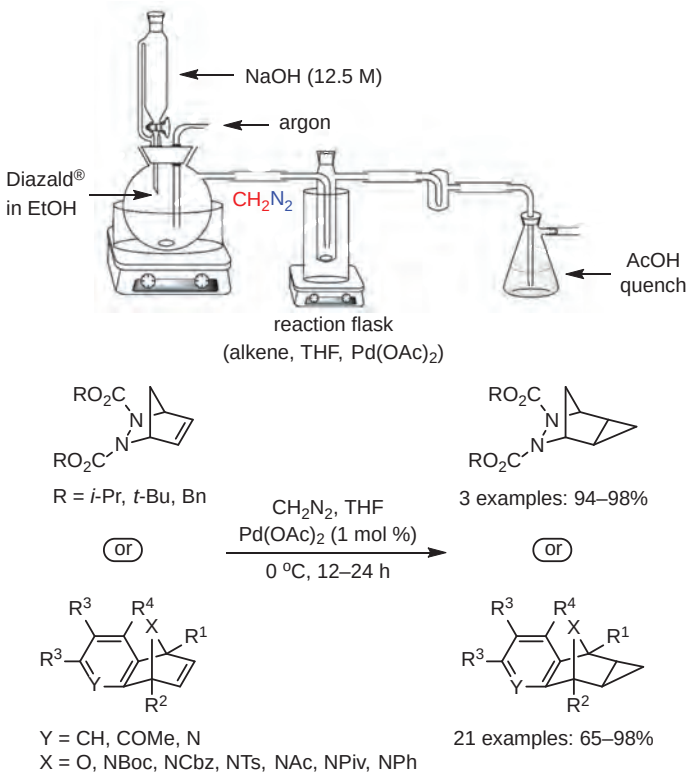
internal chaotic mixing elements.[49] In addition, a fully automated tube-in-tube reactor setup has been employed for the library synthesis of cyclopropyl boronic esters from the corresponding styrenes.[50] It has to be stressed that cyclopropanations are clearly not a trivial affair: depending on the coordination abilities of the alkenes for Pd(0), the precipitation of Pd black—and therefore termination of the reaction—can occur at different catalyst concentrations.[28] Consequently, care has to be taken with respect to channel blocking, in particular when a tube-in-tube reactor or a microreactor is used.

4.4. 1,3-Dipolar Cycloadditions

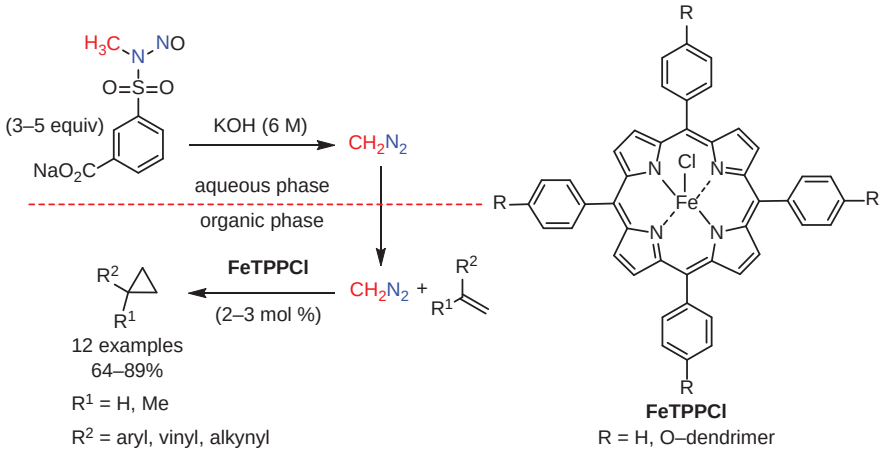
As a powerful 1,3-dipole, CH_2N_2 participates in Huisgen [2 + 3]-cycloaddition reactions with unsaturated compounds to form the corresponding nitrogen-containing heterocycles.[51] Pyrazolines are obtained when an alkene functions as dipolarophile, whereas pyrazoles can be prepared from alkynes (**Scheme 13**).[27,28] The cycloaddition of CH_2N_2 to *N*-phenylmaleimide gave the expected 1-pyrazoline, **6**, in essentially quantitative conversion in a tube-in-tube reactor.[27] By employing the tube-in-flask setup, the 3-substituted pyrazole, **7**, was regioselectively generated from ethyl propiolate and CH_2N_2.[28]

5. Conclusion and Outlook

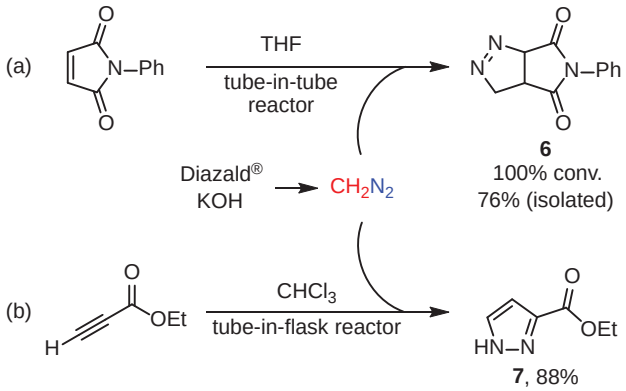
The shortest and most elegant synthesis of a molecule often requires the use of hazardous reagents. Since diazomethane provides such a multitude of applications in organic synthesis, methods for its safe preparation are continuously being developed. An on-demand, in situ production and transformation of diazomethane are highly desirable in order to minimize or eliminate the risks associated with the handling, storage, and human exposure to this toxic and explosive compound. Recent advances in continuous-flow technologies have opened new avenues for the usage of this versatile intermediate with improved safety over traditional batch processes. In particular, the excellent heat and mass transfer, efficient mixing, and the comparatively low reactor volumes make these devices uniquely suited for carrying out hazardous reactions. Furthermore, these new technologies permit multiple reaction steps and workup procedures to be integrated into a single apparatus. Depending on the sensitivity of the individual reactions, especially toward water and strongly basic conditions, different processes for diazomethane generation are now available. If anhydrous diazomethane is required, as in the synthesis of α-diazoketones, the most promising route is the membrane separation and purification approach, where pure gaseous diazomethane diffuses through a semipermeable membrane. Various scales of anhydrous diazomethane can be provided by means



Scheme 12. Cyclopropanations of Heterobicycloalkenes. *(Ref. 17,48)*



Scheme 11. Biphasic Cyclopropanations Employing Diazomethane. *(Ref. 15,47)*



Scheme 13. 1,3-Dipolar Cycloadditions of Diazomethane with: (a) Alkenes (Tube-in-Tube) and (b) Alkynes (Tube-in-Flask). *(Ref. 27,28)*

of different reactor designs ranging from 1–2 mmol of CH_2N_2/h in a commercially available tube-in-tube reactor up to ca. 40 mmol of CH_2N_2/h employing a tube-in-flask device. In addition to in situ diazomethane generation, its precursors, which themselves are either noxious and/or explosive, have also been synthesized in situ in a continuous-flow upstream process. Such a reaction sequence renders the overall process even more hazard-free.

With continuous-flow techniques, we believe that the potential of diazomethane as a sustainable reagent will be further exploited and, hopefully, more intensively used in contemporary organic synthesis.

6. References

(1) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3.
(2) Gompper, R. *Adv. Heterocycl. Chem*. **1963**, *2*, 245.
(3) Gutmann, B., Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed*. **2015**, *54*, 6688.
(4) Poechlauer, P.; Braune, S.; Dielemans, B.; Kaptein, B.; Obermüller, R.; Thathagar, M. *Chim. Oggi/Chem. Today* **2012**, *30 (4)*, 51.
(5) De Boer, T. J.; Backer, H. J. In *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 250.
(6) Diazomethane (July 22, 2015). Centers for Disease Control and Prevention Web site. http://www.cdc.gov/niosh/ipcsneng/neng1256.html (accessed Sep 19, 2016).
(7) National Research Council (US) Committee on Prudent Practices in the Laboratory. *Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards: Updated Version* [Online]; National Academies Press: Washington, DC, 2011. http://www.ncbi.nlm.nih.gov/books/NBK55878/ (accessed Sep 19, 2016).
(8) Schoental, R. *Nature* **1960**, *188*, 420.
(9) Lewis, C. E. *J. Occup. Med.* **1964**, *6*, 91.
(10) Arndt, F. In *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 165.
(11) (a) McKay, A. F. *J. Am. Chem. Soc.* **1948**, *70*, 1974. (b) Firsan, S. J. *Aldrichimica Acta* **2001**, *34*, 35.
(12) Mandell, J. D.; Greenberg, J. *Biochem. Biophys. Res. Commun.* **1960**, *3*, 575.
(13) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.
(14) Fales, H. M.; Jaouni, T. M.; Babashak, J. F. *Anal. Chem.* **1973**, *45*, 2302.
(15) Morandi, B.; Carreira, E. M. *Science* **2012**, *335*, 1471.
(16) Nefedov, O. M.; Tomilov, Y. V.; Kostitsyn, A. B.; Dzhemilev, U. M.; Dokitchev, V. A. *Mendeleev Commun*. **1992**, *2*, 13.
(17) Carlson, E.; Duret, G.; Blanchard, N.; Tam, W. *Synth. Commun.* **2016**, *46*, 55.
(18) Cohen, J. D. *J. Chromatogr.* **1984**, *303*, 193.
(19) Deadman, B. J.; Collins, S. G.; Maguire, A. R. *Chem.—Eur. J.* **2015**, *21*, 2298.
(20) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.
(21) Müller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245.
(22) Gutmann, B.; Kappe, C. O. *Chim. Oggi/Chem. Today* **2012**, *33* (3), 18.
(23) Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884.
(24) Archibald, T. G.; Barnard, J. C.; Reese, H. F. US Patent 5,854,405, Dec 29, 1998.
(25) The tube-in-tube device was originally developed in Ley's laboratory as a gas addition tool. For a review, see Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res*. **2015**, *48*, 349.
(26) Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327.
(27) Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett*. **2013**, *15*, 5590.
(28) Dallinger, D.; Pinho,V. D.; Gutmann, B.; Kappe, C. O. *J. Org. Chem.* **2016**, *81*, 5814.
(29) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett*. **2010**, *12*, 1596.
(30) Greene, J. F.; Preger, Y.; Stahl, S. S.; Root, T. W. *Org. Process Res. Dev*. **2015**, *19*, 858.
(31) Struempel, M.; Ondruschka, B.; Daute, R.; Stark, A. *Green Chem.* **2008**, *10*, 41.
(32) Struempel, M.; Ondruschka, B.; Stark, A. *Org. Process Res. Dev*. **2009**, *13*, 1014.
(33) Rossi, E.; Woehl, P.; Maggini, M. *Org. Process Res. Dev.* **2012**, *16*, 1146.
(34) Martin, L. J.; Marzinzik, A. L.; Ley, S. V.; Baxendale, I. R. *Org. Lett*. **2011**, *13*, 320.
(35) (a) Barkawi, L. S.; Tam, Y.-Y.; Tillman, J. A.; Pederson, B.; Calio, J.; Al-Amier, H.; Emerick, M.; Normanly, J.; Cohen, J. D. *Anal. Biochem.* **2008**, *372*, 177. (b) Barkawi, L. S.; Cohen, J. D. *Nature Protoc.* **2010**, *5*, 1619.
(36) Veith, M.; Agustin, D.; Huch, V. *J. Organomet. Chem.* **2002**, *646*, 138.
(37) Archibald, T. G. *Chim. Oggi/Chem. Today* **2000**, *18* (6), 34.
(38) Poechlauer, P.; Reintjens, R. W. E. G.; Dielemans, H. J. A.; Thathagar, M.; Konings, J. H. G. U.S. Patent Appl. 2014/0100360 A1, April 10, 2014.
(39) Proctor, L. "Taming Nitrogen." Industrialization of Diazomethane – The Application of Flow Technology towards Hazardous Chemistry. Presented at The RSC Symposium 2006: Elements of Success - P, Si, F & N [Online], June 14–15, 2006. Chemspec Europe. http://www.chemspeceurope.com/de/the-rsc-conference/the-rsc-symposium-2006-elements-of-success-p-si-f-n (accessed Sep 19, 2016).
(40) Maurya, R. M.; Park, C. P.; Lee, J. H.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5952.
(41) Pinho, V. D.; Gutmann, B.; Miranda, L. S. M.; de Souza, R. O. M. A.; Kappe, C. O. *J. Org. Chem*. **2014**, *79*, 1555.
(42) Pinho, V. D.; Gutmann, B.; Kappe, C. O. *RSC Adv*. **2014**, *4*, 37419.
(43) Garbarino, S.; Guerra, J.; Poechlauer, P.; Gutmann, B.; Kappe, C. O. *J. Flow. Chem.* **2016**, *6*, 211.
(44) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(45) Charette, A. B.; Janes, M. K.; Lebel, H. *Tetrahedron: Asymmetry* **2003**, *14*, 867.
(46) Vallgårda, J.; Appelberg, U.; Csöregh, I.; Hacksell, U. *J. Chem. Soc., Perkin Trans. 1* **1994**, 461.
(47) Vinš, P.; de Cózar, A.; Rivilla, I.; Nováková, K.; Zangi, R.; Cvačka, J.; Arrastia, I.; Arrieta, A.; Drašar, P.; Miranda, J. I.; Cossío, F. P. *Tetrahedron* **2016**, *72*, 1120.
(48) Carlson, E.; Tam, W. *Synthesis* **2016**, *48*, 2449.
(49) Loebbecke, S.; Antes, J.; Ferstl, W.; Boskovic, D.; Tuercke, T.; Schwarzer, M.; Krause, H. Microreactors for Processing of Hazardous

and Explosible Reactions. In *Loss Prevention and Safety Performance in the Process Industries*; IChemE Symposium Series 153; The Institution of Chemical Engineers: Rugby, U.K., 2007.
(50) Koolman, H. F.; Kantor, S.; Bogdan, A. R.; Wang, Y.; Pan, J. Y.; Djuric, S. W. *Org. Biomol. Chem.* **2016**, *14*, 6591.
(51) Maas, G. Diazoalkanes. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; The Chemistry of Heterocyclic Compounds Series, Vol. 59; Taylor, E. C., Wipf, P., Series Eds.; Wiley-Interscience: Hoboken, NJ, 2002; pp 539–622.

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Doris Dallinger obtained her M.Sc. and Ph.D. degrees with Professor Kappe at the University of Graz, Austria, working on research projects relating to microwave chemistry and the high-throughput synthesis of biologically active heterocycles. Doris then carried out postdoctoral work at the Christian Doppler Laboratory for Microwave Chemistry in the same university, where her research focused on microwave effects and scale-up studies. She then joined the Institute of Chemistry at the University of Graz as Senior Scientist in 2011. Her main research interests are reaction optimization by microwave technology and its adaptation to continuous-flow conditions, as well as introducing hazardous reagents such as diazomethane into new reactions and conditions.

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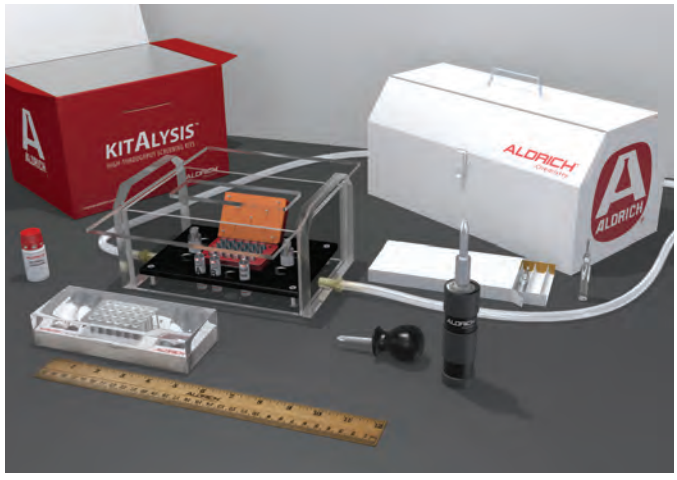

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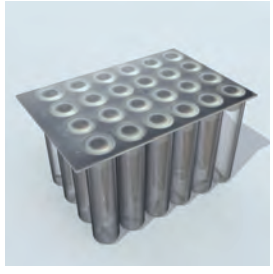

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