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

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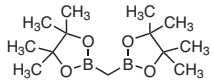
(1) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (2) Coombs, J. R.; Zhang, L.; Morken, J. P. *Org. Lett.* **2015**, *17*, 1708. (3) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455.



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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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References:
(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.

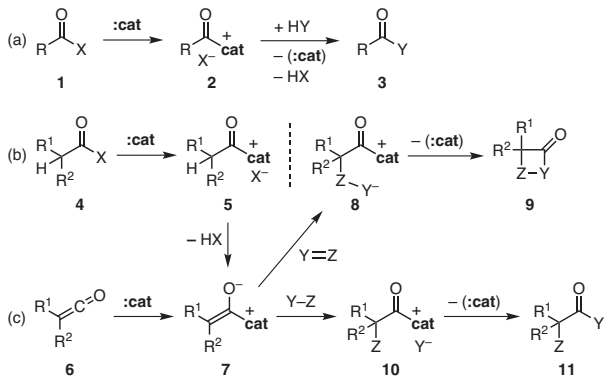
These and conceptually related modes of reactivity of acyl donors (vide infra) present rich opportunities from the point of view of asymmetric catalysis. Consequently, many research groups worldwide have been involved in the design of chiral, Lewis base catalysts that are capable of asymmetric induction 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

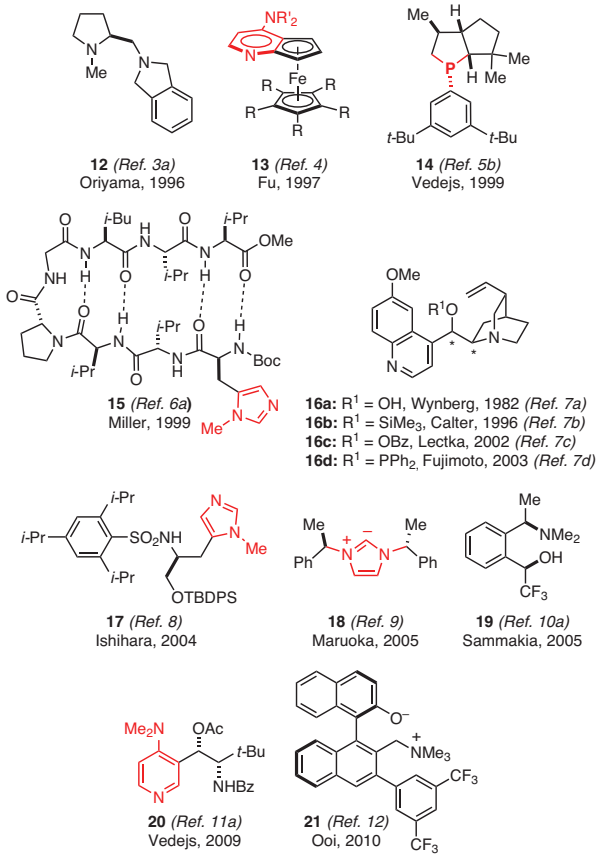
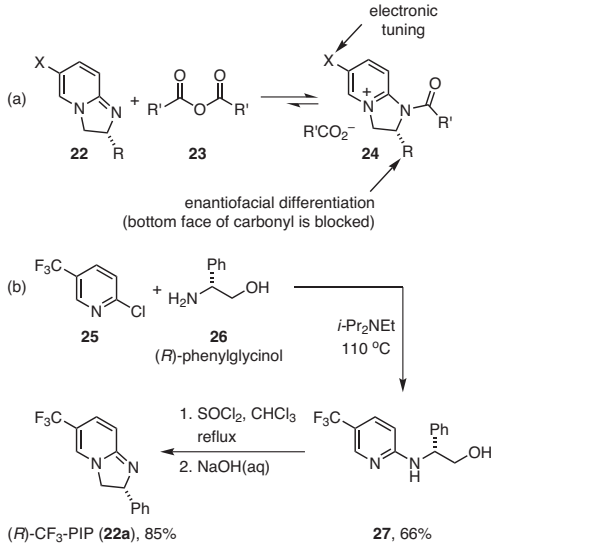


Figure 1. Best Enantioselective Acyl-Transfer Catalysts Developed by Other Groups. *(Ref. 3–12)*



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

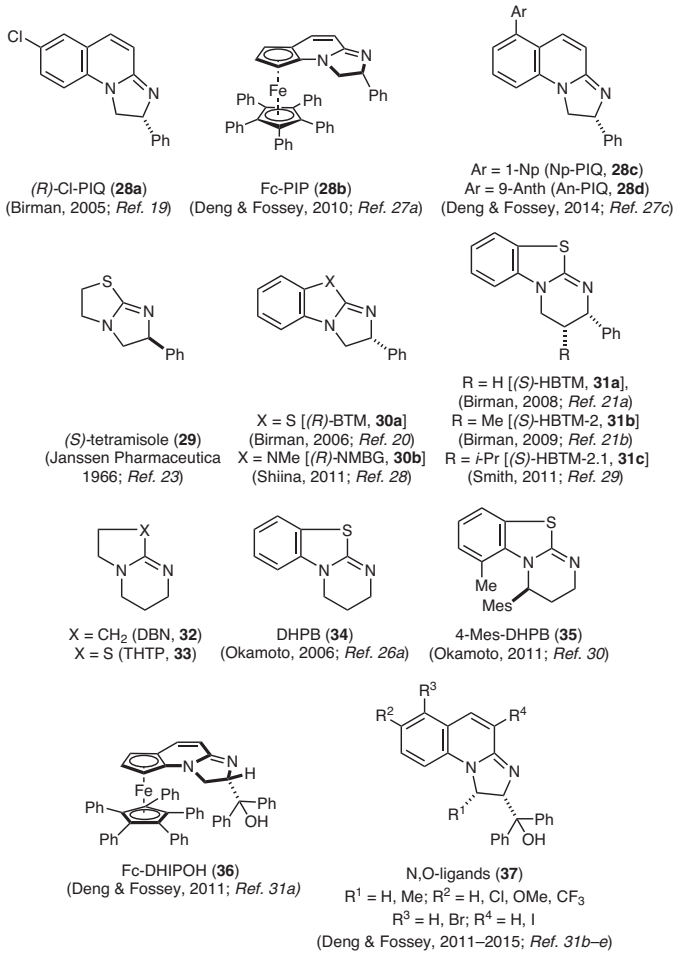
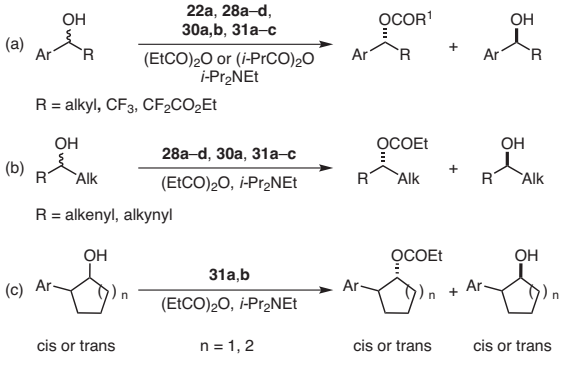


Figure 2. Representative Amidine-Based Catalysts (ABCs) and Related Ligands.



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]

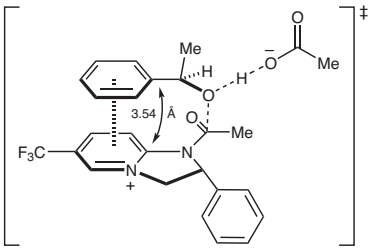
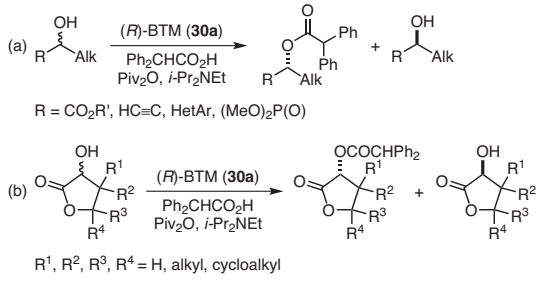
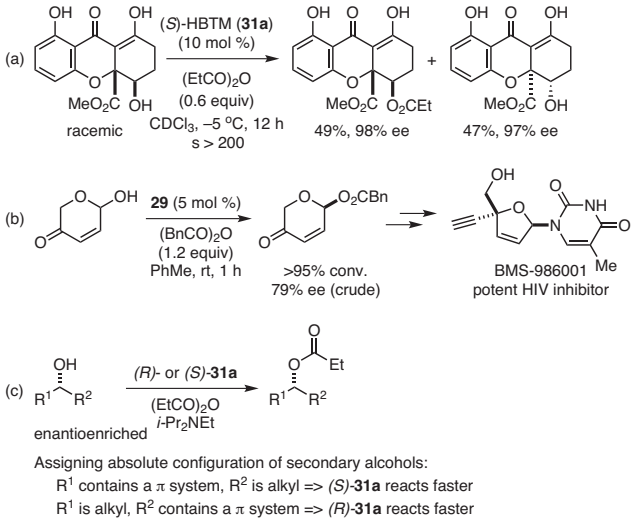


Figure 3. Transition-State Model for the Asymmetric Acylation of 1-Phenylethanol Promoted by **22a**. *(Ref. 41)*



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)).

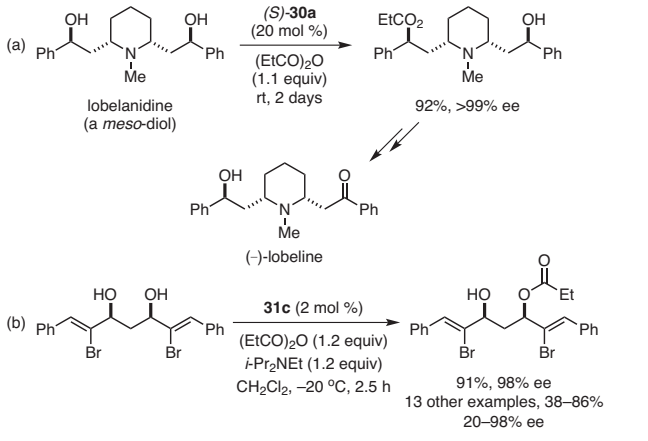
3.1.2. Desymmetrization of Diols

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]



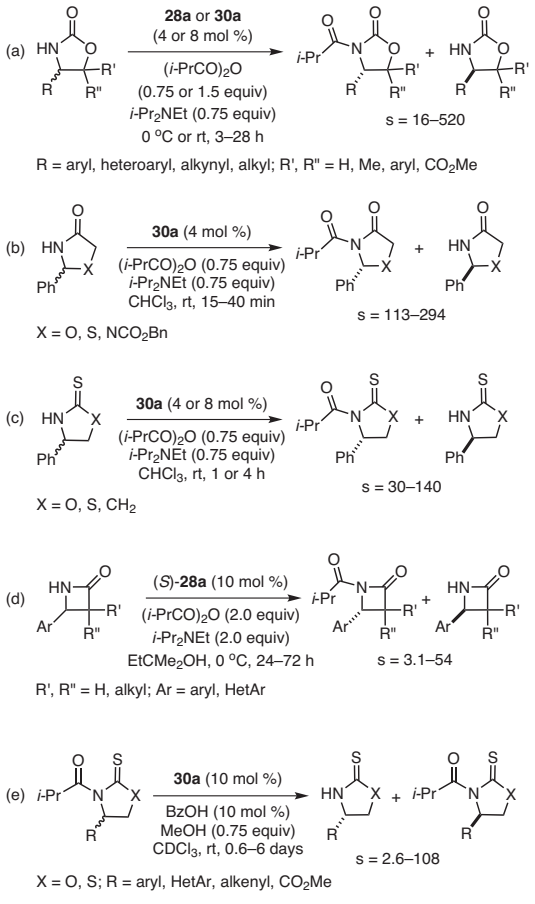
Scheme 6. (a) BTM-Catalyzed Desymmetrization of a *meso*-Diol as a Key Step in the Concise Synthesis of the Alkaloid Lobeline. (b) HBTM-2.1 Catalyzed Desymmetrization of Allylic and Benzylic 1,3-Diols. *(Ref. 46, 47)*

3.1.4. C-Acylations

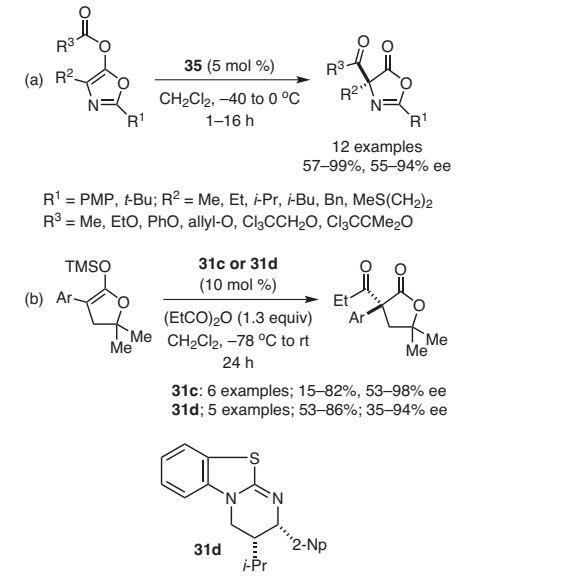
An enantioselective Steglich rearrangement has been achieved using three types of isothiourea-based catalysts. Dietz and Gröger achieved the first acetyl migration (Z = Me) with moderate enantioselectivity using tetramisole (**29**) and BTM (**30a**).[51] Smith and co-workers employed HBTM-2.1 (**31c**) 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

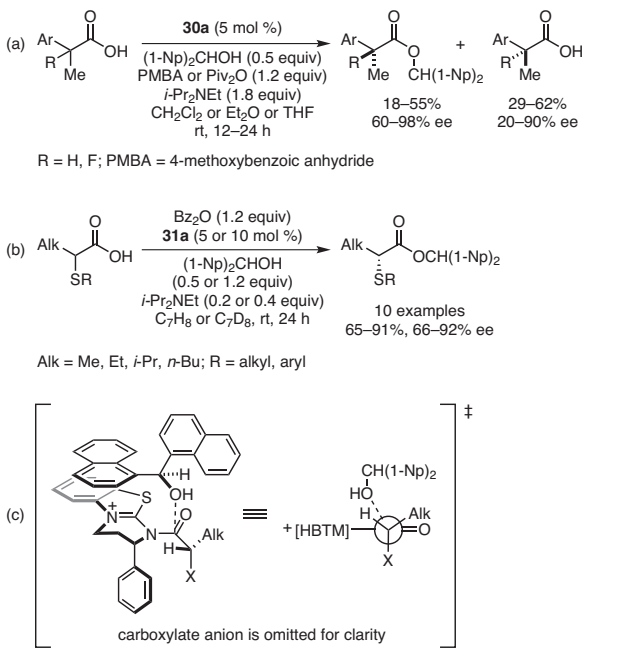
Alkanoic acids bearing an aryl or electron-withdrawing group at the α position have been resolved via enantioselective esterification with di(1-naphthyl)methanol. Shiina's group utilized BTM (**30a**) and its naphth-2-ylanalogue, **30c**, to promote this transformation, and activated the racemic substrates 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

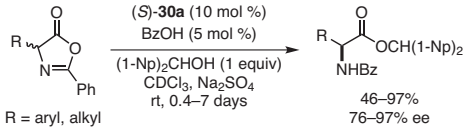
Most ABC reactions in this category are formal cycloadditions, as illustrated by Scheme 1, Part (b).[64] Asymmetric induction observed in these processes can usually be rationalized in a straightforward manner by invoking a zwitterionic enolate formed from the ABC and the substrate (**Figure 4**).

3.2.1. Formal [2 + 2] Cycloadditions

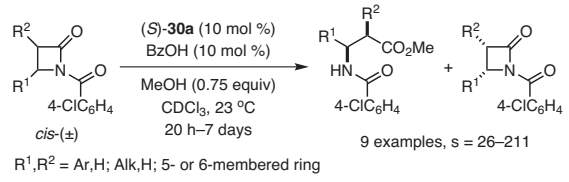
Romo's group has pioneered the use of ABCs in formal cycloadditions of zwitterionic enolates. They first demonstrated the utility of tetramisole (**29**) in a stoichiometric, enantioselective, aldol-lactonization (NCAL) reaction featuring *double* enantioselection (**Scheme 10**, Part (a)).[65] They 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)*

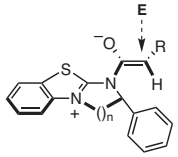
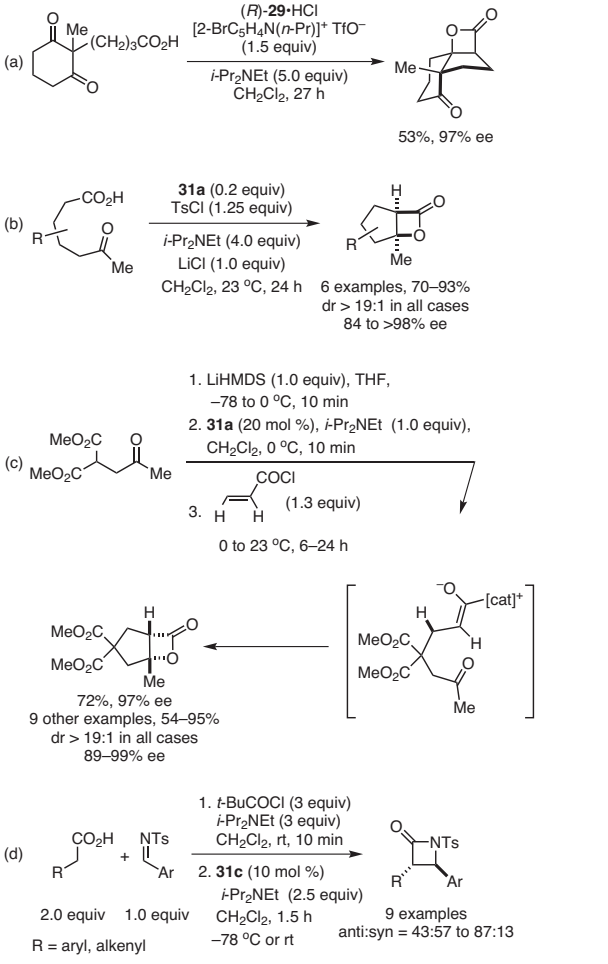


Figure 4. Predictive Model for ABC-Derived Zwitterionic Enolates.



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

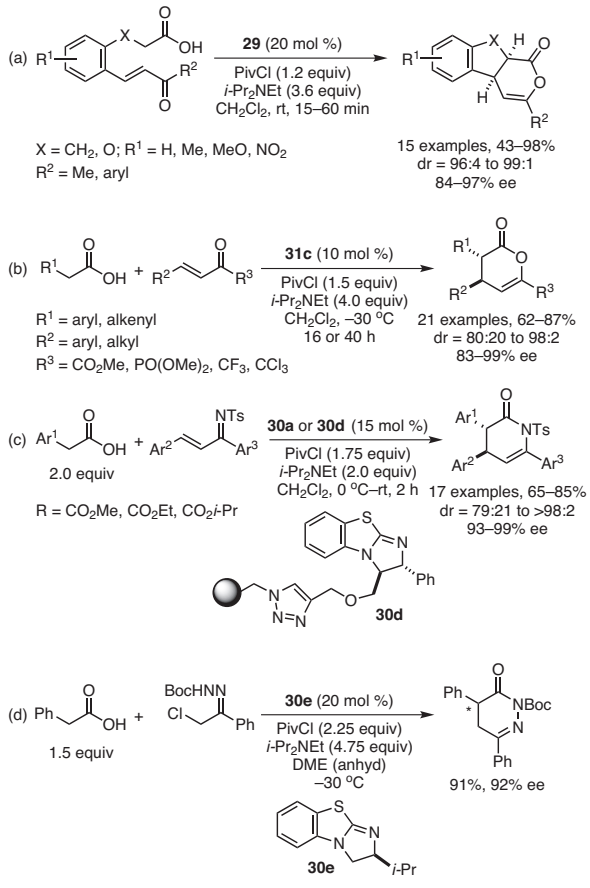
Most of the cycloadducts featured in Scheme 11, Parts (a)–(c) undergo facile alcoholysis, which renders the overall transformation equivalent to an enantioselective Michael addition. Lin, Yao, and collaborators recently developed a DHPB-catalyzed racemic synthesis of dihydropyridazinones via alkenyldiazenes 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

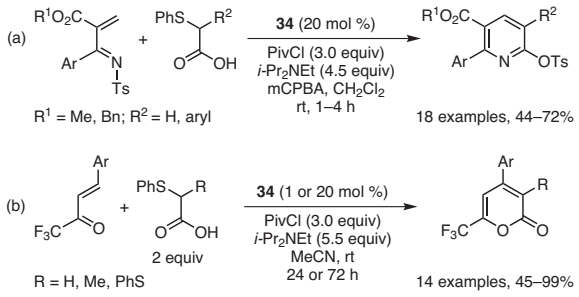
Apart from their extensive use in formal cycloaddition reactions (Schemes 10–13), C1-ammonium enolates generated from chiral ABCs have been utilized by Smith and co-workers in a highly enantio- and diastereoselective [2,3]-rearrangement of quaternary allylic ammonium salts (**eq 3**). The resulting reactive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



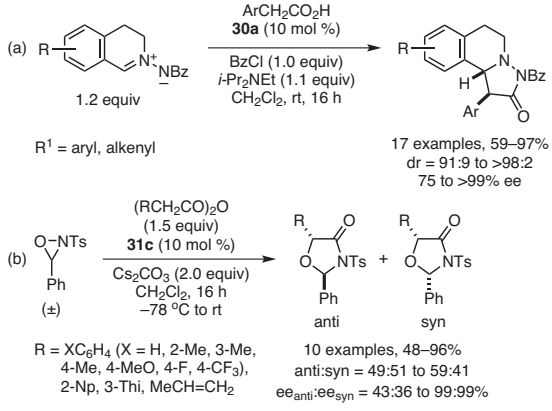
Scheme 11. Formal [4 + 2] Cycloadditions Enabled by Amidine-Based Catalysts. *(Ref. 70–80)*

3.3. Activation of α,β-Unsaturated Acyl Donors

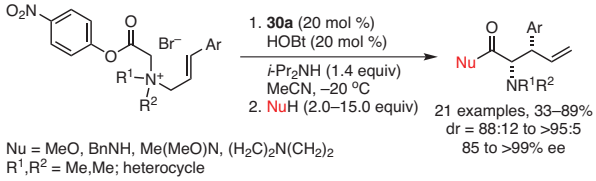
Reactions in this category take advantage of the fact that nucleophilic acyl substitution at the acyl carbonyl lowers the LUMO of the entire conjugated system and thus enhances the reactivity of the double bond towards conjugate additions and cycloadditions. The enantioselectivity observed in these processes 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]

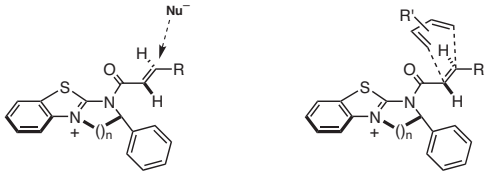
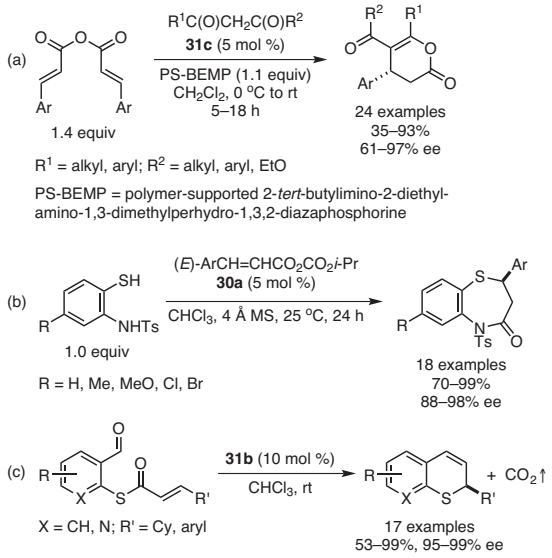
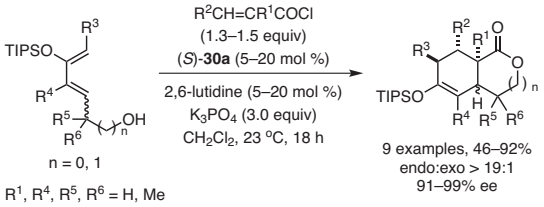


Figure 5. Predictive Models for ABC-Catalyzed Conjugate Additions and Cycloadditions.



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

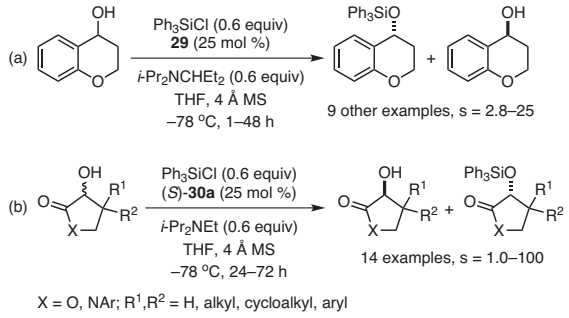
A BTM-enabled, highly diastereo- and enantioselective intermolecular Diels–Alder reaction and lactonization organocascade has recently been disclosed by Romo and co-workers. In this sequence, activated α,β-unsaturated acyl chlorides, acting as dienophiles, lead to cis- and trans-fused bicyclic 5- and 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

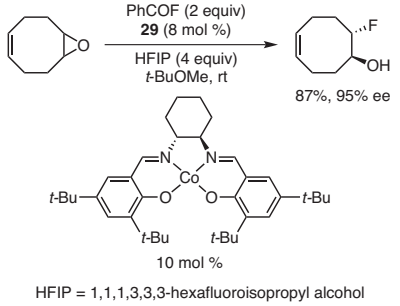
Apart from their widely recognized utility as enantioselective acylation catalysts, ABCs also promote enantioselective O-silylations. Using this approach, Wiskur and co-workers achieved the KR of several classes of cyclic alcohols (**Scheme 15**).[90]

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.

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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]

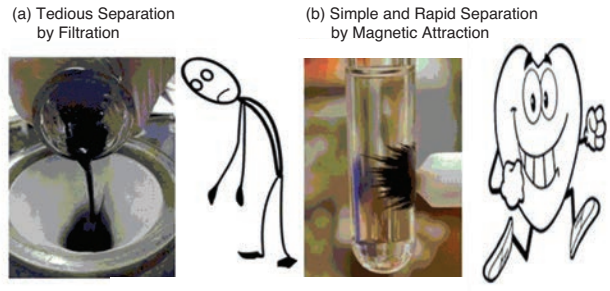


Figure 1. Catalyst Separation by Magnetic Attraction vs Filtration.

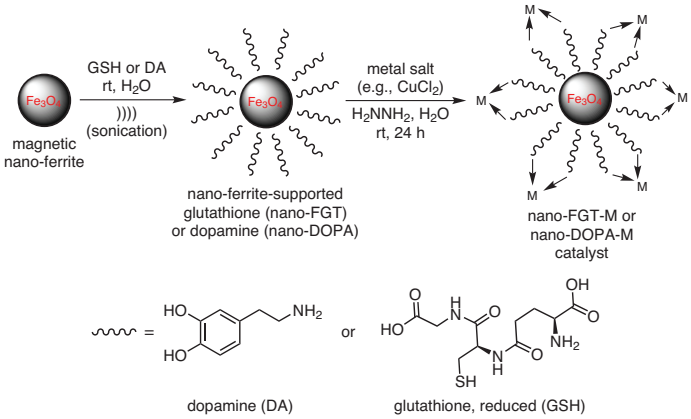
4. Attaching Organic Ligands to Magnetite

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

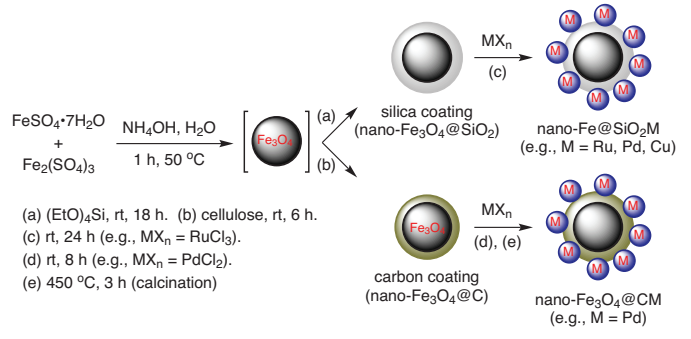
employed and the use of unconventional energy sources such as microwave irradiation. Most of the time, the reactions are carried out in volatile organic solvents over longer periods of time. We envisaged the use of glutathione, a tripeptide and an essential component of plant and human cells, as an organocatalyst, 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.

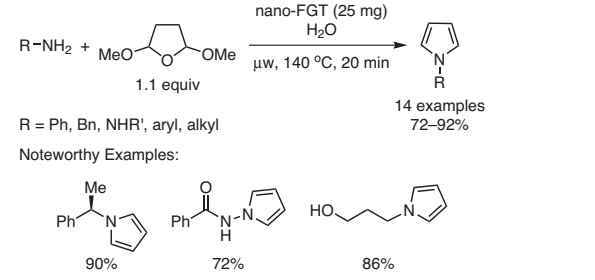
Cross-coupling reactions play an important role in organic synthesis, and are key steps in the synthesis of many molecules that are of interest in biology and materials science. A variety of applications of organosulfur compounds are known in diverse fields such as in the treatment of diabetes, cancer, 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–



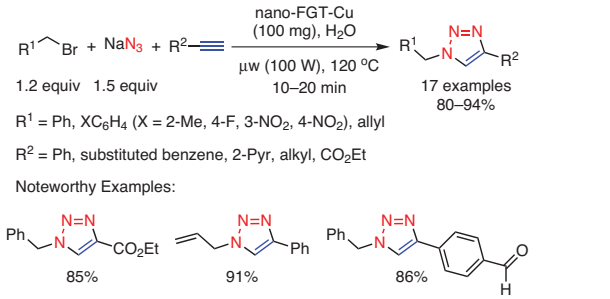
Scheme 1. Synthesis of Glutathione- and Dopamine-Coated Magnetite Followed by Immobilization of the Active Metal. *(Ref. 21,22)*



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)*



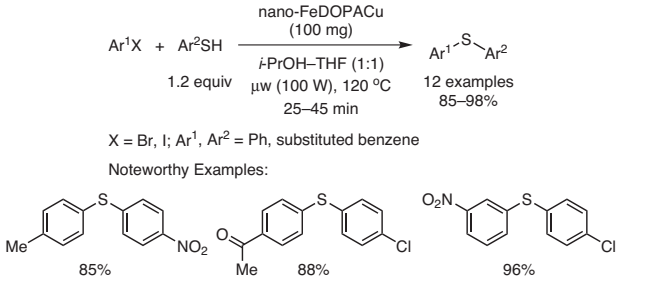
eq 2 *(Ref. 26)*

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.

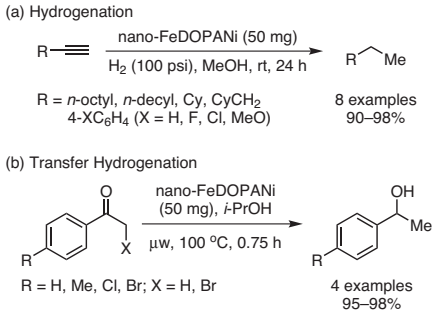
Nano-DOPA was used for the immobilization of Ni, Pd, and Ru metals. This immobilization resulted in the formation of nano-ferrite-Ni (nano-DOPANi),[27] nano-ferrite-Ru (nano-DOPARu),[28] and nano-ferrite-Pd (nano-DOPAPd)[29] catalysts. Nano-DOPANi was explored for the hydrogenation of a variety of alkynes 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]

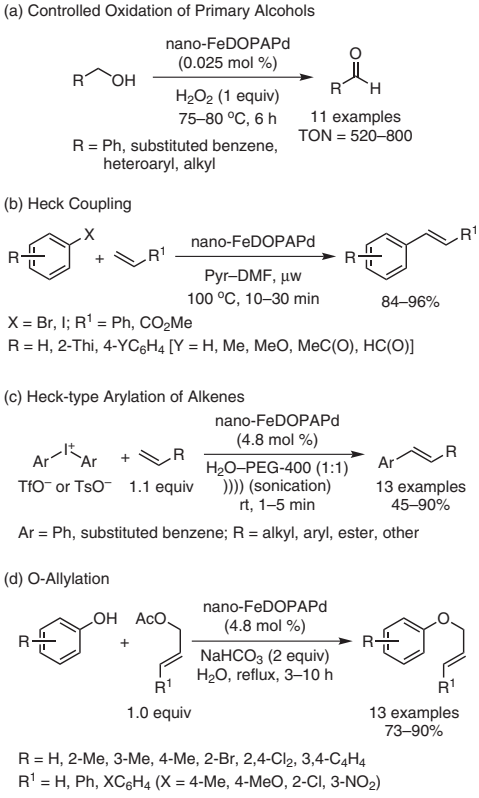
Traditionally, amides have been synthesized by the oxidative hydration of nitriles in acidic or basic media, wherein byproducts are formed due to hydrolysis of the nitriles and/or amides. In addition,



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.

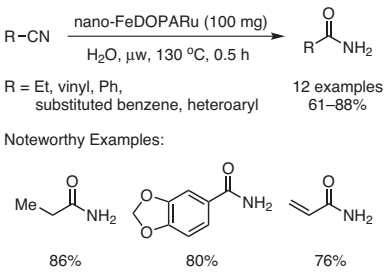
The wider applicability of nano-Fe@SiO_2Ru was demonstrated in the aqueous hydration of nitriles to the corresponding amides and the transfer-hydrogenation reaction of carbonyl compounds using isopropanol. Nano-Fe@SiO_2Pd has proven to be a robust high-surface-area heterogeneous catalyst for the synthesis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

6. Catalysis with Palladium Supported on Carbon-Coated Magnetite

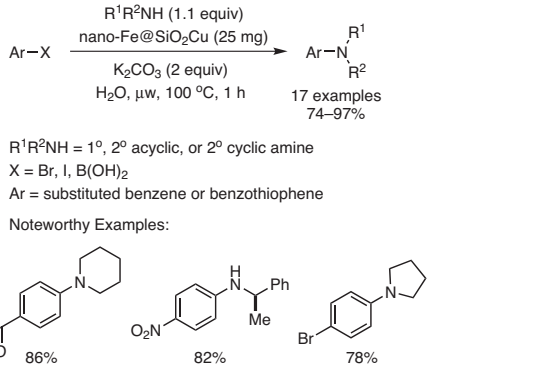
The carbon coating of magnetite is accomplished in one pot by the sequence of nanoparticle synthesis, coating with cellulose, and calcination. Magnetite (Fe_3O_4) was generated in situ by stirring a solution of 1:1 $FeSO_4$•$7H_2O$ and $Fe_2(SO_4)_3$ in water at pH 10, followed by digestion at 50 °C. 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

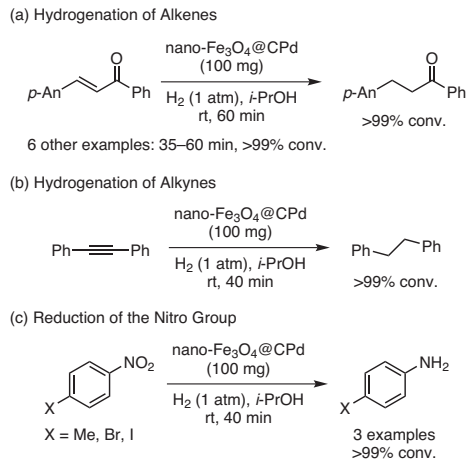
Hoveyda–Grubbs-type metathesis catalysts can be loaded onto magnetic iron oxide supports either by modification of the surface of magnetic nanoparticles (MNP) or by coprecipitation during the synthesis of MNPs. Zhu and co-workers have heterogenized a second-generation Hoveyda–Grubbs catalyst over iron 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

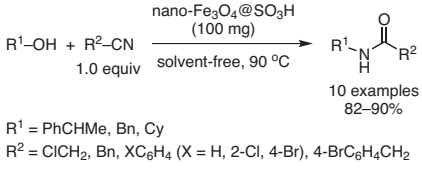
Our group has immobilized magnetic nano-ferrite over a graphitic carbon nitride surface (g-C_3N_4), and demonstrated the applicability of the resulting catalyst (Fe@g-C_3N_4) to the C–H activation of amines (**eq 7**).[36] The resulting α-aminonitriles can be utilized for the synthesis of natural products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

10. Separation and Measurement of Silver Nanoparticles in Wastewater

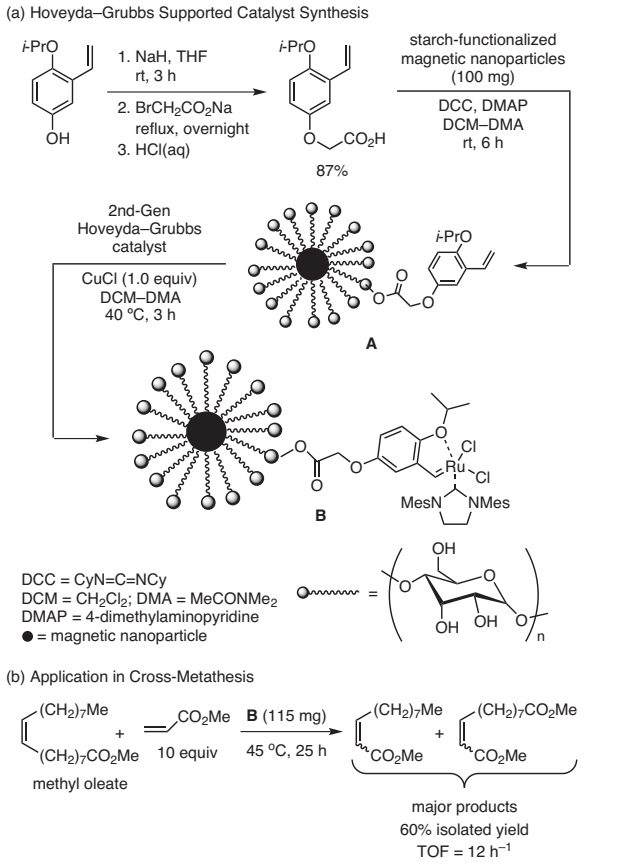
Magnetic particles as sorbents can provide a simple method for the separation and isolation of trace amounts of nanoparticles. Magnetic nano-ferrites are superparamagnetic, but do not remain permanently magnetized after the field is removed, and can be easily tuned by surface modification to develop 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]



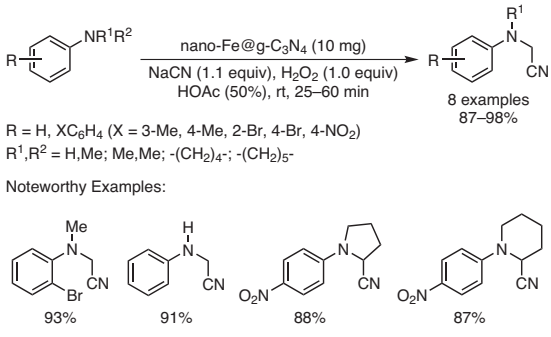
Scheme 5. Nano-Fe_3O_4@C-Supported Palladium Effectively Catalyzes Hydrogenations and Reductions. *(Ref. 33)*



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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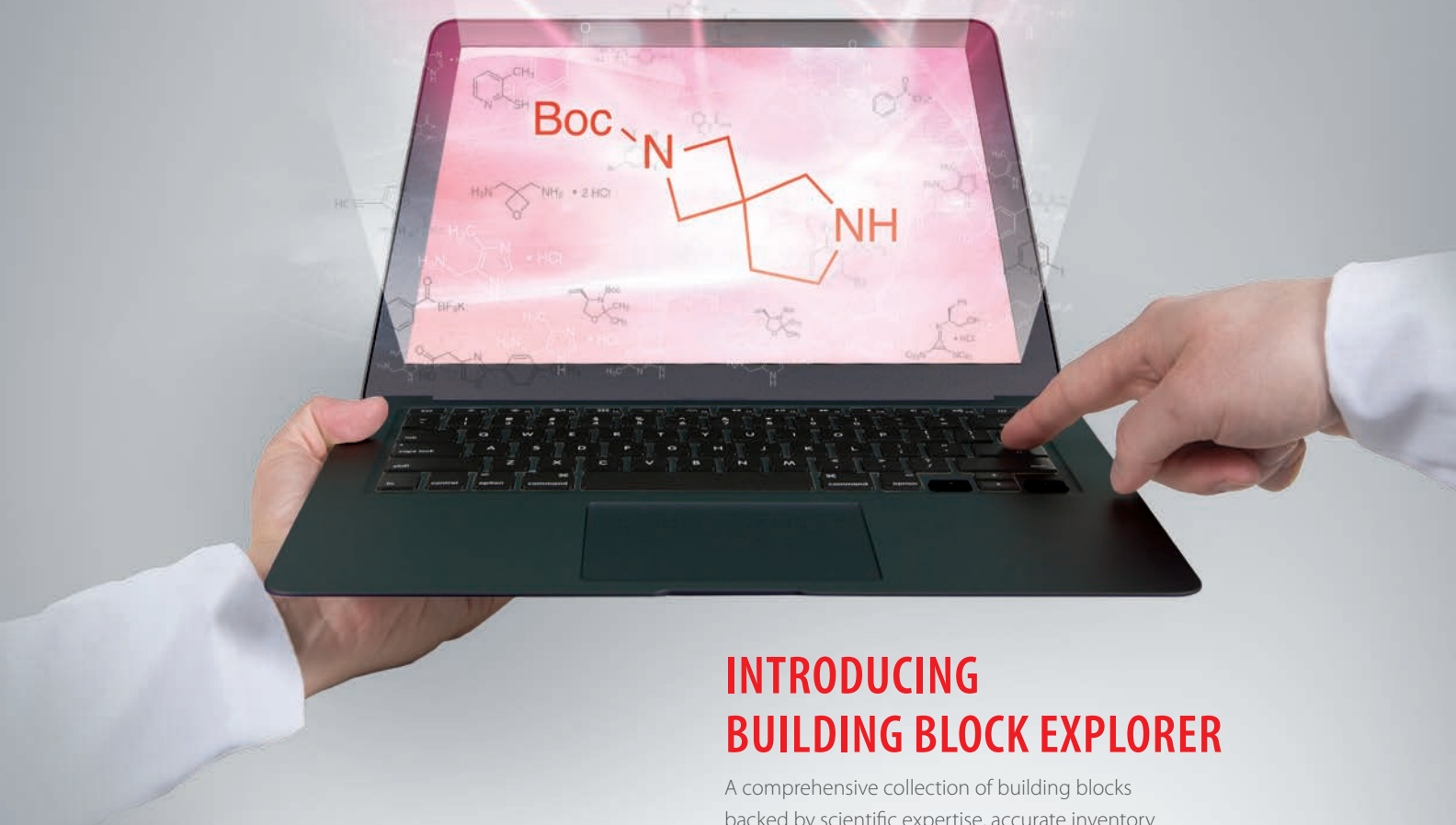

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