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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b06699 • Publication Date (Web): 25 Jul 2018

C–H Functionalization of Amines *via* Alkene-Derived Nucleophiles through Cooperative Action of Chiral and Achiral Lewis Acid Catalysts: Applications in Enantioselective Synthesis

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ABSTRACT: Catalytic transformations of α-amino C–H bonds to afford valuable enantiomerically enriched α-substituted amines, entities that are prevalent in pharmaceuticals and bioactive natural products, have been developed. Typically, such processes are carried out under oxidative conditions, and require precious metal-based catalysts. Here, we disclose a strategy for enantioselective union of *N*-alkylamines and α,β-unsaturated compounds, performed under redox-neutral conditions, and promoted through concerted action of seemingly competitive Lewis acids, $B(C_6F_5)_3$ and a chiral Mg–PyBOX complex. Thus, a wide variety of β-amino carbonyl compounds may be synthesized, with complete atom economy, through stereoselective reaction of an *in situ* generated enantiomerically enriched Mg-enolate and an appropriate electrophile.

INTRODUCTION

Cooperative catalysts (e.g., Fig. 1a, **A1**–**A4**), which are capable of two distinct and simultaneous functions, can doubly activate substrate molecules.[1-6] One advantage of this strategy in catalysis is the considerable rate enhancement that can become available as a result of increased proximity of the reacting substrates. Cooperative acid/base enantioselective catalysis has previously been applied to the development of reactions between *in situ* generated, acid-activated electrophiles and base-activated nucleophiles. The wasteful pre-activation step may thus be obviated.[1-6] Nevertheless, notable shortcomings remain unaddressed. For instance, self-quenching might occur in a mixture that contains an electrophile, a nucleophile, together with an acid and a base catalyst. One way to circumvent acid–base complexation is by avoiding a combination that exhibits high affinity (i.e., hard–hard or soft–soft pairing). However, this latter approach has thus far been limited to cases in which weakly to moderately acidic and/or basic promoters are involved, where only highly acid- or base-sensitive substrates can be used. Development of potent and unquenchable cooperative two-catalyst systems that facilitate

reactions between unactivated substrates is an important and largely unresolved problem in enantioselective catalysis.

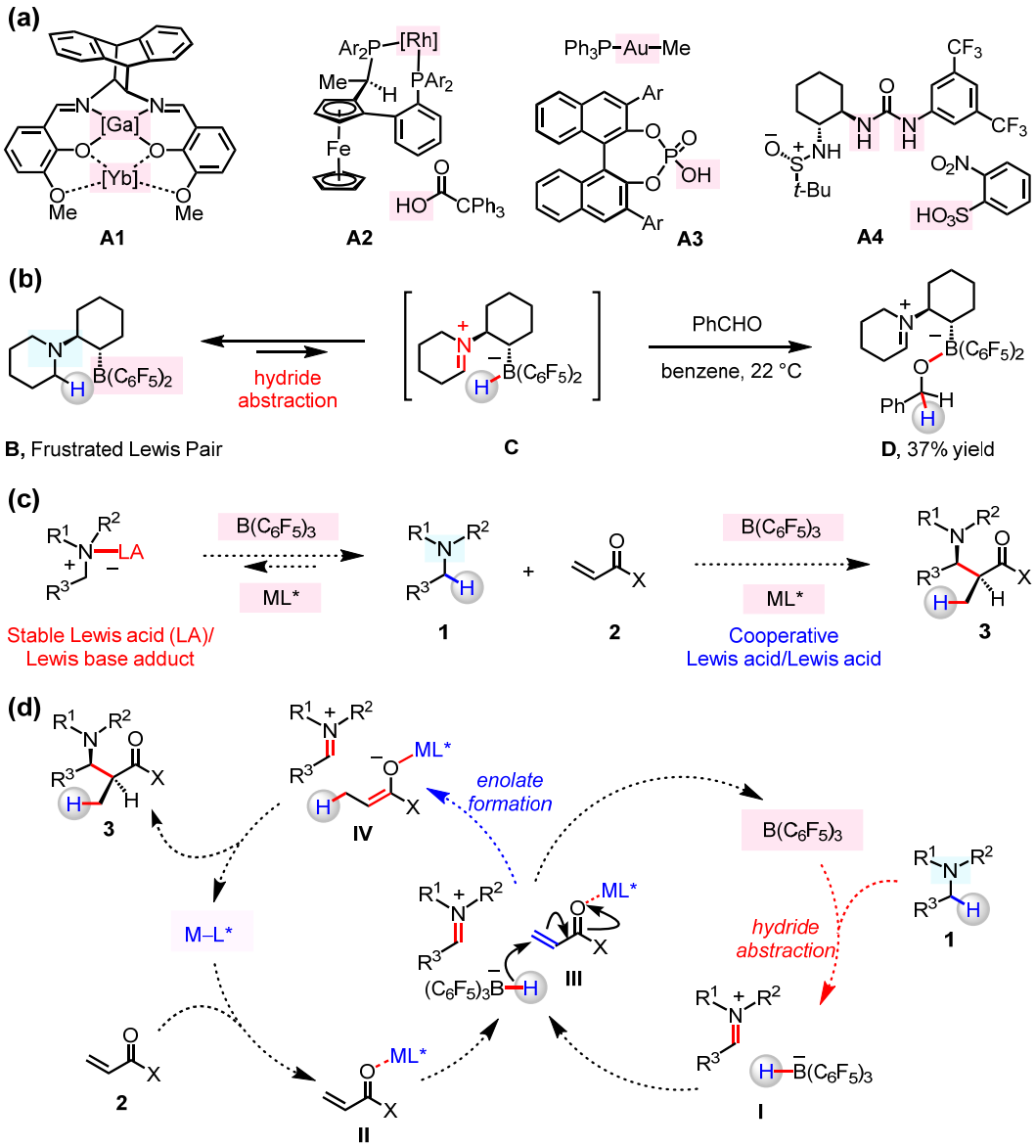


Figure 1. Structures and reactivity of cooperative catalysts. (a) Previously reported examples of cooperative acid/acid catalysts involve structurally and/or functionally disparate acidic promoters. (b) Intramolecular hydride transfer occurs within a frustrated Lewis pair complex to afford zwitterionic iminium ions. (c) Enantioselective coupling of *N*-alkylamines and α,β-unsaturated compounds by cooperative acid/acid catalysis. (d) A possible mechanism might involve enantio- and diastereoselective C–C bond formation between iminium ion and chiral enolate, generated *in situ* by cooperative functions of a chiral and an achiral Lewis acid catalyst. The reaction affords β-amino carbonyl compounds atom economically and under redox neutral conditions.

The application of frustrated Lewis pairs (FLPs), consisting of hindered and electronically disparate Lewis acids and Lewis bases, has recently emerged as an attractive strategy for overcoming mutual quenching. An unquenched acid/base pair may thus be utilized for synergistic activation of otherwise unreactive molecules such as H_2 and CO_2.[7-9] Furthermore, FLPs that are comprised of a boron-based Lewis acid and a Lewis basic amine substrate, and contain easily accessible α-hydrogens (e.g., **B**; Fig. 1b), have been shown to engage in Lewis acid-mediated hydride abstraction. Such processes produce an iminium cation and a borohydride anion (**C**),[10-13] the latter of which might then react with a carbonyl-containing species to afford **D**.[10] A related investigation illustrates that the presence of stoichiometric amounts of $B(C_6F_5)_3$ can lead to C–C bond forming reactions between *N*-alkylamines and α,β-unsaturated molecules to afford β-amino carbonyl compounds.[13] Still, engagement of iminium ions formed by organoboron-catalyzed hydride abstraction from amines in the context of a catalytic transformation has been confined to dehydrogenation of *N*-containing heterocycles.[14,15] To the best of our knowledge, such strategies are yet to be successfully applied to catalytic C–C bond forming transformations.[16,17] One way to address this problem would be by designing a catalyst that can abstract a hydride from an amine substrate, mediate enantioselective C–C bond formation, and regenerate the active Lewis pair without significant deactivation due to the presence of a Lewis basic moiety.

While contemplating how to design a catalytic process for stereoselective coupling of *N*-alkylamines and carbon-based nucleophiles, we envisioned utilizing two potent Lewis acid catalysts for accomplishing separate tasks (Fig. 1c-d). We imagined that $B(C_6F_5)_3$ could receive a hydride from amine **1**, generating a borohydride and an iminium ion (**I**). Concurrently, a chiral Lewis acid co-catalyst would activate the α,β-unsaturated substrate (e.g., **2**) to facilitate reduction by the aforementioned borohydride (**III**), furnishing the corresponding chiral enolate (**IV**). An ensuing stereoselective reaction between the iminium ion and the enantiomerically enriched enolate would deliver a β-amino carbonyl product (**3**). One key advantage of the approach would be that efficiency and stereoselectivity might be optimized through evaluation of pairs of readily accessible Lewis acids and chiral ligands. Accordingly, a central design principle is that the untethered Lewis acid catalysts must perform their separate tasks without any overlapping of their function, as otherwise, stereoselectivity would suffer (due to reaction facilitated by the achiral component).[18] Enantioselective transformations promoted by the shared action of two different metal complexes,[1-5,19] as well as Brønsted acid and organometallic complexes[20,21] or hydrogen-bond donors[22] are known (e.g., Fig. 1a, **A1**–**A4**). However, in contrast to what we aimed to accomplish, in the previous approaches, the Lewis acidic promoters

were structurally and/or functionally disparate, translating to minimal overlay in their modes of action; namely, their simultaneous presence did not pose a complication. Here, we report that functionally similar $B(C_6F_5)_3$ and a chiral Lewis acid co-catalyst can operate in concert to promote enantioselective coupling of *N*-alkylamines and various α,β-unsaturated compounds.

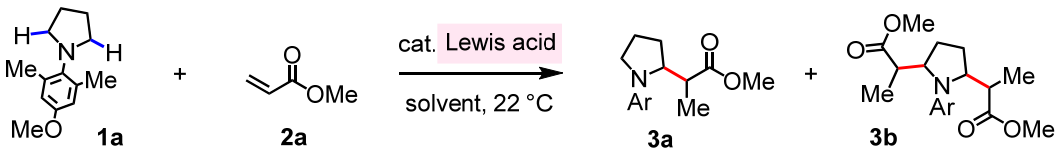
The plan outlined above is distinct from the traditional "direct" Mannich-type reactions, where Lewis acid and Brønsted base catalysts cooperate to generate first an enolate, and then promote its addition to an aldimine, which has already been prepared through a separate operation.[4,5,23,24] There are a small number of reported examples regarding direct Mannich-type reactions that involve esters, amides or thioesters; deprotonation is more difficult in these instances, because of diminished acidity (pKa in the range of 25–30). We sought to generate the requisite electrophilic and the nucleophilic species *in situ* from readily available *N*-alkylamines and α,β-unsaturated compounds. Thus, under redox-neutral conditions and without the need for a precious metal salt,[25] we would synthesize α-substituted amines **3**, entities that are difficult to access by "direct" Mannich strategies. Many of the reported methods for α-amino C–H functionalization rely on transition metal-based catalysts (e.g., Fe-, Cu-, Ru-, Rh-, Pd-, Ir-, Pt-based), and, often, demand oxidative conditions.[26-36] These catalyst systems may either forge C–C bonds directly,[36] or first convert a substrate amine into a more active intermediate, such as an α-amino radical,[26] an iminium ion,[27-30] an α-halo, an α-hydroxyl or an α-metalated species.[31-35] Catalytic stereoselective α-amino C–H functionalization has been investigated as well.[27,29,30,34,36] However, the development of non-precious metal-based methods that complements the existing stereoselective techniques represents a compelling problem.

RESULTS AND DISCUSSION

To begin, we set out to identify an appropriate combination of an acidic catalyst and an amine substrate that would allow for efficient hydride abstraction (as opposed to formation of a stable acid–base adduct). We first probed the ability of $B(C_6F_5)_3$ to catalyze the reaction between *N*-aryl pyrrolidine (**1a**) and methyl acrylate (**2a**), affording β-amino ester **3a** (Table 1; see the Supplementary Information for data regarding screening of *N*-substituents). In this representative process, a single Lewis acid $B(C_6F_5)_3$ would be responsible for activation of the amine as well as the Michael acceptor (Fig. 1d, M–L* = $B(C_6F_5)_3$). Treatment of **1a** and **2a** with 5.0 mol% $B(C_6F_5)_3$ in CH_2Cl_2 at 22 °C for 12 hours afforded **3a** in >95% yield as a separable mixture of diastereomers (entry 1, *anti*:*syn* = 2.3:1); there was less than 5% of the di-substituted product (**3b**). With Et_2O and THF as the solvent, **3a** was formed in 94% and 26% yield, respectively (entries 2–3). When the reaction was carried out in a relatively non-polar aromatic hydrocarbon,

such as toluene and benzene, **3a** was obtained in 81% and >95% yield (entries 4–5); in benzene, **3a** was isolated in >95% yield in just 30 minutes (entry 6). At lower loading of $B(C_6F_5)_3$ (2.5 mol%), longer reaction time was needed (48 h, **3a** in 84% yield; entry 7).[37] None of the desired product was formed in the absence of $B(C_6F_5)_3$ (entry 8), or when the less hindered BF_3•OEt_2 or the less acidic BPh_3 were used (entries 9–10). The latter findings support the notion that highly acidic $B(C_6F_5)_3$ together with sterically demanding and electron-rich *N*-alkylamines represent the most effective combination.

Table 1. Evaluation of Reaction Parameters[a,b]



entry	Lewis acid (mol%)		solvent	reaction time (h)	yield (%), *anti*:*syn* **3a**	yield (%) **3b**
1	$B(C_6F_5)_3$	5.0	CH_2Cl_2	12	>95, 2.3:1	<5
2	$B(C_6F_5)_3$	5.0	Et_2O	12	94, 2.3:1	<5
3	$B(C_6F_5)_3$	5.0	THF	12	26, 1.9:1	<5
4	$B(C_6F_5)_3$	5.0	Toluene	12	81, 2.4:1	5
5	$B(C_6F_5)_3$	5.0	Benzene	12	>95, 2.4:1	<5
6	$B(C_6F_5)_3$	5.0	Benzene	0.5	>95, 2.4:1	<5
7	$B(C_6F_5)_3$	2.5	Benzene	48	84, 1.7:1	<5
8	none	0	Benzene	12	0	0
9	BF_3•OEt_2	5.0	Benzene	12	0	0
10	BPh_3	5.0	Benzene	12	0	0

[a]Conditions: 1-(4-Methoxy-2,6-dimethylphenyl)pyrrolidine (0.2 mmol), methyl acrylate (0.3 mmol), Lewis acid, solvent (0.3 mL), under N_2, 22 °C. [b]Yields were determined by ^{1}H NMR analysis of unpurified product mixtures with mesitylene as the internal standard. See the Supporting Information for details.

A variety of α,β-unsaturated carbonyl compounds and related electrophiles may be used in reaction with *N*-arylpyrrolidine **1a** to generate the corresponding α-substituted amines (**3a**–**3k**, Fig. 2). Reaction with methyl acrylate (**2a**) and benzyl acrylate (**2c**) afforded **3a** and **3c** in 97% and 91% yield, respectively. Whereas isopropyl acrylate (**2d**) gave **3d** in 78% yield, no product was obtained with *tert*-butyl acrylate; this decline in efficiency probably arises from inferior ability of $B(C_6F_5)_3$ in coordinating with the more sterically encumbered acrylates. Transformation with the less electrophilic thioacrylate (**2e**) gave **3e** (53% yield), and acrylonitrile (**2f**) proved to be a viable starting material, furnishing **3f** in 50% yield. Reaction with methyl methacrylate (**2g**) gave **3g**, containing an α-quaternary carbon center, in 97% yield. Dimethyl

acetylenedicarboxylate (**2h**) was converted *in situ* to an allenolate nucleophile, which reacted with **1a**-derived iminium ion to deliver **3h** in 52% yield as a separable mixture of *E* and *Z* isomers (1:1.6). Transformations with *N*-phenylmaleimide (**2i**), *trans*-fumaronitrile (**2j**), and (*E*)-*β*-nitrostyrene (**2k**) furnished **3i**–**3k** (84% to >95% yield).

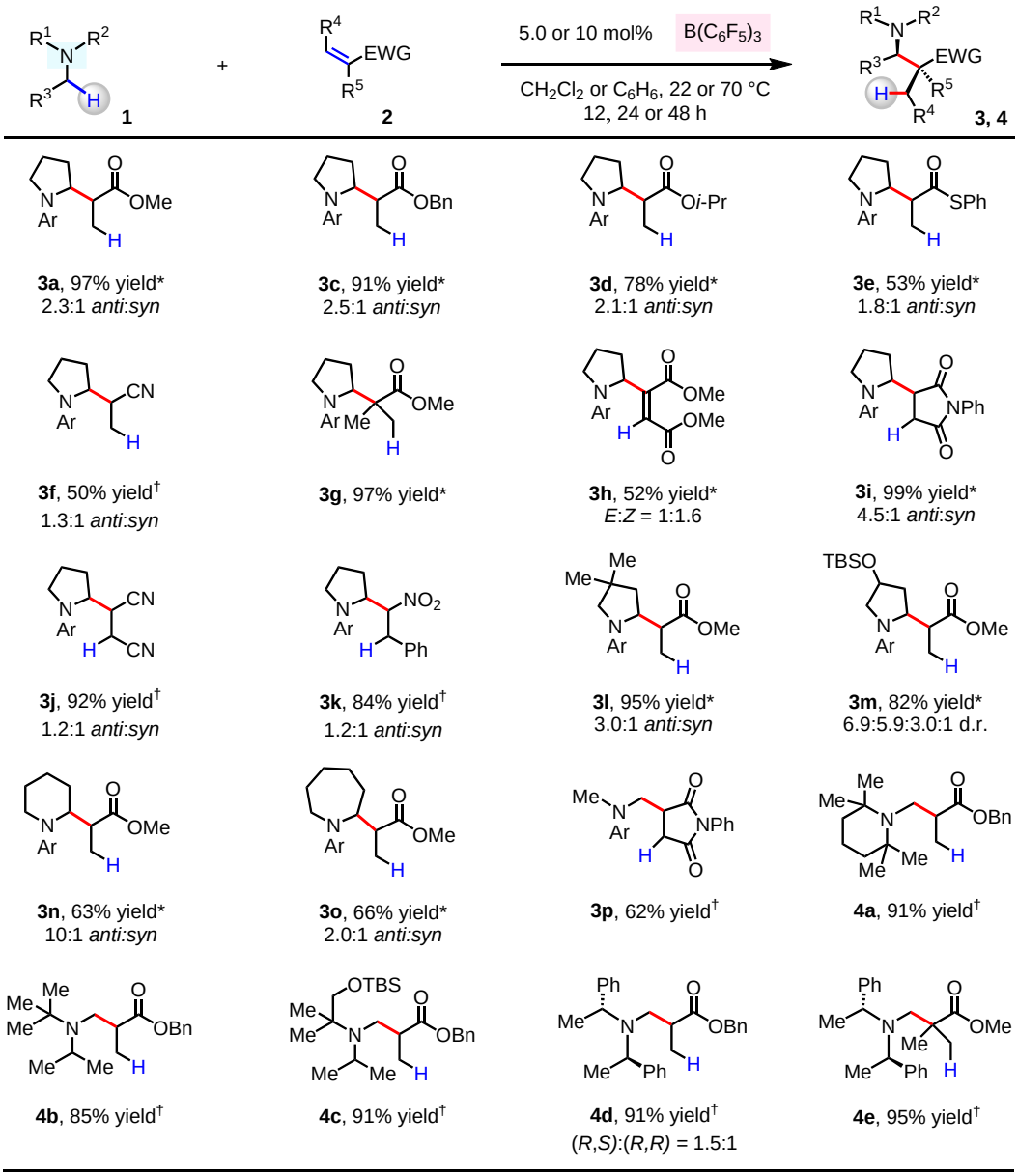


Figure 2. Coupling of *N*-alkylamines and *α,β*-unsaturated compounds through $B(C_6F_5)_3$-catalyzed hydride abstraction. The values correspond to yields of isolated and purified products. Diastereomeric ratio (d.r.) values were determined by analysis of the unpurified product mixture through analysis of ^1H NMR spectra. *5.0 mol% of $B(C_6F_5)_3$ was used. †10 mol% of $B(C_6F_5)_3$ was used. See the Supplementary Information for details.

Next, we investigated reactions with cyclic and acyclic *N*-alkylamines. 3,3-Dimethyl-,3-((*tert*-butyldimethylsilyl)oxy)-substituted *N*-aryl pyrrolidines (**1l**, **1m**), *N*-aryl piperidine (**1n**) and *N*-aryl azepane (**1o**) gave the corresponding products (**3l**–**3o**) in 63% to 95% yield. There was efficient hydride abstraction at the *N*-methyl site of various amines. 4-Methoxy-*N*,*N*,2,6-tetramethylaniline (**1p**) reacted with *N*-phenylmaleimide to afford **3p** (62% yield). A series of trialkyl-substituted amines that lack the fused *N*-aryl group were coupled efficiently with acrylates, leading to the formation of **4a**–**4e** (85%–95% yield). Reaction of (*R*)-*N*-methyl-1-phenyl-*N*-((*R*)-1-phenylethyl)ethan-1-amine with benzyl acrylate (**2c**) delivered **4d** as a 1.5:1 mixture of diastereomers, which were separable through silica gel chromatography, allowing us to secure the *β*-amino esters in enantiomerically pure form (see the Supplementary Information for details). The less hindered *N*-alkylamines (e.g., *N*-methyl pyrrolidine) did not react with **2c**, probably due to the formation of stable $B(C_6F_5)_3$–amine adducts, which may compete with Lewis acid-catalyzed hydride abstraction.

Having realized the single-catalyst racemic transformation based on the hydride abstraction concept, we chose to develop an enantioselective version of the catalytic process by employing $B(C_6F_5)_3$ in combination with an appropriate chiral Lewis acid. With *N*-arylpyrrolidine (**1a**) and 3-acryloyloxazolidin-2-one (**2q**) as model substrates, systematic evaluation of Lewis acid/chiral ligand complexes was performed (Fig. 3a). In the presence of 10 mol% of $B(C_6F_5)_3$ and $Mg(OTf)_2$, various bis-oxazoline ligands were tested (12 mol%, **L1**–**L4**). Whereas in the presence of PhBOX (**L1**) and DBFOX (**L2**) there was minimal conversion to **3q** (<10% yield), with PyBOX (**L3**, (*S*,*S*)-2,2'-(2,6-pyridinediyl)bis(4-phenyl-2-oxazoline)) we obtained **3q** in 35% yield, 1.1:1 *anti*:*syn* ratio, and 71:29 e.r. and 80:20 e.r. (*syn* and *anti* isomer, respectively). There was further improvement in efficiency (**3q** in >95% yield) when 2,6-bis((*S*)-4-(3-chlorophenyl)-4,5-dihydrooxazol-2-yl)pyridine (**L4**) was utilized as the chiral ligand. There was minimal conversion to the desired product and/or low enantioselectivity with $Mg(OTf)_2$/**L4**, or when Cu(OTf), $Ni(OTf)_2$, $Zn(OTf)_3$, $Sc(OTf)_3$, $Mg(ClO_4)_2$, and other Lewis acid co-catalysts were employed in combination with various ligands (see the Supplementary Information for details). Because $B(C_6F_5)_3$ catalyzes the C–C bond forming reaction between **1a** and **2q** in the absence of the chiral Mg-based co-catalyst (Fig. 3b; ***rac*-3q**, 35% yield), the presence of this Lewis acid can engender considerable diminution in e.r. However, we subsequently discovered that the reaction of **1a** with 3-acryloyl-4,4-dimethyloxazolidin-2-one (**2r**), catalyzed by the combination of $B(C_6F_5)_3$ and $Mg(OTf)_2$/**L4** can deliver either diastereoisomer of **3r** in high e.r. (**3r-*anti*** and **3r-*syn*** in 97:3 and 98:2 e.r., respectively, 88% yield; Fig. 3c). The higher enantioselectivity probably arises from a preference for Mg-activated **VIII** over $B(C_6F_5)_3$-

activated **VII**, the latter of which might suffer from severe steric repulsion between the *gem*-dimethyl group of **2r** and $B(C_6F_5)_3$, a contention supported by the fact that **2r** does not react in the absence of $Mg(OTf)_2$/**L4**.

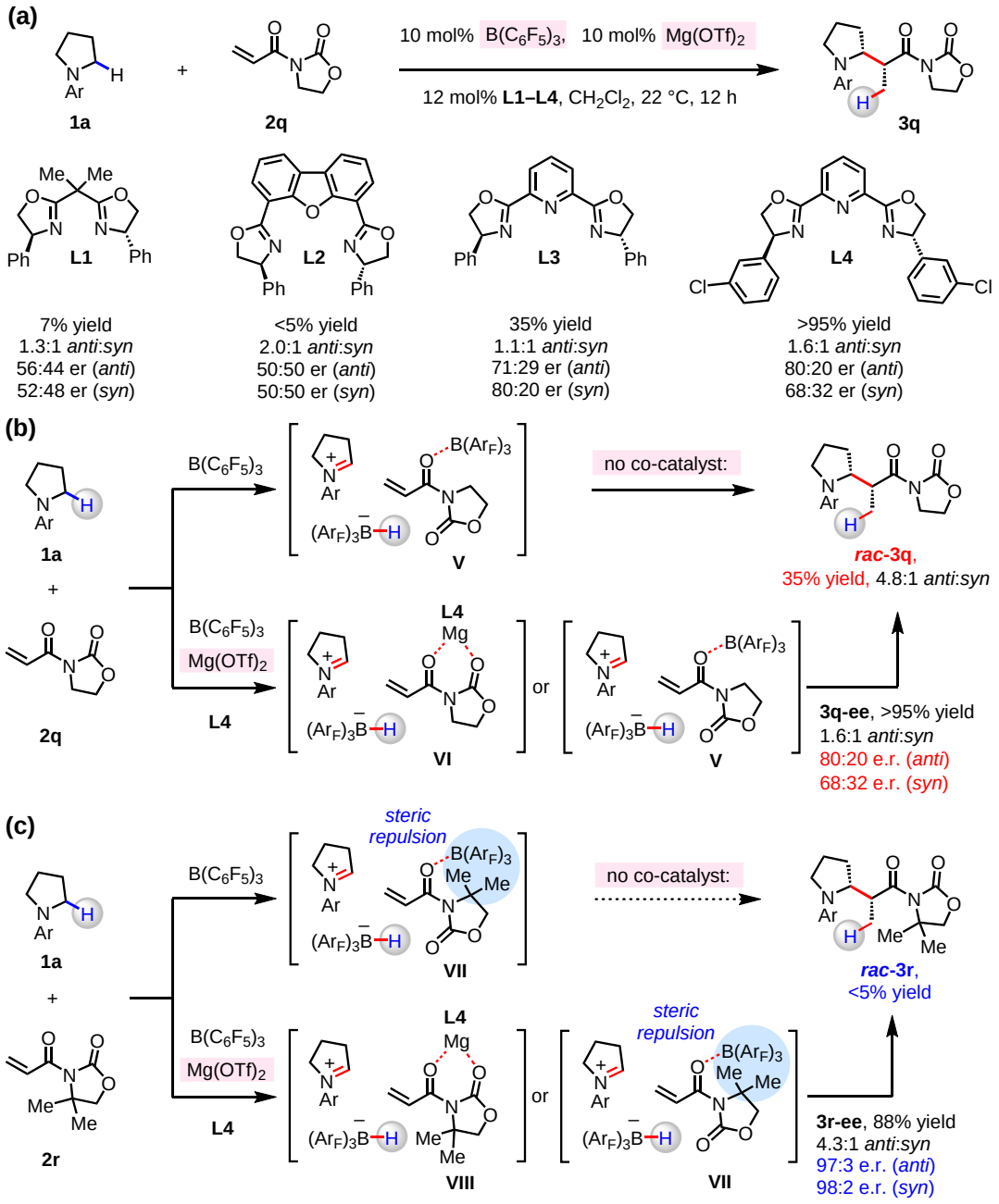


Figure 3. The effect of chiral Lewis acid co-catalysts on enantioselective coupling of an *N*-alkylamine and *N*-acryloyloxazolidinones. (a) Initial evaluation of chiral co-catalysts revealed that $Mg(OTf)_2$/bis(oxazoline) complexes catalyze stereoselective C–C bond formation. (b) Competing $B(C_6F_5)_3$-catalyzed racemic C–C bond forming reaction could deteriorate overall enantioselectivity. (c) The use of more hindered *N*-acryloyl oxazolidinone suppresses the racemic process to achieve C–C bond formation with higher enantioselectivity.

With **2r** as the electrophilic partner, fine-tuning of PyBOX ligands was performed (**L3**–**L12**, Fig. 4a). With derivatives that possess a halophenyl moiety (**L4**, **L7**–**L10**), **3r** was generated in superior yield and stereoselectivity (compared to other alkyl- or aryl-substituted ligands, **L3**, **L5**, **L6**, **L11**, **L12**). Whereas reaction with phenyl-substituted **L3** gave **3r** in low yield (18%; 94:6 e.r. for *anti* and *syn* isomers), that of 3-chlorophenyl-subsituted **L4** afforded **3r** in 88% yield as a 4.3:1 mixture of *anti*:*syn* isomers (97:3 and 98:2 e.r., respectively). The size and position of the halogen substituent within the chiral catalyst can influence a reaction outcome. With 3-fluorophenyl- (**L7**) or 3-bromophenyl-substituted (**L8**) ligands, the transformations were moderately efficient (**3r** in 36% and 54% yield, respectively), but highly enantioselective (97:3 e.r. (**3r-*anti***) and 98:2 e.r. (**3r-*syn***)). With 2-chlorophenyl- (**L9**) and 4-chlorophenyl-substituted (**L10**) ligands, on the other hand, while **3r** was isolated in higher yield 88% and 72%, respectively), there was some diminution in diastereo- and enantioselectivity (ca. 2:1 *anti*:*syn*, ca. 90:10 e.r. for **3r-*anti***). What is more, reactions performed in the presence of *meta*-tolyl-substituted **L11** or electron-withdrawing 3-trifluoromethylphenyl-substituted **L12** were much less efficient (<20% yield). Although the precise origin of such notable effects by the catalyst structure remains to be elucidated, the present findings suggest that non-covalent interactions[38,39] (e.g., π–cation, π–π interactions) between ligand substituents and *in situ*-generated iminium ion and/or Mg–enolate might be critical.

With $B(C_6F_5)_3$ and $Mg(OTf)_2$/**L4** as optimal catalysts, we surveyed a series of achiral and chiral *N*-acryloyloxazolidinones (Fig. 4b). In contrast to dimethyl-substituted oxazolidinone **3r** was obtained in 88% yield and up to 98:2 e.r. (Fig. 3c), the less hindered **3q** was generated in >95% yield, but only in up to 80:20 e.r., presumably as a result of competing transformation catalyzed by $B(C_6F_5)_3$. Cyclohexyl-substituted **3s** was obtained in *anti*:*syn* ratio of 5.6:1 (*vs.* **3q** (1.6:1) and **3r** (4.3:1)), and enantiomerically pure *N*-acryloyloxazolidinones containing benzyl (**2t**) or phenyl (**2u-(*S*)**, **2u-(*R*)**) moieties proved to be suitable starting materials as well. (*R*)-3-Acryloyl-4-phenyloxazolidin-2-one (**2u-(*R*)**) represents the "matched" enantiomer with $Mg(OTf)_2$/**L4** pairing to afford **3u-(*R*)** in >95% yield and 6.8:1:0:0 d.r.; with **2u-(*S*)**, **3u-(*S*)** was obtained in 61% yield and 3.7:1:0:2.1 d.r. The significant impact of the chiral co-catalyst on efficiency and stereoselectivity is evident as **3u-(*R*)** was produced in just 14% yield and 2.5:2.5:1:1 d.r. in its absence. With $B(C_6F_5)_3$ and $Mg(OTf)_2$/**L4** loadings reduced to 5.0 mol%, **3u-(*R*)** was obtained in 93% yield (6.8:1:0:0 d.r.).

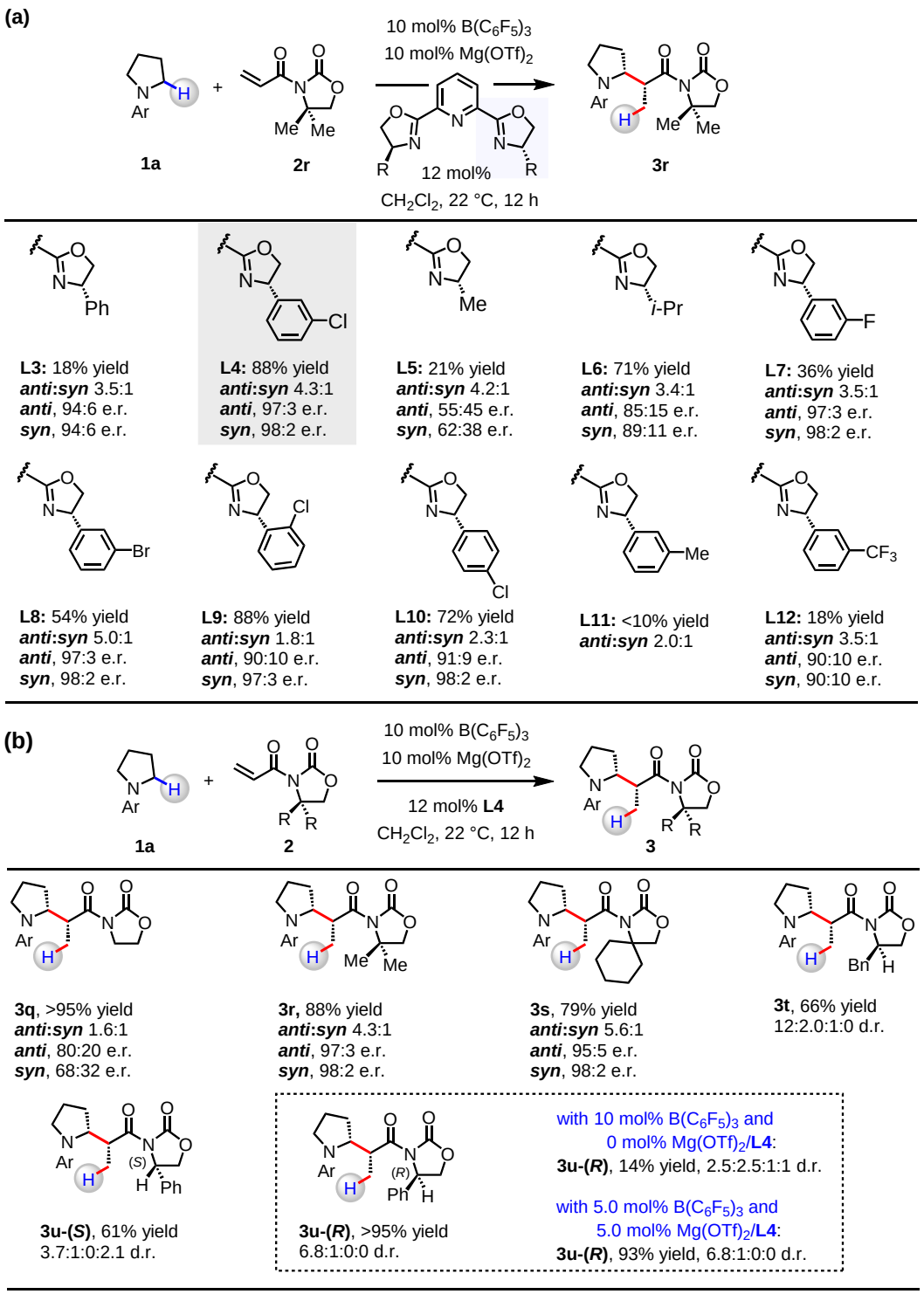


Figure 4. The influence of different PyBOX ligand and oxazolidinone substituents. (a) Notable improvements in reaction efficiency and stereoselectivity were observed with halophenyl-substituted PyBOX ligands. (b) *β*-Amino amides were prepared in up to 98:2 e.r. from the achiral *N*-acryloyloxazolidinone. With chiral oxazolidinones and $Mg(OTf)_2$/**L4**, enantiomerically pure *β*-amino amide **3u-(*R*)** could be obtained after separation of diastereomers by silica gel chromatography. Catalyst loading can be lowered to 5.0 mol% without deterioration in yield of isolated and purified product.

The catalytic protocol is amenable to scale-up; for instance, 5.0 mmol of **1a** was converted to **3u-(*R*)** in 6.7:1:0:0 dr (>95% conv.; Fig. 5a). The diastereomers were separated readily by silica gel chromatography to afford the major isomer in 1.47 g (70% yield; minor diastereomer: 0.16 g, 8% yield). The predominant diastereomer was then converted to *β*-amino ester (**5a**), *β*-amino acid (**5b**), and *β*-amino alcohol (**5c**) in 64–91% yield and >99:1 er. Furthermore, treatment of **3u-(*R*)** with NaOMe in methanol led to the formation of **5d** in 97% yield. X-ray crystallographic analysis of **5d** revealed its absolute configuration to be (*R*,*R*,*R*).[40] The two-catalyst protocol is applicable to synthesis of a variety of *N*-alkylamines, affording **3v** and **4f**–**4h** as separable mixtures of diastereomers (see the Supplementary Information for details). After chromatographic separation, each of the diastereomers was converted into the corresponding benzyl ester (**5**), and HPLC analysis showed that **3v** and **4f**–**4h** were generated in >99:1 e.r. in either isomeric form. The presence of $Mg(OTf)_2$/**L4** was essential, as otherwise **4h** was produced in only 32% and 1:1 d.r. in its absence. Reactions of various *N*-substituted pyrrolidines with 3-acryloyl-4,4-dimethyloxazolidin-2-one (**2r**) catalyzed by $B(C_6F_5)_3$ and $Mg(OTf)_2$/**L4** were investigated. While no desired product was obtained with *N*-phenylpyrrolidine (see the Supplementary Information for details), **3w**, **3x** and **3y** possessing the hindered and electron-donating 2,6-dimethylaryl substituents were produced in 71, 69 and 70% overall yield, respectively. An increase in enantioselectivity for both *anti* and *syn* diastereomers was observed with more hindered *para*-*t*-Bu-substituted **3y** (91:9 e.r. (**3y-*anti***) and 98:2 e.r. (**3y-*syn***)) over *para*-H-substituted **3w** (89:11 e.r. (**3w-*anti***) and 93:7 e.r. (**3w-*syn***)). Sterically encumbered *N*,*N*,*N*-trialkylamines could also react with **2r** to afford **4i** (52% yield, 88:12 er) and **4j** (46% yield, 96:4 er).

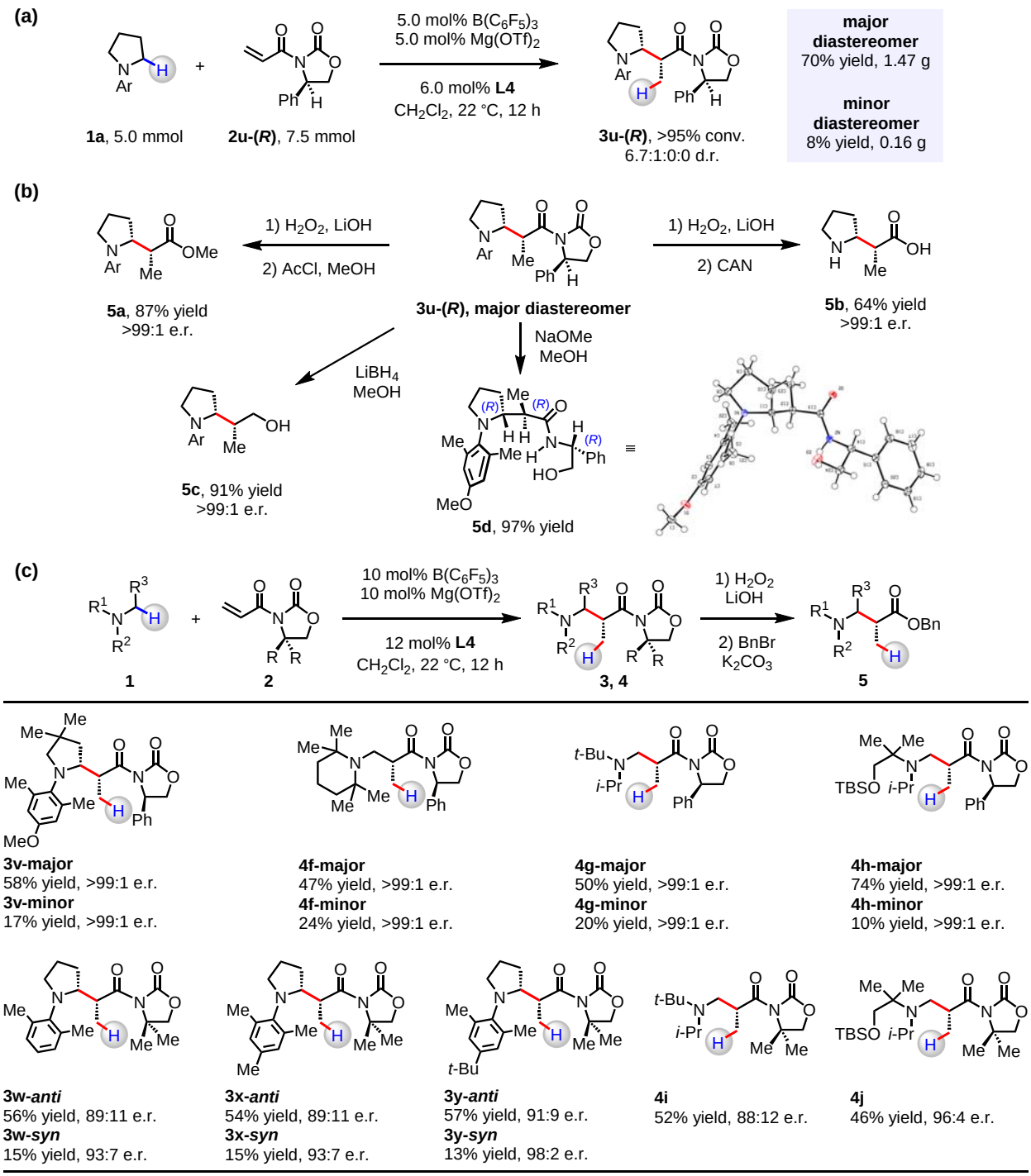


Figure 5. Synthesis of chiral *α*-substituted amines. (a) As demonstrated through preparation of *β*-amino amide **3u-(*R*)**, the catalytic reactions are amenable to gram-scale operations. (b) The versatility of **3u-(*R*)** was demonstrated by its conversion into a *β*-amino ester, a *β*-amino alcohol and a *β*-amino acid. The absolute configuration of **3u-(*R*)** was determined by X-ray crystallographic analysis of **5d**. (c) A series of *N*-alkylamines reacted with **2** to afford the corresponding *β*-amino amides. For **3v** and **4f**–**4h**, diastereomers were isolated by silica gel chromatography and then converted into *β*-amino esters (**5**) that were determined to be enantiomerically pure.

We have developed a stereochemical model for reaction of the **L3**–Mg–enolate complex with the *in situ* generated iminium ion by means of density functional theory (DFT) studies (Fig. 6). These investigations suggest that the enantiomers of the minor diastereomer are probably formed via **IX** and **X** (ΔG = 20.6 and 21.1 kcal/mol respectively), whereas **XI** and **XII** generate enantiomers of the major diastereomer (ΔG = 18.1 and 18.8 kcal/mol, respectively). High enantioselectivity for the major as well as the minor diastereomer is due to effective blocking of the *re* face of the Mg bound enolate (**IX** and **XI**). Nonetheless, we should note that highly accurate modeling of diastereoselectivity is difficult, and depends strongly on attenuation of dispersion interactions in solution.[41,42] It is possible that modes other than **IX** and **X** might similarly contribute to formation of the minor diastereomer (see the Supplementary Information).

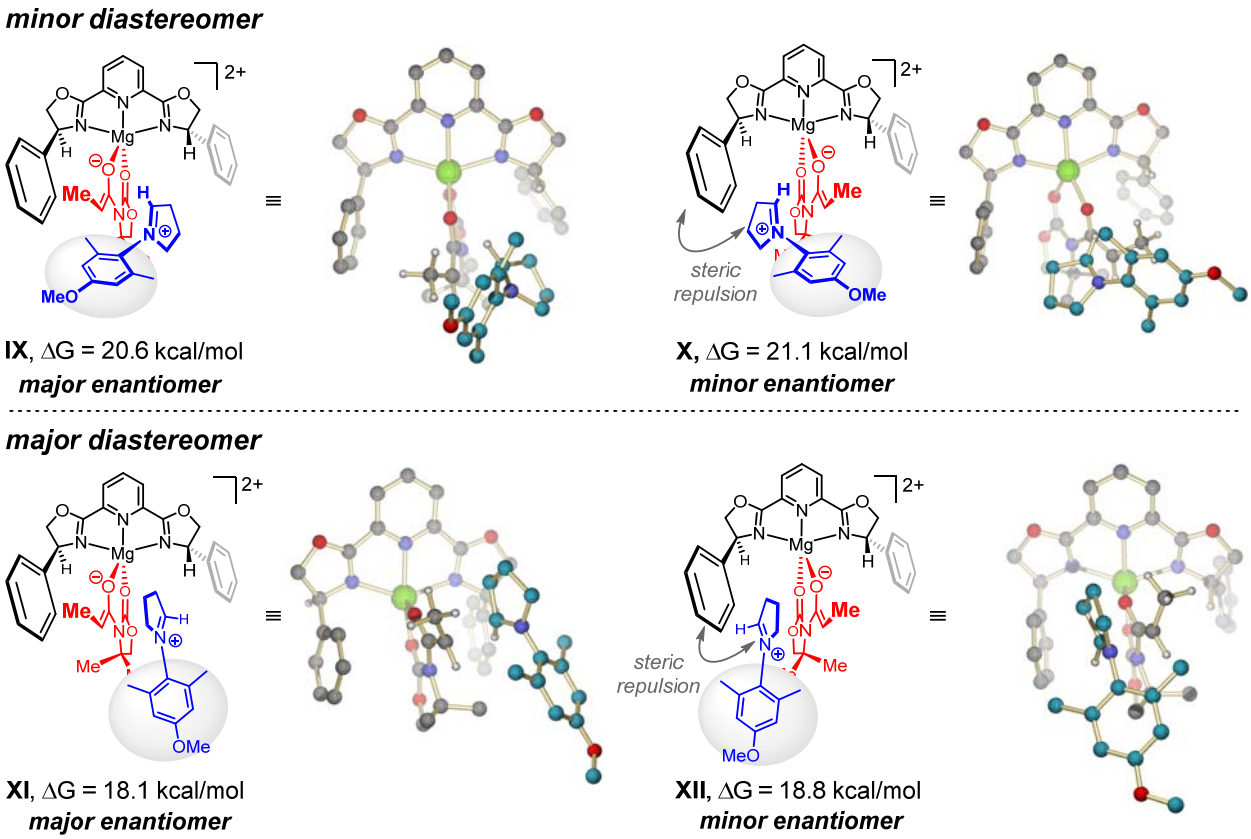


Figure 6. Stereochemical models to account for the observed sense of stereoselectivity. Stereochemical model for reaction of **L3**–Mg–enolate complex with iminium ion; DFT studies were performed at the PBE0-D3BJ/def2TZVPP//M06L/DF-def2SVP level of theory in CH_2Cl_2 (SMD solvation model). See the Supplementary Information for details. Abbreviations: **L3**, PyBOX ligand; SMD, solvation model based on density; $\Delta\Delta E_{disp} = \Delta\Delta E(PBE0\text{-}D3BJ) - \Delta\Delta E(PBE0)$.

CONCLUSIONS

In brief, we have designed an efficient and diastereo- and enantioselective C–C bond forming transformation by implementing the cooperative action of two non-precious metal-based Lewis acid catalysts that possess overlapping functions. We illustrate that by proper tuning of different features of structurally and electronically different Lewis acids and substrates, the ability of Lewis acid catalysts to serve as a hydride acceptor from amines, or an activator of α,β-unsaturated compounds, can be adjusted. Accordingly, enhancements in both the efficiency and stereoselectivity of C–C bond forming reactions between amines and α,β-unsaturated compounds can be attained without concomitant loss in enantioselectivity arising from any undesirable mode of catalysis by the achiral Lewis acid component. The principles outlined herein serve as a conceptual framework for the development of new processes that demand separate and independently operational Lewis acidic co-catalysts whose functions might easily overlap and the simultaneous use of which might initially seem to have a negative impact on enantioselectivity. Studies aimed at achieving highly enantioselective C–C bond forming reactions with a broader scope of hydride donors and pro-nucleophiles are in progress.

ASSOCIATED CONTENT

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We are grateful for financial supports from the National Institutes of Health (GM-128695) and Boston College. We are thankful to Professor Amir H. Hoveyda (BC) for helpful discussions. Dr. Juan del Pozo del Valle, Dr. Filippo Romiti, Mr. Malte S. Mikus (BC), and Mr. Richard Y. Liu (MIT) are thanked for their assistance with this project. We are grateful to Professor James P. Morken for a loan of PyBOX ligands, and Dr. Bo Li for the X-ray crystallographic analysis.

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37 As suggested by one of the reviewers, the significant difference in reaction rate observed when the loading of $B(C_6F_5)_3$ is lowered from 5.0 mol% to 2.5 mol% suggests that the mechanism of the reaction proposed in Figure 1d is not the complete picture. Formations of aggregates or other preorganized states requiring multiple equivalents of $B(C_6F_5)_3$ or substrate may be involved. Kinetic and spectroscopic studies carried out using *N*-aryl pyrrolidine (**1a**) and isopropyl acrylate exhibited approximately second order dependence with respect to $B(C_6F_5)_3$ (see the Supplementary Information for details). Detailed mechanistic investigations are being carried out.

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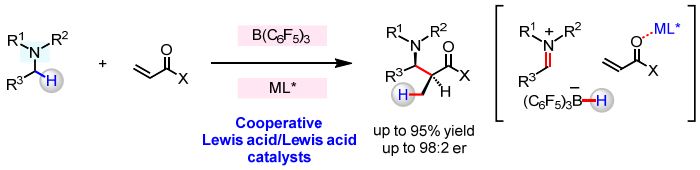
B(C6F5)3
ML*
Cooperative
Lewis acid/Lewis acid
catalysts
up to 95% yield
up to 98:2 er