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Enantioselective Synthesis of *N*-Alkylamines through *β*-Amino C–H Functionalization Promoted by Cooperative Actions of $B(C_6F_5)_3$ and a Chiral Lewis Acid Co-Catalyst

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Abstract

We disclose a catalytic method for *β*-C(sp^3)–H functionalization of *N*-alkylamines for synthesis of enantiomerically enriched *β*-substituted amines, entities prevalent in pharmaceutical compounds and used to generate different families of chiral catalysts. We demonstrate that a catalyst system comprising of seemingly competitive Lewis acids, $B(C_6F_5)_3$ and a chiral Mg- or Sc-based complex, promotes the highly enantioselective union of *N*-alkylamines and *α*,*β*-unsaturated compounds. An array of *δ*-amino carbonyl compounds was synthesized under redox-neutral conditions by enantioselective reaction of a *N*-alkylamine-derived enamine and an electrophile activated by the chiral Lewis acid co-catalyst. The utility of the approach is highlighted by late-stage *β*-C–H functionalization of bioactive amines. Investigations in regard to the mechanistic nuances of the catalytic processes are described.

Graphical Abstract

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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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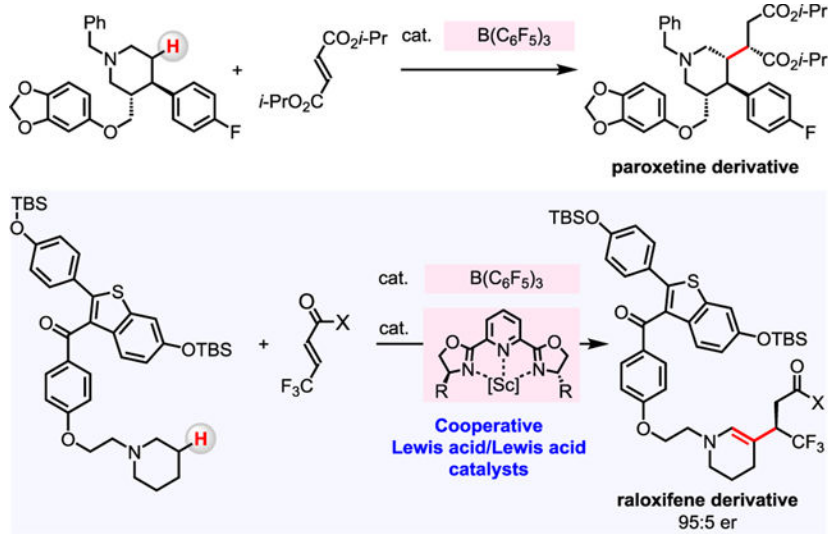

1. INTRODUCTION

Enantioselective synthesis of *N*-alkylamines through the transformations of amino C(sp^3)–H bonds has emerged as a powerful strategy to access key building blocks of N-based natural products, drugs and catalysts for stereoselective synthesis.[1–18] A plethora of organometallic catalysts have been introduced that can promote reaction at an α-amino C–H bond by conversion of an amine substrate to appropriately reactive intermediate (e.g., α-amino radical, iminium ion),[19–31] metal–carbenoid insertion,[32–33] or heteroatom-directed metalation.[34–36] More remote γ-amino C–H bonds may be activated by L_nPd-catalyzed and N-directed cyclometalation.[37–41] However, development of methods for synthesis of enantiomerically enriched amines by β-amino C–H functionalization is a major challenge that remains to be addressed.[42–50] α-Amino C–H activation by hydrogen atom or hydride transfer is facilitated by stabilization of the resulting species through hyperconjugation with the nitrogen lone pair. Nonetheless, such processes do not readily occur at the β position of amines. Furthermore, L_nPd-catalyzed β-amino C–H activation requires the presence of a strained 4-membered palladacycle (vs a more favorable 5-membered metallacycle formed by γ-amino C–H activation).[42–44]

There are only a limited number of protocols for preparing enantiomerically enriched β-substituted amines through activation of a β-amino C–H bond.[51–54] A notable strategy is Pd/phosphoric acid-catalyzed and IOAc-mediated desymmetrization of gem-dimethyl groups in tetramethyl-morpholinone **1a** to give organometallic intermediate **I** en route to aziridine **2a** (Figure 1a).[52] Equally noteworthy is Pd/PR_3-catalyzed stereospecific cross-coupling of 1,3-oxazinane **1c** (prepared by *s*-BuLi/(+)-sparteine-mediated α-lithiation of **1b** and Li/Zn exchange with $ZnCl_2$) and Ph–Br to give **2c** via L_nPd–enamine **II** (Figure 1b).[54] Still, key shortcomings remain unaddressed. For instance, acid–base complexation often occurs in a mixture that contains a Lewis acidic catalyst (e.g., $Pd(OAc)_2$) and a Lewis basic *N*-alkylamine substrate and/or product which may also contain other Lewis acid-sensitive functional groups.[55–62] Additionally, because these methods require IOAc or *s*-BuLi, moieties that readily react with oxidants and Lewis bases can be problematic. As a result, substrate scope is confined to highly sterically encumbered and/or Boc-protected amines (**1a**, **1b** and analogues) with minimal electronic and steric affinity towards Lewis acids, Lewis bases or oxidants. Development of a sustainable element-based, highly functional group tolerant and enantioselective catalyst system which allows access to *β*-substituted *N*-alkylamines via *β*-amino C–H functionalization under redox-neutral conditions therefore constitutes a compelling research objective.

Conversion of *β*-amino C–H bonds can be achieved nonstereoselectively through in situ generation of enamines from *N*-alkylamines;[63–85] but enamine precursors are largely limited to *N*,*N*-dialkylanilines. In the case of more Lewis basic trialkylamines and substrates containing acid- and/or base-sensitive moieties, catalyst deactivation can become problematic.[55–62] One strategy to overcome mutual quenching would be to use strongly Lewis acidic and sterically hindered $B(C_6F_5)_3$[86–88] to convert trialkylamines into enamines;[63–76] this would involve $(F_5C_6)_3B$-mediated hydride abstraction from the amine to give a borohydride/iminium complex,[63–76] which would in turn be deprotonated to yield an enamine (Figure 1c, **1** → **III** → **IV**).[89–92] Chang and co-workers have shown that $B(C_6F_5)_3$ is capable of promoting *β*-silylation of *N*-arylpiperidines to generate *rac*-bridged sila-*N*-heterocycles.[64] We have introduced a method for $(F_5C_6)_3B$-catalyzed hydrogen isotope exchange involving *β*-amino C–H bonds of various bioactive molecules.[65] Still, engagement of the enamine intermediates formed by $(F_5C_6)_3B$/Brønsted base-catalyzed dehydrogenation of *N*-alkylamines has not been utilized in an enantioselective transformation.

In contemplating ways to develop a protocol that involves *β*-C–H alkylation of *N*-alkylamines (**1**) through an enantioselective union with *α*,*β*-unsaturated compounds (**3**), we envisioned using a set of $B(C_6F_5)_3$, a Brønsted base catalyst, and a chiral Lewis acid co-catalyst (M–L*) that might be induced to function cooperatively (Figure 1c).[63–76, 93–102] We imagined that $B(C_6F_5)_3$ being the recipient of a hydride from an amine (**1**), leading to the formation of a borohydride and an iminium ion (**III**). A Brønsted base catalyst would subsequently deprotonate **III** to furnish enamine **IV**. An ensuing enantio- and diastereo-selective C–C bond formation between enamine **IV** and *α*,*β*-unsaturated compound, activated by the chiral Lewis acid co-catalyst (**V**), would deliver zwitterionic **VI**. This would be followed by protonation and reduction to give *β*-alkylation product **4**. A key advantage of using untethered and independently operational catalysts is that efficiency and stereoselectivity may be easily optimized by evaluation of readily accessible Lewis acids, Lewis bases and chiral ligands (vs bifunctional catalysts that require tethering of different catalytic sites). However, $B(C_6F_5)_3$ and the chiral Lewis acid co-catalyst must be able to perform their independent roles without overlapping functions, as otherwise, $B(C_6F_5)_3$ could promote the racemic reaction through activation of both substrates, most likely resulting in diminished enantioselectivity. Here, we report that functionally similar $B(C_6F_5)_3$ and a chiral Lewis acid co-catalyst can operate in concert to engender enantioselective coupling of *N*-alkylamines and *α*,*β*-unsaturated compounds.

2. RESULTS AND DISCUSSION

2.1. Method Development

2.1.1. Identification of Optimal Conditions.—To begin, we set out to investigate if $B(C_6F_5)_3$ might activate both *N,N*-dibenzylethanamine (**1d**) and diisopropyl fumarate (**3d**), generating **4d** (Table 1). Treatment of **1d** and **3d** with 10 mol % $B(C_6F_5)_3$ and 10 mol % Et_3N, 2,2,6,6-tetramethylpiperidine (TMP) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded **4d** in 50%, 25%, and <5% yield, respectively (entries 1–3). Other than **4d**, over alkylation product **5d** was also formed (entries 1–6), probably through *in situ* conjugate addition of an enolate (**VI**, Figure 1c) to **3d**. When the transformation was carried out without a Brønsted base, **4d** (73% yield) and **5d** (25% yield) were formed more efficiently (entry 4), suggesting that **1d**, **4d** and/or **5d** can deprotonate an iminium to form an enamine (**III** → **IV**, Figure 1c). To suppress formation of **5d**, the mixture was diluted (entries 5–6); by using 10 mol % of $B(C_6F_5)_3$ and 0.80 mL of benzene (vs 0.20 mL used in entries 1–4), we were able to obtain **4d** (91% yield) within 12 hours (entry 6).[103] Moreover, no **4d** was formed when less hindered BCl_3 or less acidic BPh_3 were involved (entries 7–8). Without $B(C_6F_5)_3$, **4d** was not generated (entry 9). These findings support the notion that strongly Lewis acidic $B(C_6F_5)_3$ in combination with sterically demanding and electron-rich *N*-alkylamines constitute the most effective catalyst–substrate combination.

2.1.2. Scope.—Many acyclic and cyclic *N*-alkylamines may be used in the reaction with diisopropyl fumarate **3d** to generate the corresponding *β*-substituted amines (**4d**–**4o**, Figure 2). Reaction with *N,N*-dibenzylethanamine **1d** and **3d** afforded **4d** in 88% yield. *N*-Benzhydryl-substituted secondary amines **1e** and **1f** were suitable substrates, furnishing **4e** (93% yield) and **4f** (87% yield, 2.1:1 dr), respectively. None of the 1,4-addition product was observed in the case of a secondary amine bearing a more hindered trityl group (e.g., *N*-tritylethanamine); this may be attributed to rapid substrate decomposition. With less hindered *N*-benzylethanamine, the formation of $(F_5C_6)_3B$–amine adduct may compete with Lewis acid-catalyzed hydride abstraction, resulting in minimal formation of the desired product. We then investigated reactions with different chiral *N*-alkylamines (**1g**–**1i**, Figure 2). Accordingly, **4g** was produced in 90% yield as a 1.4:1 mixture of easily separable diastereomers, allowing us to secure the amino ester in enantiomerically pure form. As indicated by synthesis of **4h** and **4i**, chiral pyrrolidines may be used as starting materials. Whereas the reaction with the less hindered 1-(4-methoxy-2,6-dimethylphenyl)piperidine furnished **4j** as the only product in 89% yield, with the bulkier 4,4-dimethyl-substituted piperidine substrate, enamine **4k** was obtained in 93% yield.[104]

The method is applicable to late-stage modification of *N*-containing bioactive molecules that possess an array of Lewis acid-sensitive functional groups (**1l**–**1n**; Figure 2). In addition to the *N*-alkylamine moieties of **1l**–**1n**, a ketone (**1l**), a benzothiophene (**1l**), an ether (**1l**, **1n**), a pyrimidinone (**1m**) and a benzoisoxazole (**1m**) were tolerated. Thus, structures of piperidine-based compounds, such as raloxifene (osteoporosis treatment), risperidone (anti-psychotic) and paroxetine (antidepressant) could be readily altered. Silyl-protected raloxifene **1l** reacted efficiently with **3d** to afford **4l** in 80% yield and 2.5:1 dr. Risperidone **1m**, possessing more sterically hindered *β*-amino C–H bonds (vs. **1l**), was merged with **3d**, furnishing enamine **4m** (32% yield); minimal amounts (<5%) of the product derived from alkylation of acyclic *β*-amino C–H bond (H labelled in red) could be observed (^{1}H NMR analysis). The process involving *N*-benzyl paroxetine **1n** and **3d** afforded **4n** and **4o** in 39% and 14% yield, respectively.

2.1.3. Diastereo- and Enantio-selective Processes.

To develop a highly diastereoselective and catalytic *β*-amino C–H alkylation variant, we chose to utilize the prolinol derivative **1i**[105–108] and (*S,E*)-4-phenyl-3-(4,4,4-trifluorobut-2-enoyl)oxazolidin-2-one **6a** as model substrates (Figure 3a). In the event, $(F_5C_6)_3B$-catalyzed reaction of **1i** and diisopropyl fumarate **3d** gave *β*-alkylation product **4i** in only 56% yield and 2.5:1 dr (Figure 2). To probe whether the use of enantiomerically pure electrophile leads to improved dr, we reacted **1i** and **6a** in the presence of $B(C_6F_5)_3$ to find that product **7a** was formed in <5% yield. These findings suggest that $B(C_6F_5)_3$ facilitates the conversion of **1i** into an enamine but does not sufficiently activate **6a**. We therefore decided to evaluate a blend of $B(C_6F_5)_3$ and various Lewis acid co-catalysts, latter of which may activate **6a**, to establish that, with 10 mol % $B(C_6F_5)_3$ and ZnI_2, **7a-(*R,R,R,S*)** can be obtained in 82% yield and as a single diastereomer (>20:1 dr; see the Supporting Information for details). The presence of HBPin led to enhanced dr, as **7a** was isolated in 67% yield and 10:1 dr in its absence (see the Supporting Information for details). We also explored the suitability of developing an enantioselective *β*-amino C–H alkylation reaction between achiral substrates **1o** and **6b**, promoted by a combination of $B(C_6F_5)_3$ and an enantiomerically pure organometallic co-catalyst (Figure 3b). We discovered that, with a complex of PyBOX **L1**–$Mg(ClO_4)_2$, *β*-amino C–H alkylation of **1o** proceeds to afford **7b** in 67% yield (1.6:1 dr, up to 90:10 er). However, neither efficiency nor enantioselectivity could be improved by further catalyst optimization (with **6b** as electrophile; see the Supporting Information for details).

To improve enantioselectivity, we probed the transformations involving a number of chiral Lewis acid co-catalysts and *α*,*β*-unsaturated compounds bearing different auxiliaries.[109–112] We found that 1-(4-methoxyphenyl)pyrrolidine **1p** reacts efficiently with 2-acryloylpyrazolidinone derivative **6c** in the presence of 10 mol % of $B(C_6F_5)_3$ together with $Sc(OTf)_3$ and various chiral bisoxazoline ligands (Figure 4). We then found that reactions with Ph–BOX, Ph–DBFOX and Ph–PyBOX ligands (e.g., **L2**–**L4)** are hardly enantioselective (58:42–50:50 er). The situation improved considerably with alkyl-substituted PyBOX ligands (e.g., **L5**–**L8**), and in the presence of (*S*)-*i*-Bu–PyBOX (**L8**), **7c** was formed in 72% yield, 2.7:1 dr and up to 98:2 er. Reaction efficiency improved (85% yield) when **L9** and its diastereomer **L10** were used. The stereochemical course of **1p**-derived enamine addition to [**L10**–$Sc(OTf)_3$]-activated **6c** can be rationalized by the models presented in Figure 5.[113–115] Models **VII** and **VIII** represent the energetically minimized structures of [**L10**–$Sc(OTf)_3$] docked with **6c**.[113–115] As shown in model **VII**, the high level of enantioselectivity observed in the formation of **7c-(*R,S*)** can be explained by selective 1,4-addition of the enamine to the *re*-face of [**L10**–$Sc(OTf)_3$]-bound **6c**; as depicted in model **VIII**, the *si*-face is effectively shielded by a *sec*-butyl group of the PyBOX ligand.

Enantioselective reactions with an array of *N*-alkylamines were carried out in the presence of $B(C_6F_5)_3$, a **L**–$Sc(OTf)_3$ complex and **6c–6f** (Figure 6). *β*-Alkyl derivatives of 1-(4-

methoxyphenyl)pyrrolidine (**1p**) bearing γ-ester, ketone or CF_3 groups (**7c–7f**) were thus synthesized in 62–83% yield, 2.0:1–6.7:1 dr and 95:5–98:2 er. The reaction of **1p** with **6c** (R^5 = Et) and **6d** (R^5 = Bn) gave **7c** (2.0:1 dr, up to 98:2 er) and **7d** (3.0:1, up to 95:5 er), respectively, indicating that *N*-substituents of the pyrazolidinone unit have influence over both diastereo- and enantio-selectivity. When acyclic *N*-ethyl-4-methoxy-*N*,2,6-trimethylaniline **1q** was reacted with F_3C-substituted **6f** (Figure 7a), *N*-arylpiperidine derivative **7g** was produced in 67% yield (>20:1 dr, 95:5 er); generation of **7g** probably entails β-amino C–H alkylation of **1q** by **6f** to afford a zwitterionic intermediate containing an iminium and an enolate (**IX**), followed by isomerization of the iminium to give **X**; ensuing intramolecular Mannich-type reaction gives **7g**. The unions of *N*-arylpiperidines (**1j**–**1k**) or *N*-arylazapene (**1r**) with **6f** afforded enamines **7h**–**7j** in 74–95% yield and 94:6–96:4 er. The reaction of *N*-arylpiperidine-3,3,5,5-d_4 **1j-*d*** (0.10 mmol) and **6f** (0.20 mmol) gave **7h-*d*** (84% yield, 95:5 er) and **8h-*d*** (0.08 mmol; Figure 7b). Spectroscopic analysis of **7h-*d*** and **8h-*d*** revealed that there is deuterium incorporation at their enolizable α-carbonyl units, and that there is D/H exchange at C5 of **7h-*d*** (>95% in **1j-*d*** → 81% in **7h-*d***).[65] These results imply that in situ generated $[(F_5C_6)_3B–H]^-$ $[base–D]^+$ reacts with **6f** to produce **8h-*d*** to regenerate $B(C_6F_5)_3$ (vs by releasing H–D). We were able to functionalize the β-Amino C–H bonds of bioactive trialkylamines, including cloperastine (cough suppressant) **1s** and raloxifene **1l**, to generate enamines **7k** and **7l** in 53% yield (90:10 er) and 57% yield (95:5 er), respectively.

2.1.4. Scalability and Modifications of β-Functionalized Amines.—

The catalytic method is scalable. For example, treatment of 4.0 mmol of *N*-arylpiperidine **1j** and **6f** with 10 mol % $B(C_6F_5)_3$ and 10 mol % **L10**–$Sc(OTf)_3$, (CH_2Cl_2, 12 h, 60 °C) afforded **7h** in 95% yield (1.9 g; Figure 8a). Treatment of **7f-(*R,S*)** with LiSEt followed by reduction of the resulting thioester with $LiAlH_4$ furnished alcohol **9a-(*R,S*)** in 95% overall yield (Figure 8b). Compound **9a-(*R,S*)** was subsequently converted to its derived carbamate **9b-(*R,S*)** which was subjected to the X-ray crystallographic analysis for determination of absolute configuration (see the Supporting Information for details). Enamines obtained by enantioselective β-alkylation were found to be versatile intermediates (Figure 8c). Hydrogenation of enamine **7h** by a chiral Ir-based catalyst afforded **9c** in 83% yield and 5.0:1 dr,[116] and treatment of **7h** with NFSI and TMSCN gave fluorocyanation product **9d** in 88% yield and 4.0:1 dr.[117]

2.2. Mechanistic Investigations

We designed and performed studies to gain insight regarding the mechanistic nuances of the catalytic process.[118] These studies included determining reaction orders, kinetic isotope effects, and Hammett ρ values (Figures 9, 12, and 13, respectively). Additionally, these investigations led to revised pathways for catalytic β-C–H alkylation reaction (Figures 10–11).

2.2.1. Determination of Reaction Orders and a Consistent Mechanistic Pathway.—

We found that the reaction of *N*-arylpyrrolidine **1p** with α,β-unsaturated compound **6g** has a second-order dependence on $B(C_6F_5)_3$ concentration (Figure 9a) but is not at all impacted by the concentration of **L6**–$Sc(OTf)_3$ complex (Figure 9b). Furthermore, we found a first-order dependence on amine concentration of **1p** (Figure 9c) but, a reverse first-order dependence on the concentration of electrophile **6g** (Figure 9d). The independence of the reaction rate on the initial concentration of **L6**–$Sc(OTf)_3$ suggests that enantioselective C–C bond forming event between in situ generated enamine and [**L6**–$Sc(OTf)_3$]-activated **6g** (Figure 10, **XV** → **XVI**) occurs after the turnover-limiting step. Furthermore, the negative first-order dependence on the concentration of **6g** implies that the resting state consists of **6g** and the Lewis acid. Spectroscopic analysis of the reaction mixture (^{19}F NMR) supports the proposal in regard to formation of [**6g**–$B(C_6F_5)_3$] (**XI**).[119]

Thus, it is likely that *β*-C–H alkylation proceeds by the release of $B(C_6F_5)_3$ from **XI**, which then abstracts a hydride from **1** to form an iminium/borohydride complex (**XII**). Borohydride reduction of $(F_5C_6)_3B$-activated **6** delivers a $[(F_5C_6)_3B\text{–enolate}]^-[\text{iminium}]^+$ complex (**XII** → **XIII**).[28, 120] Subsequent irreversible isomerization of the iminium into an enammonium (**XIII** → **XIV**) is likely the turnover-limiting step (see the following kinetic isotope effect and Hammett studies, as well as the Supporting Information for details).[121–124] Protonolysis of $[(F_5C_6)_3B\text{–enolate}]^-$ in **XIV** releases $B(C_6F_5)_3$, **8**, and an enamine (**XV**). Then, enantioselective C–C bond forming reaction between the enamine and [**L**–$Sc(OTf)_3$]-activated electrophile **6** leads to a zwitterionic intermediate that bears an iminium and an enolate moiety (**XV** → **XVI**). Finally, proton transferwithin **XVI** produces **7-enamine** and regenerates **L**–$Sc(OTf)_3$, thus closing the cycle. Alternatively, borohydride reduction of the iminium and protonation of the resulting enolate in **XVI** produces an *N*-alkylamine product (**7-alkylamine**), as illustrated by the studies described below.

2.2.2. Origins of Enamine and *N*-Alkylamine Products.—*β*-Amino C–H

alkylation products (Figures 2 and 6) were obtained either as an enamine, an *N*-alkylamine, or a mixture of the two (e.g., **4n** and **4o**, Figure 2). We wondered if the *N*-alkylamine products were formed by transfer hydrogenation of **XVI** (**XVI** → **7-alkylamine**, Figure 10), or whether they were generated through reduction of enamines (**7-enamine** → **7-alkylamine**). To identify each product's origins, we studied the progress of $(F_5C_6)_3B$-catalyzed reaction between *N*-arylpiperidine **1j** and **3d** (Figure 11a) which gives a mixture of *N*-alkylamine **4j** (57% yield) and enamine **5j** (29% yield) using 0.4 mL of C_6D_6 (vs the process involving 1.6 mL of C_6H_6 which selectively gives **4j**; Figure 2). We found that there is minimal transformation of **5j** into **4j** as evidenced by the mostly unchanged concentration of **5j** once the *β*-alkylation reaction completed (2 h; Figure 11b). These results are consistent with the scenario that **7-alkylamine** (Figure 10a) is formed by transfer hydrogenation of **XVI** without the intermediacy of **7-enamine**. Nonetheless, the source of proton and hydride remained to be identified.

To probe further if, and under precisely what conditions **5j** can be converted to **4j**, we investigated the transformation of **5j** (isolated and purified by flash silica gel chromatography) in the presence of 20 mol% $B(C_6F_5)_3$ (C_6H_6, 12 h; Figure 11c). This led us to observe that there was 30% conversion to **4j**; in addition, $[\text{pyridinium}]^+[C_6F_5]^-$ (**9j**, 15 %) was also produced. Treatment of **5j** with *N*-arylpiperidine-3,3,5,5-d_4 **1j-*d*** furnished **4j-*d*** in 50% yield, and not only was there significant deuterium incorporation at **C3** and **C5** positions of **4j-*d*** (71% and 67%, respectively), recovered **1j-*d*** had also undergone D/H exchange. These data suggest that $B(C_6F_5)_3$ can catalyze transfer hydrogenation of **5j** in the presence of another molecule of **5j** and/or **1j-*d*** serving as sources of H^+ (or D^+) and hydride (Figure 11c). Nevertheless, under the standard conditions for $(F_5C_6)_3B$-catalyzed *β*-C–H alkylation reaction (Figures 10 and 11a), in situ generated $[(F_5C_6)_3B–H]^-[Base–H]^+$ (derived from the reaction of $B(C_6F_5)_3$ and *N*-alkylamine **1**) appears to react with either a highly reactive zwitterionic intermediate (**XVI** → **7-alkylamine**) or $(F_5C_6)_3B$-activated *α*,*β*-unsaturated compounds (**XII** → **XIII** → **XIV** → **8**). As a consequence, hydrogenation of the relatively unreactive enamine **5j** to give **4j** may be outcompeted by these more facile processes.

2.2.3. Kinetic Isotope Effect Studies.—To shed light on the hydride abstraction (Figure 10, **1** → **XII**), and deprotonation steps (**XIII** → **XIV** → **XV**), deuterium-labeled *N*-arylpyrrolidines **1t-*d*** and **1u-*d*** were prepared, and their reactions with **6g** were probed (Figure 12). Based on the aforementioned rate studies (Figure 9), hinting that the turnover-limiting is prior to the stereoselective C–C bond forming process (Figure 10, **XV** → **XVI**), the overall rate of the reaction can be affected for reactions involving both *α*-deuterated **1t-*d*** and *β*-deuterated **1u-*d***.[125–126] However, independent rate measurements involving **1p** and **1t-*d*** (Figure 12a) were found to have $k_H/k_D = 1.28 \pm 0.07$.[127] On the other hand, comparison of the reaction rate between **1p** and **1u-*d*** (Figure 12b) revealed that **1p** reacts 2.5 times faster than **1u-*d*** ($k_H/k_D = 2.50 \pm 0.13$).[127] These KIE experiments support the notion that the turnover-limiting step is the conversion of iminium into enammonium (Figure 10, **XIII** → **XIV**) which entails the cleavage of *α*-imino C–H or C–D bonds; furthermore, $(F_5C_6)_3B$-catalyzed hydride abstraction (**1** → **XII**) and the following borohydride reduction (**XII** → **XIII**) steps are reversible, thus leading to the equilibrium KIE of 1.28.

2.2.4. Hammett Studies.—Hammett studies revealed a strong dependence of the reaction rate on the electronic properties of the *N*-alkylamines, with *N*-arylpyrrolidine derivatives (**1**) bearing electron-donating substituents reacting more rapidly ($\rho = -4.9$, Figures 13a and 13c). The large negative ρ value obtained supports the proposed mechanism (Figure 10) in which $B(C_6F_5)_3$ abstracts a hydride from *N*-arylpyrrolidine **1** into a *N*-aryl iminium cation (**1** → **XII**), and its isomerization into an enammonium species (**XII** → **XIII** → **XIV**); these processes take place at or prior to the turnover-limiting step. While the reaction rate was found to be less dependent of the electronic properties of *α*,*β*-unsaturated compounds **6**, those involving more electron-withdrawing groups reacted with higher efficiency ($\rho = 0.92$, Figures 13b and 13d). This latter outcome is congruent with the hypothesis that **6** reacts with in situ generated $[(F_5C_6)_3B–H]^-$ to afford a boron–enolate intermediate (Figure 10b; **XII** → **XIII**), and that this hydride transfer also occurs at or prior to the turnover-limiting step.

3. CONCLUSIONS

In brief, we have developed an efficient catalytic method for functionalization of *β*-amino C–H bonds to generate enantioenriched *δ*-amino carbonyl compounds. We find that by using a blend of $B(C_6F_5)_3$ and a chiral Sc-based complex, it is possible to convert an *N*-alkylamine into an enamine and then promote its enantio- and diastereo-selective reaction with an *α*,*β*-

unsaturated compound. The catalyst system is tolerant of a wide variety of Lewis acid-sensitive functional units and therefore applicable to late-stage modification of relatively complex (and bioactive) trialkylamine molecules. Mechanistic investigations reveal that the turnover-limiting step is probably isomerization of *N*-alkylamine-derived iminium ion into an enammonium intermediate.

The principles outlined above demonstrate that proper combination of an achiral organoborane and an enantiomerically pure organometallic catalyst may be used for chemo- and enantioselective C–H bond functionalization, providing a rational basis for future development of processes for late-stage stereoselective *β*-functionalization of multifunctional bioactive amines. Studies aimed at achieving these objectives are underway.

Supplementary Material

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(124). The proton transfer process involving the conversion of the iminium to enammonium intermediates (**XIII** → **XIV**, Figure 10) may occur through deprotonation of **XIII** by an appropriate Brønsted base (e.g., H_2O), followed by protonation of the resulting enamine species.

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(127). Intermolecular competition KIE experiments were also conducted, providing the results that are consistent with those of the independent KIE experiments. See the Supporting Information for details.

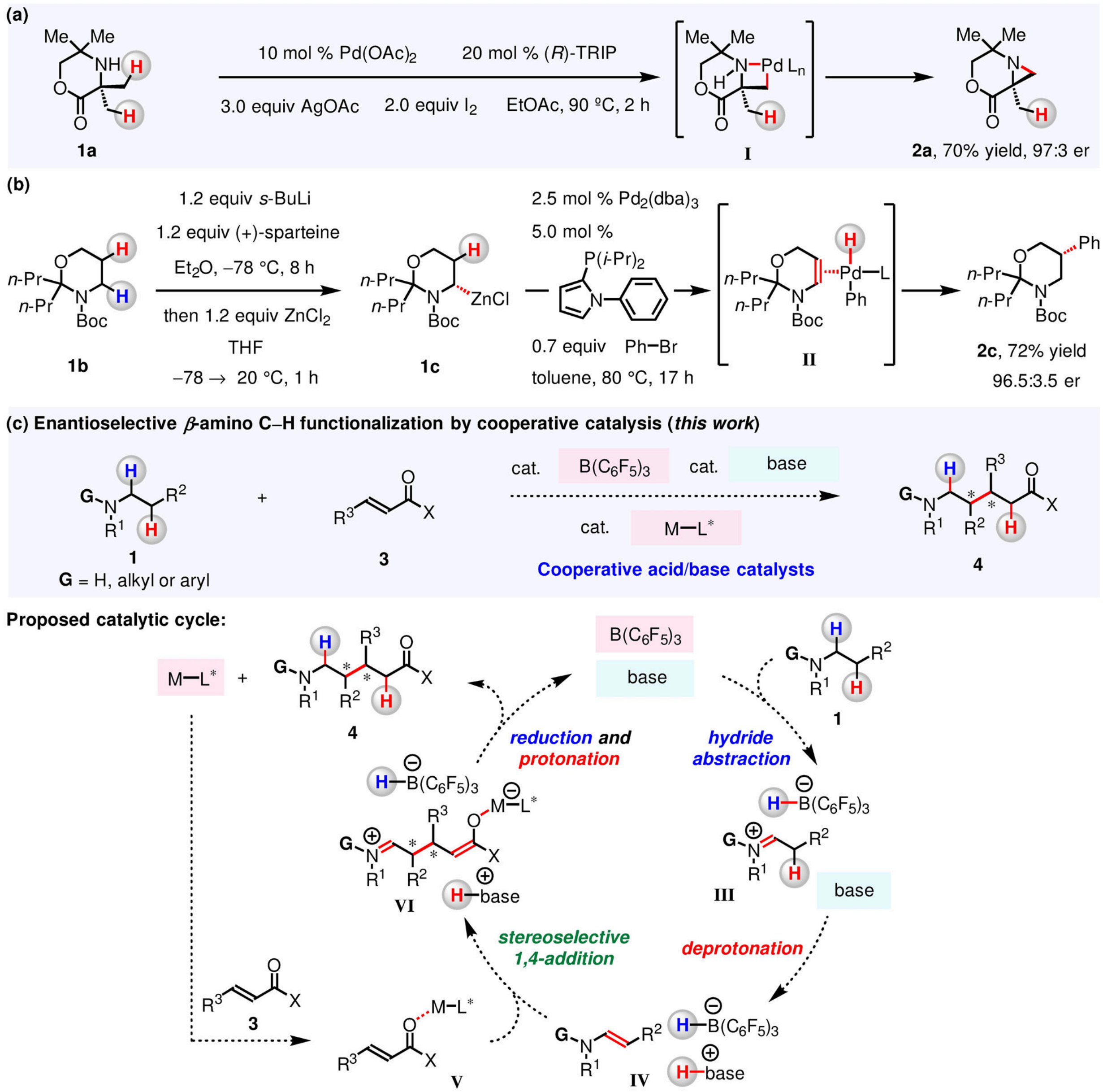


Figure 1.

Enantioselective Transformations of β-Amino C–H Bonds

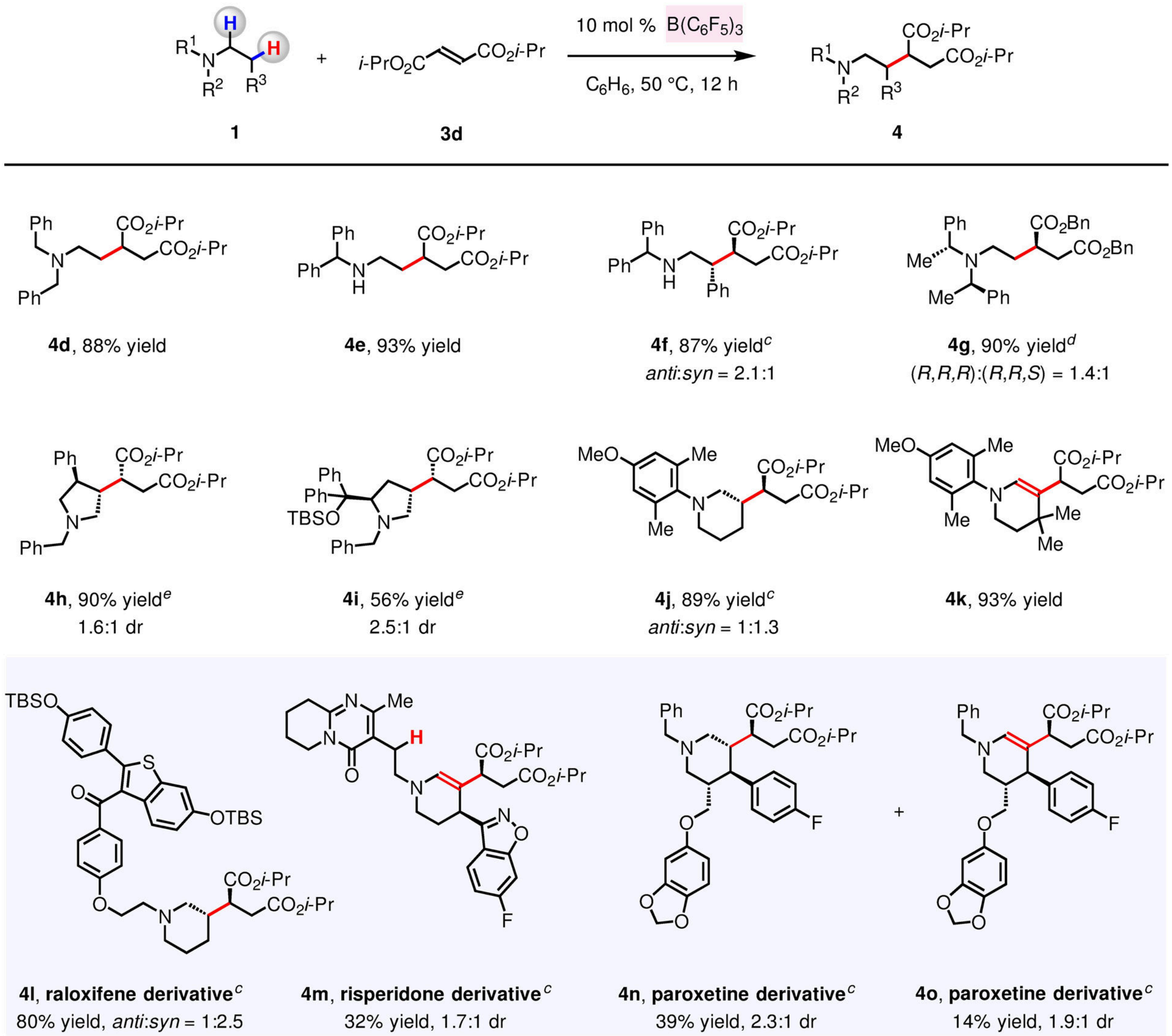


Figure 2. *β*-Alkylation of Different *N*-Alkylamines.

The values correspond to yields of isolated and purified products. [a] Conditions: *N*-alkylamine (**1**, 0.20 mmol), diisopropyl fumarate (**3d**, 0.30–0.40 mmol), $B(C_6F_5)_3$ (10 mol %), C_6H_6, under N_2, 50 °C. [b] Yield of isolated and purified product. The dr values were determined by the ^1H NMR analysis of the unpurified reaction mixtures. [c] The structure and relative configuration of **4f, 4j, 4l,** and **4m** were assigned in analogy. The stereochemistry of **4n** and **4o** was assigned in analogy and also by the NOESY studies. [d] The absolute configuration of **4g** was determined based on the specific rotation of the derivative. [e] The structure and absolute configuration of **4i** was established by the X-ray crystallographic analysis. The stereochemistry of **4h** was assigned in analogy and also by the NOESY studies. See the Supporting Information for details.

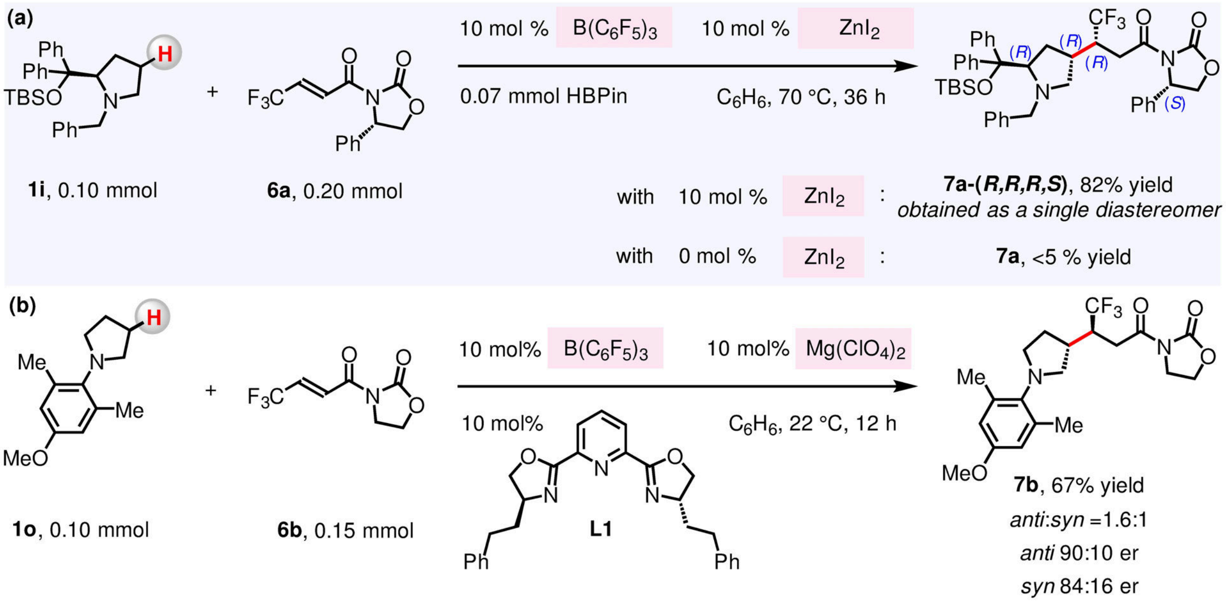


Figure 3. Stereoselective β-Functionalizations of *N*-Alkylamines.

The values correspond to yields of isolated and purified products. See the Supporting Information for details.

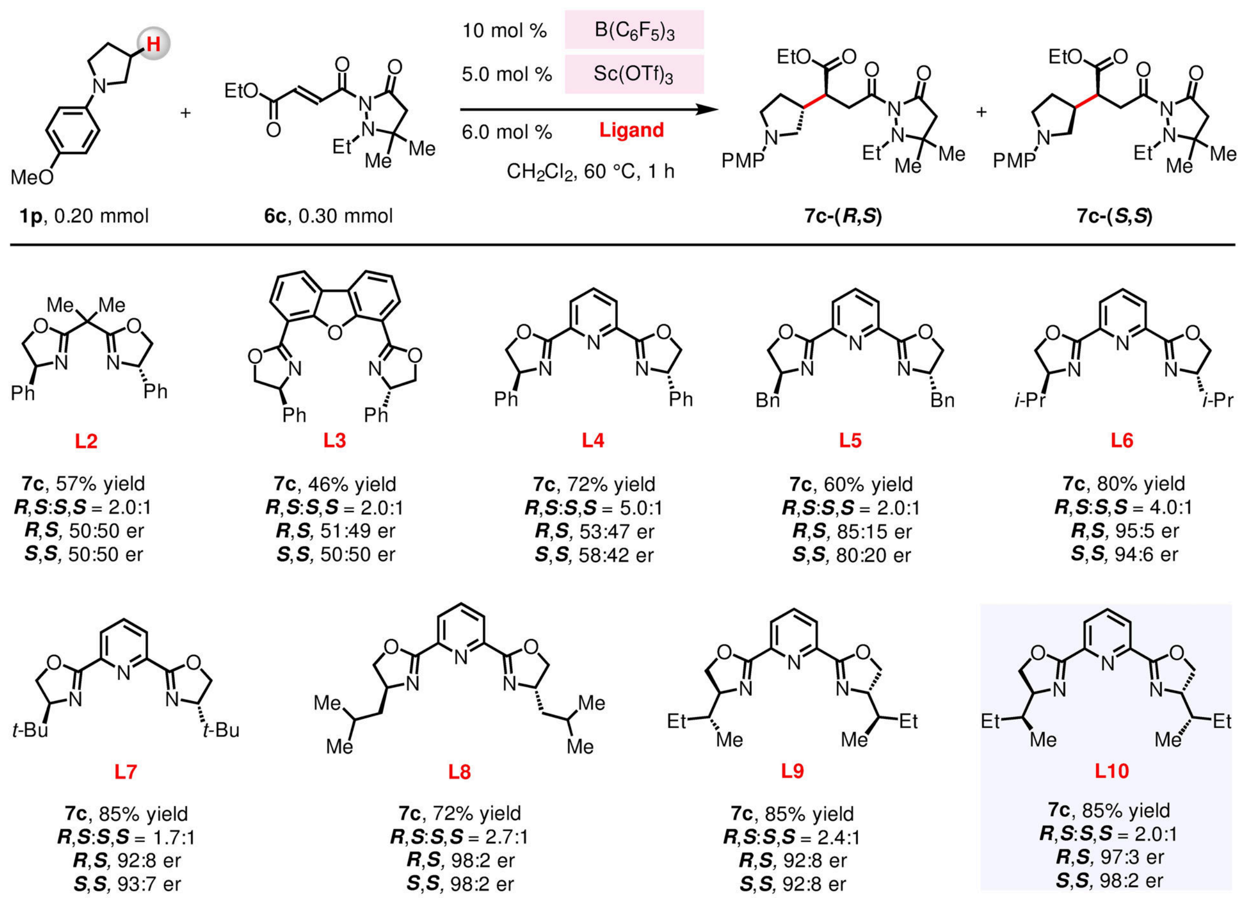
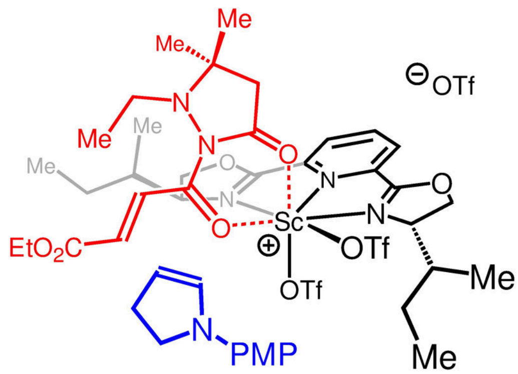
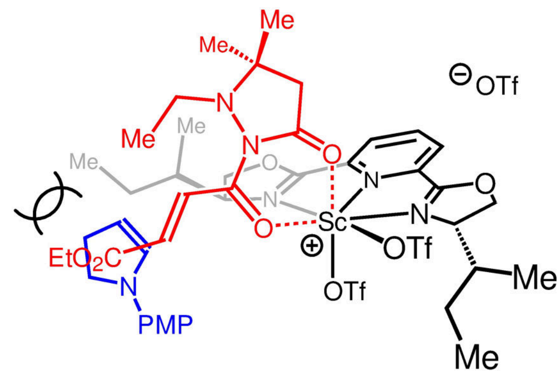


Figure 4. Evaluation of Chiral Ligands.

Yield and diastreomeric ratio (dr) values were determined by the ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) values were determined by the HPLC analysis of isolated and purified product. Conditions: *N*-arylpyrrolidine (**1p**, 0.20 mmol), α,β-unsaturated compound (**6c**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $Sc(OTf)_3$ (5.0 mol %), ligand (6.0 mol %), CH_2Cl_2 (2.0 mL), under N_2, 60 °C, 1 h. See the Supporting Information for details.



VII, favored



VIII, disfavored

Figure 5.

Stereochemical Rationale for Enamine Addition to *α*,*β*-Unsaturated Compounds Catalyzed by [L10–Sc(OTf)$_3$].

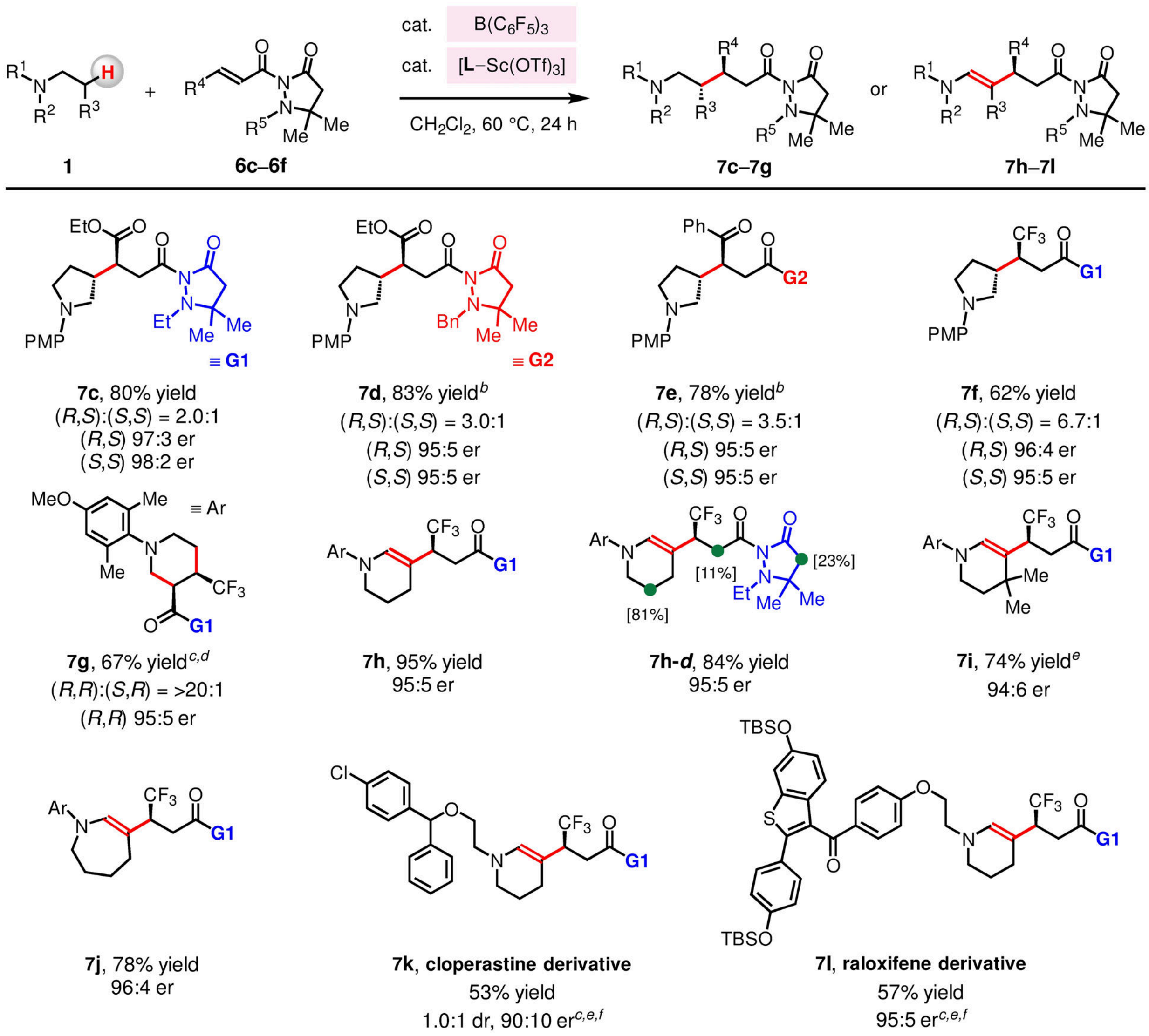


Figure 6. Stereoselective Processes.

Cooperative functions of $B(C_6F_5)_3$ and **L**–$Sc(OTf)_3$ promote stereoselective *β*-alkylation of *N*-alkylamines. [a] Conditions: *N*-alkylamine (**1**, 0.10 mmol), *α*,*β*-unsaturated compound (**6**, 0.15–0.20 mmol), $B(C_6F_5)_3$ (10 mol %), **L10**–$Sc(OTf)_3$ (10 mol %), CH_2Cl_2 (1.0 mL), under N_2, 60 °C, 1–36 h. [b] 10 mol % of **L6**–$Sc(OTf)_3$ was used. [c] 20 mol % of $B(C_6F_5)_3$ was used. [d] 20 mol % of **L10**–$Sc(OTf)_3$ was used. [e] The reaction was performed at 80 °C. [f] 10 mol % of **L8**–$Sc(OTf)_3$ was used. See the Supporting Information for details.

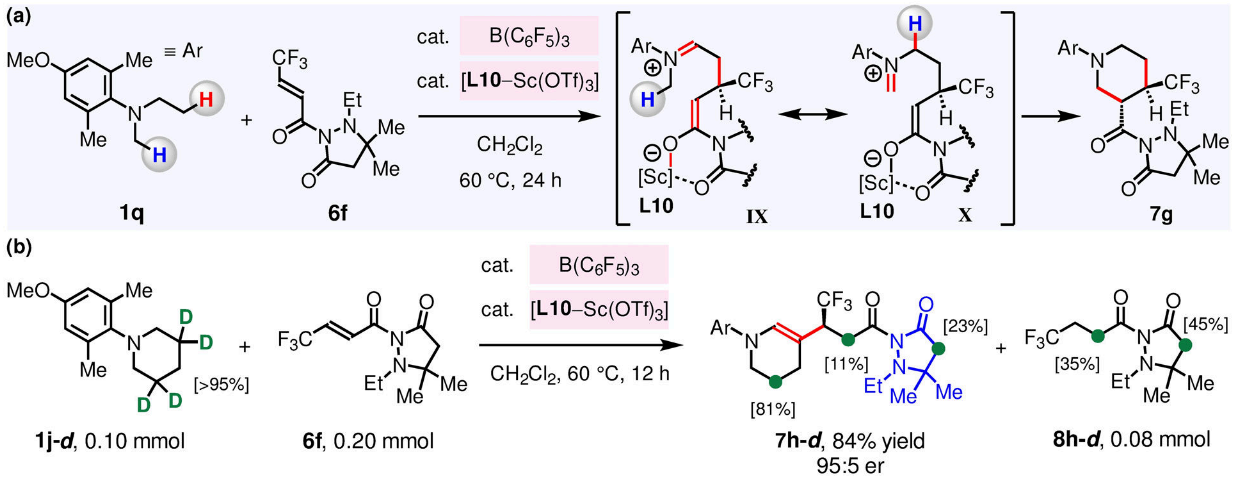


Figure 7. Additional Data Interpretation.

(a) Sequential β-alkylation and Mannich-type reaction gave piperidine derivative **7g**. (b) D^+ derived from **1j-*d*** was incorporated into enolizable positions of **7h-*d*** and **8h-*d***.

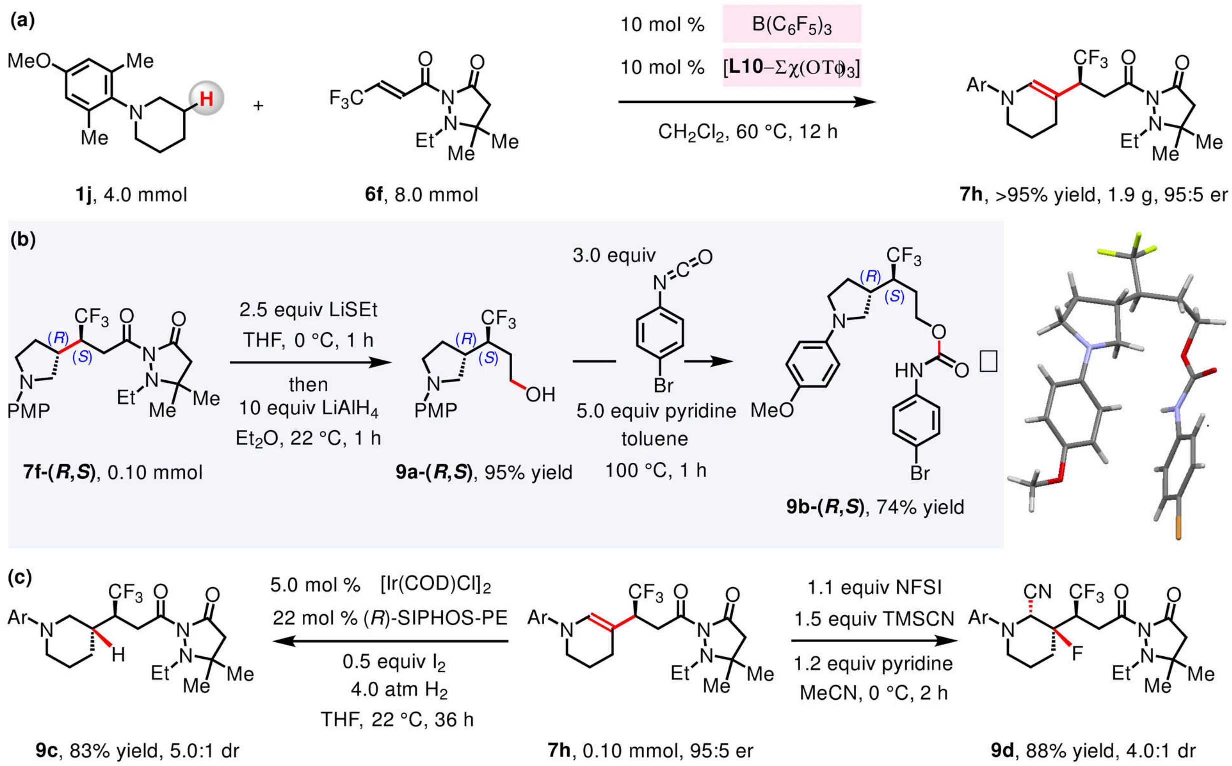


Figure 8. Modification of Products and Scalability.

(a) The enantioselective reaction is amenable to gram-scale operations. (b) Transformation of pyrazolidinone auxiliary into thioester, alcohol and then to carbamate was achieved. Absolute configuration of **9b** was obtained through X-ray crystallographic analysis. (c) Versatility of enamine **7h** was demonstrated through catalytic hydrogenation and fluorocyanation reactions. See the Supporting Information for details.

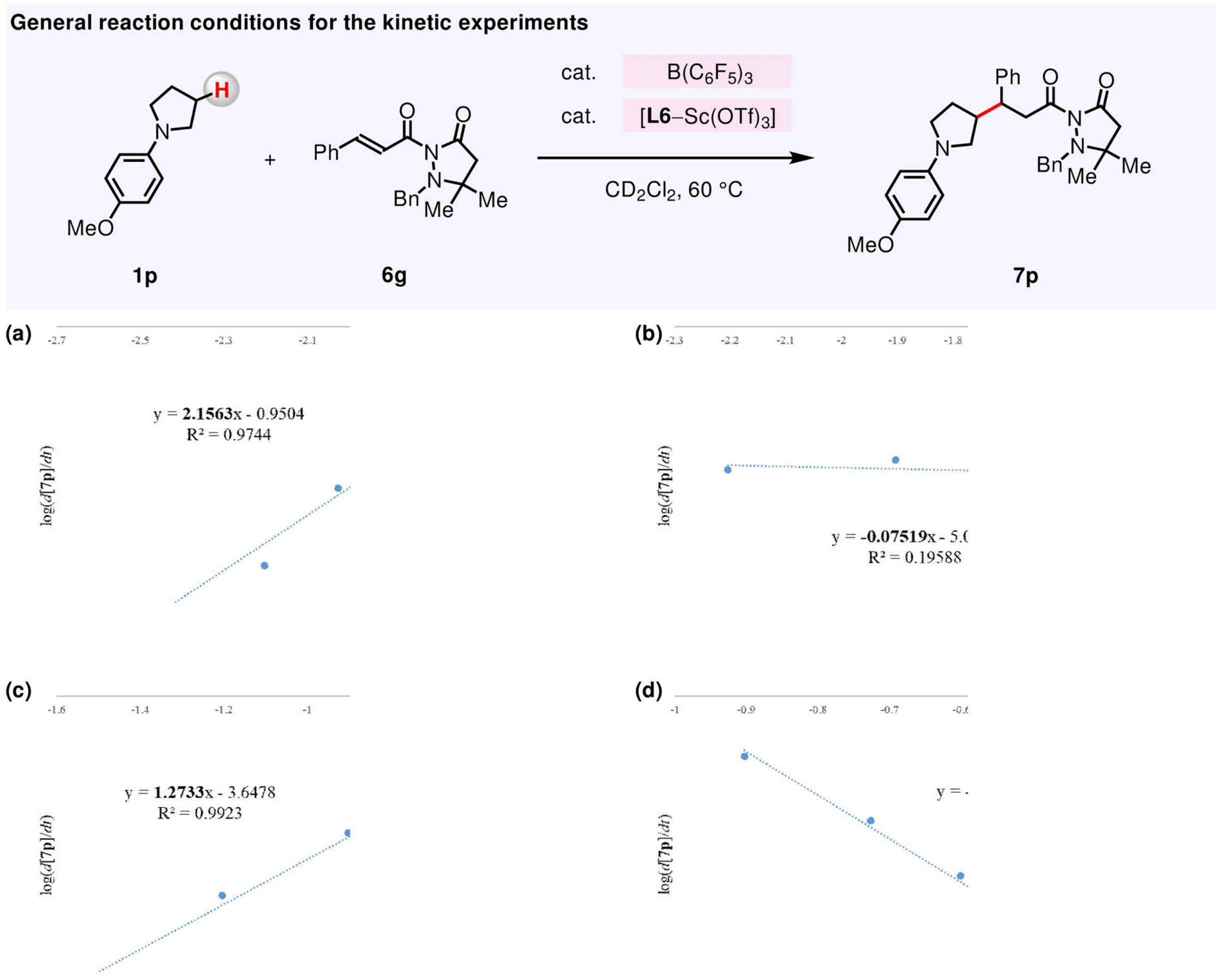


Figure 9. Determination of Reaction Orders.

Log(rate) vs log(concentration) plot is employed to determine the reaction order for: (a) $B(C_6F_5)_3$. (b) **L6**–$Sc(OTf)_3$. (c) amine **1p**. (d) *α,β*-unsaturated compound **6g**. See the Supporting Information for details.

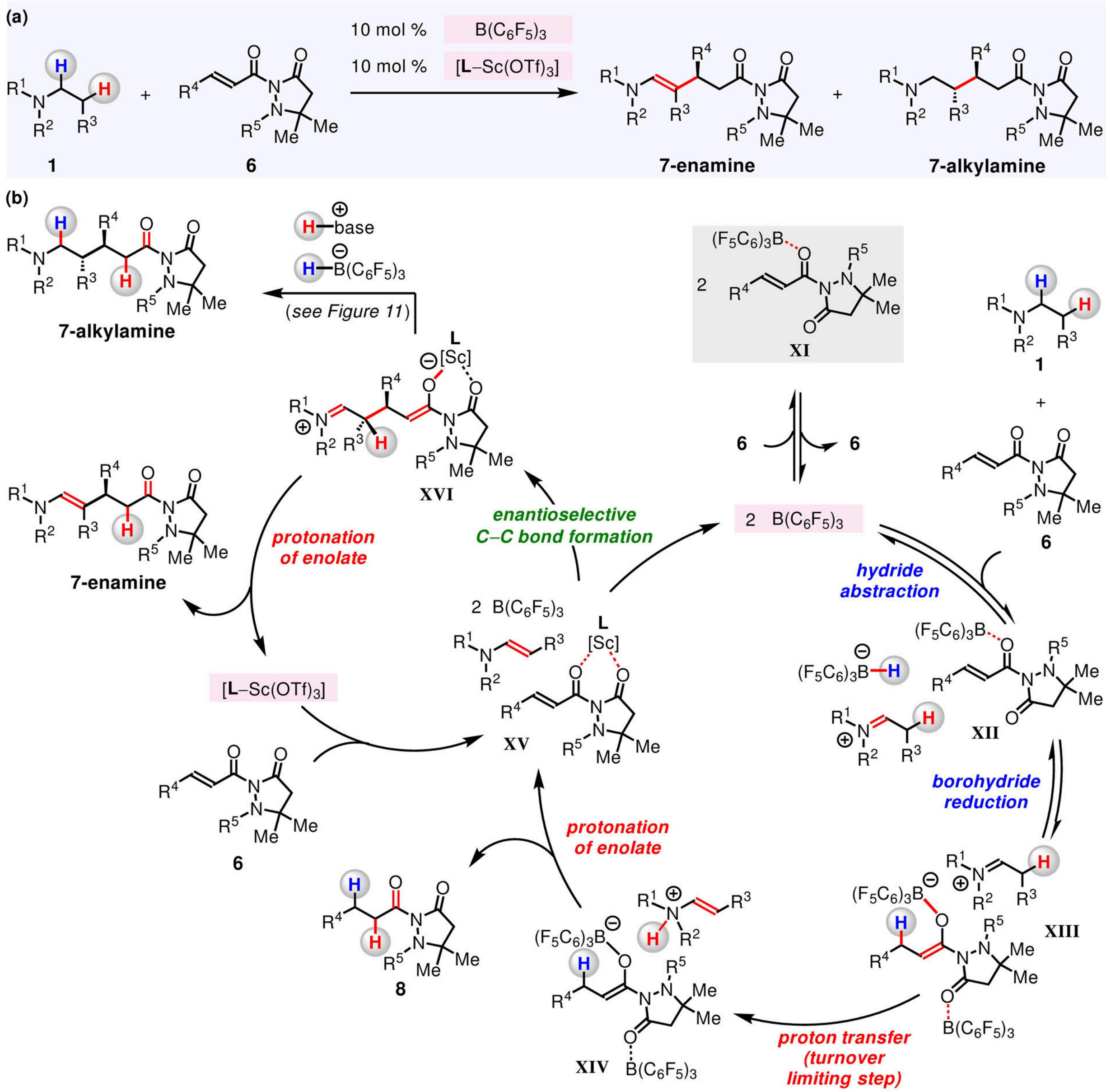


Figure 10. A Catalytic Cycle Consistent with the Results of Mechanistic Investigations.
Kinetic and NMR studies indicate that the turnover-limiting step is intramolecular proton transfer step.

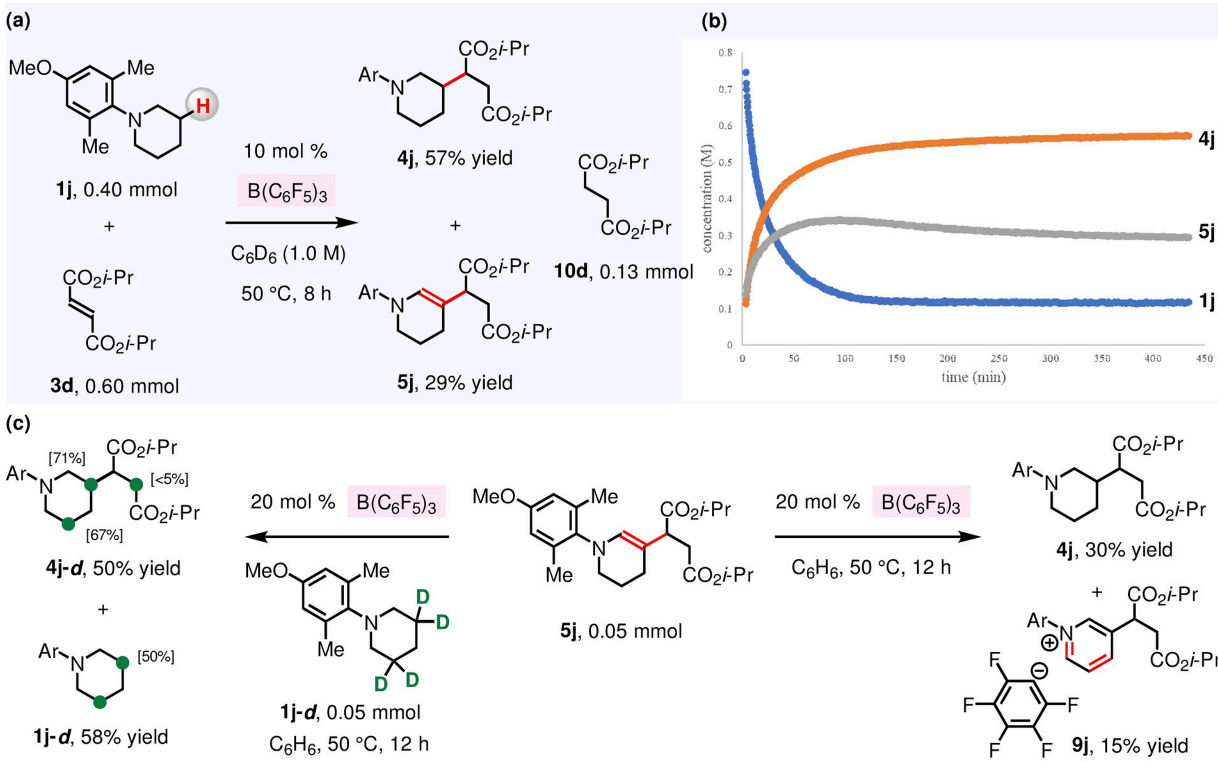


Figure 11. Origin of Enamine and *N*-Alkylamine Products.

(a), (b) Reaction progress analysis of the coupling of **1j** and **3d**. (c) **5j** and/or **1j-*d*** can serve as H^+ or D^+ and hydride source in $(F_5C_6)_3B$-catalyzed transfer hydrogenation of **5j**. See the Supporting Information for details.

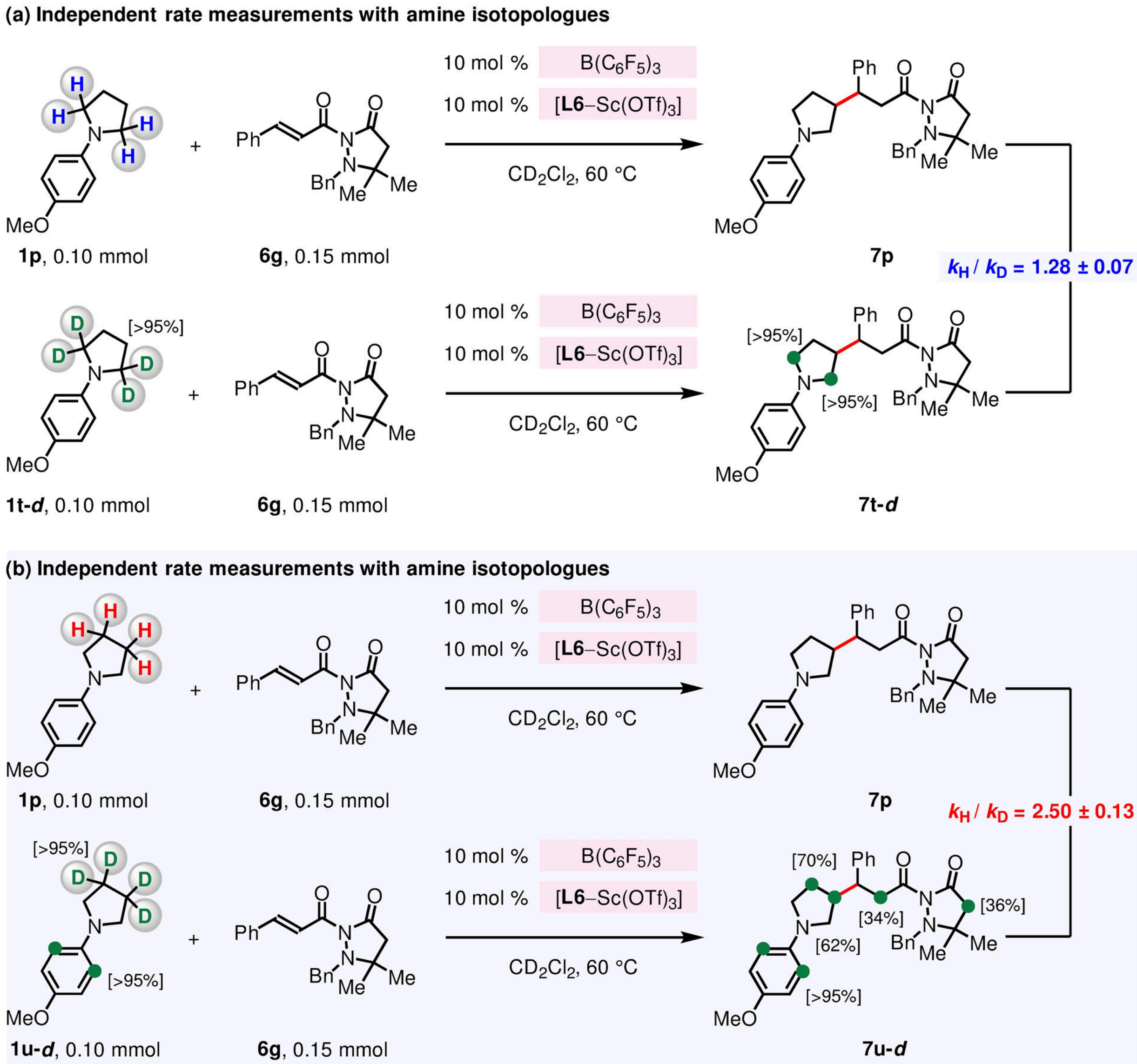


Figure 12. Kinetic Isotope Effect Studies.

The independent rate measurement studies indicate that intramolecular proton transfer is the turnover-limiting step. See the Supporting Information for details.

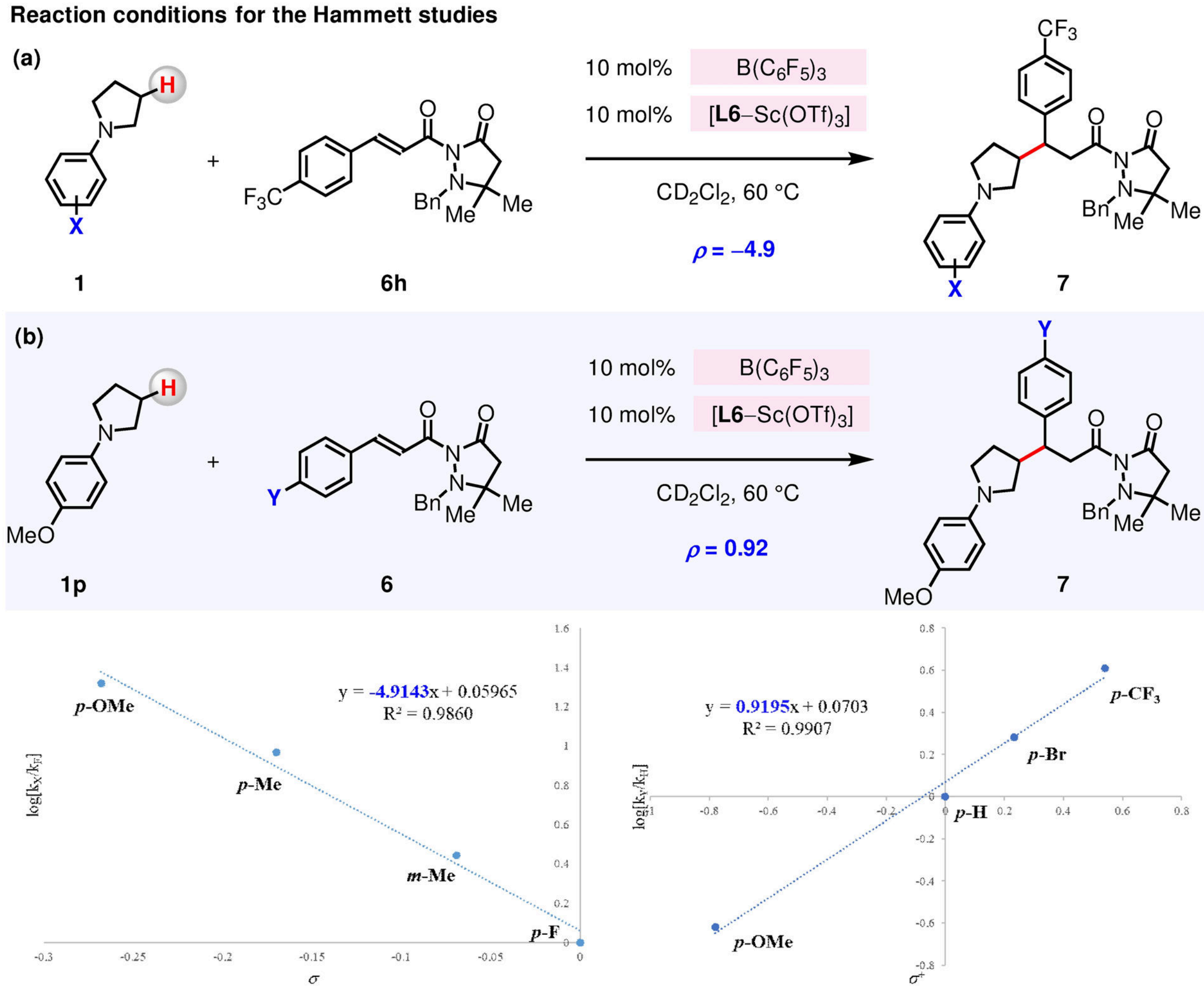
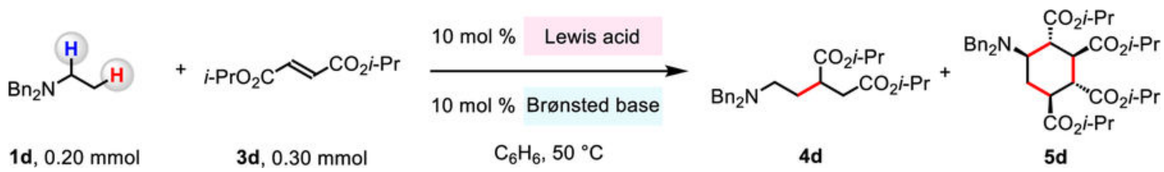


Figure 13. Hammett Studies.

Hammett plots of rates for the reaction of *N*-aryl substituted pyrrolidines **1** and aryl substituted *α*,*β*-unsaturated compounds **6**. (a), (c) *N*-Arylpyrrolidine derivatives **1** that contain electron-donating substituents reacted more rapidly. (b), (d) *α*,*β*-Unsaturated compounds **6** that contain electron-withdrawing substituents reacted more rapidly. See the Supporting Information for details.

Table 1.

Evaluation of Various Reaction Parameters[a,b,c]



entry	Lewis acid	Brønsted base	time (h)	yield of 4d (%)	yield of 5d (%)
1	$B(C_6F_5)_3$	Et_3N	3	50	23
2	$B(C_6F_5)_3$	TMP	3	25	29
3	$B(C_6F_5)_3$	DBU	3	<5	<5
4	$B(C_6F_5)_3$	none	3	73	25
5[d]	$B(C_6F_5)_3$	none	3	54	5
6[d]	$B(C_6F_5)_3$	none	12	91	7
7	BCl_3	none	12	0	0
8	BPh_3	none	12	0	0
9	none	none	12	0	0

[a]Conditions: *N,N*-dibenzylethanamine (**1d**, 0.20 mmol), diisopropyl fumarate (**3d**, 0.30 mmol), Lewis acid, Brønsted base, C_6H_6 (0.20 mL), under N_2, 50 °C.

[b]Yield was determined by the ^1H NMR analysis of unpurified reaction mixtures with *m*-xylene as the internal standard.

[c]The structure and relative configuration of **5d** were established by the nuclear Overhauser effect spectroscopy (NOESY) studies.

[d]0.80 mL of C_6H_6 was used.