Frustrated Lewis Pairs

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Direct Mannich-Type Reactions Promoted by Frustrated Lewis Acid/Brønsted Base Catalysts

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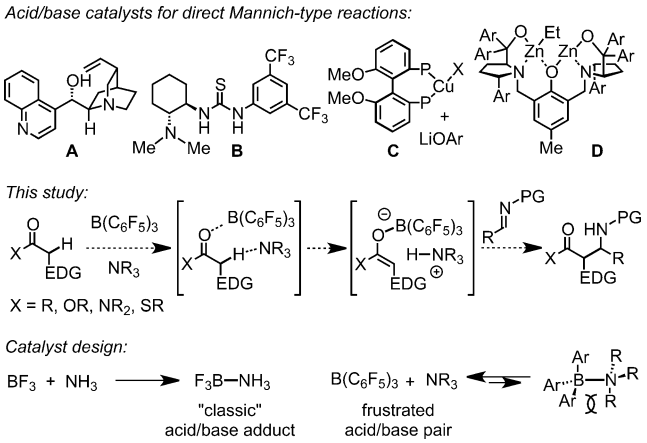
Abstract: *Direct Mannich-type reactions that afford both α- and β-amino esters by the reaction of a broad range of carbonyl compounds and aldimines are disclosed. The transformation is promoted by a sterically frustrated Lewis acid/Brønsted base pair, which is proposed to operate cooperatively: Within the catalyst complex, an enolate is generated that then reacts with a hydrogen-bond-activated imine. Noncovalent interactions between reactants and the catalyst provide selectivity and new opportunities for future catalyst design.*

Frustrated Lewis pairs (FLPs) consist of Lewis acids and Lewis bases whose mutual quenching is sterically precluded.[1] The cooperation of active nonquenched acids and bases has proven to be an effective strategy for reaction development and has led to notable discoveries in small-molecule activation.[1] Since the seminal reports by the research groups of Stephan and Erker on the R–$B(C_6F_5)_2$/phosphine-mediated splitting of H_2,[2] an array of acid/base pairs has been exploited for the stoichiometric activation of CO_2, SO_2, and N_2O, among other molecules.[1] However, FLP-catalyzed processes reported to date remain limited in scope; examples include the hydrogenation,[3] hydroboration,[4] and hydrosilylation[5] of unsaturated substrates, the hydroamination of alkynes,[6] the borylation of arenes,[7] and C–C coupling between vinyl phosphanes and aryl aldehydes.[8] The development of practical FLP-catalyzed methods has been hampered by the strong acidity of R–$B(C_6F_5)_2$, which can readily form adducts with molecules containing unhindered basic moieties. Furthermore, adducts between FLPs and small molecules are often too stable and thus of limited synthetic utility. To obviate these inherent problems associated with FLPs, we envisioned their application as cooperative acid/base catalysts capable of generating both nucleophiles and electrophiles from otherwise unreactive substrates. We now describe our initial studies in the context of the FLP-catalyzed dual activation of enolizable carbonyl compounds and imines.

The addition of enolate nucleophiles to aldimines or ketimines, known as Mannich-type reactions, is a useful way of constructing important amino ester compounds.[9] In the "direct" Mannich-type reaction, separate stoichiometric preparation of the enolate is avoided by the in situ generation of the active nucleophile.[9–11] For example, one approach employs a bifunctional catalyst whose acidic site can activate a carbonyl pronucleophile towards enol formation by the associated basic site, thus catalytically generating the enolate equivalent. Although this approach to this important class of molecules is attractive, in practice, most bifunctional catalysts (Scheme 1, **A**, **B**) can only contain mildly acidic and basic groups.[9–11] Thus, the scope of pronucleophiles is often limited to those containing highly acidic C–H bonds, such as 1,3-dicarbonyl compounds.[10] With stronger acids or bases capable of activating less acidic pronucleophiles, the formation of strongly associated acid/base adducts deactivates the catalyst. As a result, only a limited number of catalyst systems (e.g. **C**, **D**) that enable the direct Mannich-type reaction of monocarbonyl compounds exist.[11–15] Although methyl ketones are readily deprotonated with these catalysts,[14] the enolization of less acidic ketones, esters, amides, and thioesters typically requires further activation of these substrates by the installation of electron-withdrawing substituents (e.g. OH,[15a–e] NCS,[15f] SMe,[15g] CF_3,[15h,i] N_3,[15j] F[15i,k]).



Scheme 1. Use of acid/base catalysts to promote direct Mannich-type reactions. EDG = electron-donating group.

To create a cooperative acid/base catalyst capable of enolizing a broader range of unactivated pronucleophiles, we considered the development of a system based on an unquenched pair of a potent Lewis acid catalyst and a hindered Brønsted base catalyst (Scheme 1). This system would have the advantage of independent and modular control over the acid and base components, thus potentially enabling the accommodation of a broad range of unreactive pronucleophiles. Specifically, a boron-based Lewis acid would bind to pronucleophiles to generate an acidic α-C–H bond. Deprotonation by a hindered soft amine would generate the

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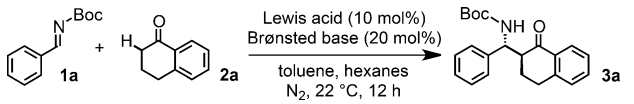
boron enolate, which could then react with an imine to deliver the β-amino ester products.

We examined the transformation between *N*-(*tert*-butoxycarbonyl)benzaldimine (**1a**) and α-tetralone (**2a**) with B(C_6F_5)$_3$/amines as potential catalysts. We found that B(C_6F_5)$_3$ (10 mol%) and Et_3N (20 mol%) promoted the reaction between **1a** and **2a** in toluene at 22 °C to afford **3a** in 65% yield with d.r. > 20:1 (Table 1, entry 2). No product formation

Table 1: Evaluation of reaction parameters.[a]

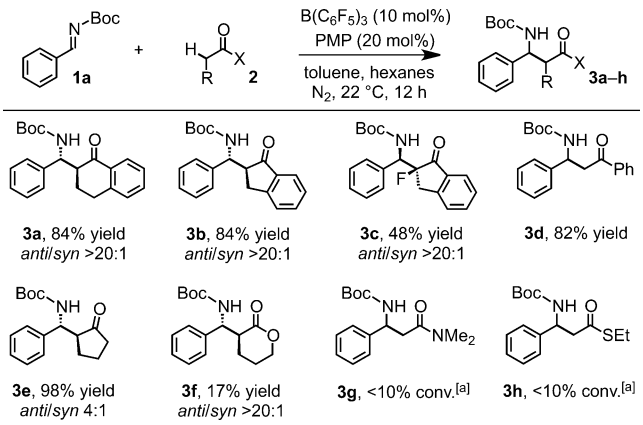


1	B(C_6F_5)$_3$	none	0	NA
2	B(C_6F_5)$_3$	Et_3N	65	>20:1
3	B(C_6F_5)$_3$	*i*Pr_2NEt	64	>20:1
4	B(C_6F_5)$_3$	PhNMe_2	<20	NA
5	B(C_6F_5)$_3$	DBU[b]	<20	NA
6	B(C_6F_5)$_3$	Barton base[b]	<20	NA
7	B(C_6F_5)$_3$	TMP[b]	79	>20:1
8	B(C_6F_5)$_3$	PMP	>95	>20:1
9	B(C_6F_5)$_3$	2,6-dimethylpyridine	26	>20:1
10	B(C_6F_5)$_3$	2,6-di-*tert*-butylpyridine	33	>20:1
11	none	PMP	0	NA
12	BPh_3	PMP	0	NA
13	BF_3•OEt_2	PMP	0	NA
14	BCl_3	PMP	0	NA

[a] Reaction conditions: imine (0.2 mmol), acid (10 mol%), base (20 mol%), α-tetralone (0.22 mmol), toluene (0.6 mL), hexanes (0.3 mL), N_2 atmosphere, 22 °C, 12 h. Yields and d.r. values were determined by ^{1}H NMR analysis of the crude product with mesitylene as the internal standard. [b] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Barton base = 2-*tert*-butyl-1,1,3,3-tetramethylguanidine, TMP = 2,2,6,6-tetramethylpiperidine.

was observed in the absence of an amine (entry 1). The selection of an amine of appropriate basicity appears to be important. Whereas the use of less basic *N*,*N*-dimethylaniline gave **3a** in less than 20% yield (entry 4), the presence of DBU or the Barton base led to decomposition of **1a** and poor yields (entries 5 and 6). Optimal results were observed with sterically encumbered 1,2,2,6,6-pentamethylpiperidine (PMP; Table 1, entry 8, > 95%). No desired product was observed either without B(C_6F_5)$_3$ or in the presence of weaker and/or less hindered boron Lewis acids (entries 11–14). These observations are consistent with the hypothesis that a sterically frustrated pair composed of highly acidic B(C_6F_5)$_3$ and hindered PMP would serve as the most efficient catalyst combination for the direct Mannich-type reaction.[16]

Various ketones were found to participate effectively in direct Mannich-type reactions of **1a** catalyzed by B(C_6F_5)$_3$ and PMP (Scheme 2). A 2:1 mixture of toluene and hexanes was found to further improve the product yield. Cyclic as well as acyclic ketones were converted into the desired products in 48–98% yield (products **3a**–**e**). Cyclic ketones, including 2-fluoroindanone, underwent highly diastereoselective reactions (products **3a**–**c**, d.r. > 20:1). Cyclopentanone, which

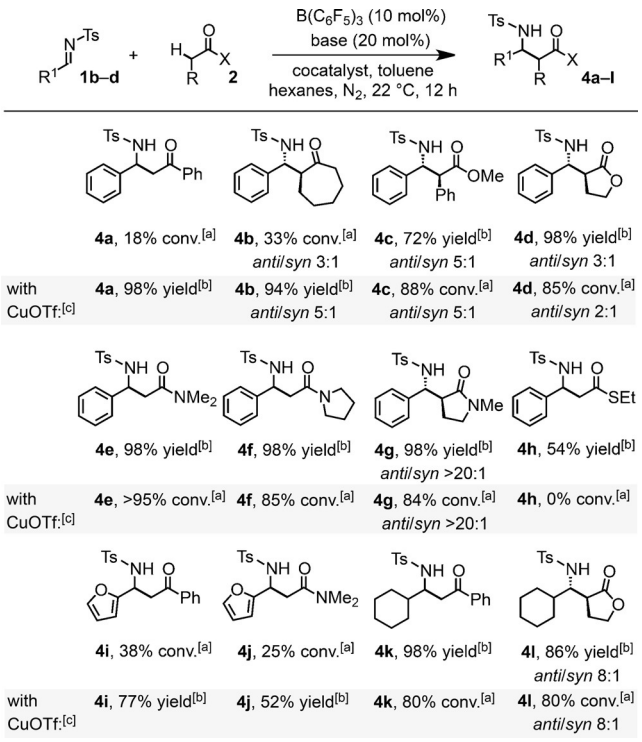


Scheme 2. Mannich-type reactions of *N*-(*tert*-butoxycarbonyl)benzaldimine (**1a**). Reaction conditions: imine (0.3 mmol), B(C_6F_5)$_3$ (10 mol%), PMP (20 mol%), pronucleophile (0.33 mmol), toluene (0.6 mL), hexanes (0.3 mL), N_2 atmosphere, 22 °C, 12 h. Yields are for the isolated product. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. The structure and absolute configuration of **3a** were established by X-ray crystallography, and the configuration of all other products was assigned by analogy. [a] The yield was determined by ^{1}H NMR analysis of the crude product with mesitylene as the internal standard.

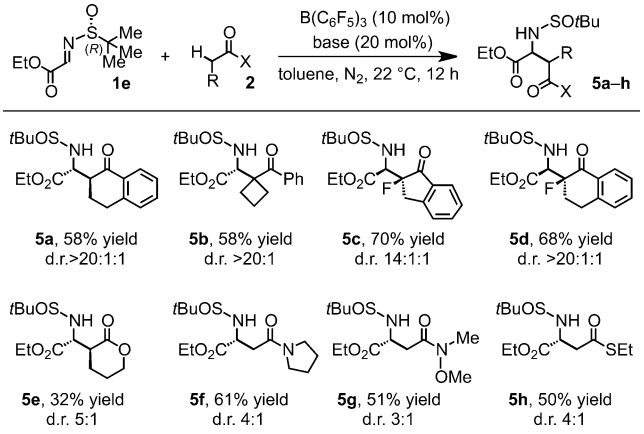
lacks a fused aromatic group, gave **3e** in quantitative yield, albeit with diminished diastereoselectivity. When we evaluated ester, amide, and thioester substrates, the corresponding products **3f**–**h** were formed in less than 20% yield.[17]

Next, we evaluated benzaldimine substrates bearing other *N*-protecting groups. Reactions of *N*-tosylbenzaldimine (**1b**) with ketones under the catalysis of B(C_6F_5)$_3$/PMP afforded β-amino ketone products in only poor yield (Scheme 3, **4a**,**b**). Nonetheless, the inclusion of CuOTf (5 mol%) as a soft Lewis acid cocatalyst in the reactions as a means to activate the imine resulted in a significant improvement in efficiency (**4a**, 98 versus 18%).[13a] Importantly, CuOTf was found not to catalyze the direct Mannich-type reaction, as none of these products could be obtained in the absence of B(C_6F_5)$_3$. Intriguingly, more nucleophilic ester and amide enolates were found to react with **1b** smoothly even in the absence of CuOTf to give the corresponding products **4c**–**g** in 72–98% yield. Deprotonation of the less acidic amides required the use of more basic DBU, as PMP did not furnish the desired products **4e**–**g**. The reaction of a thioester gave **4h** in 54% yield; no product was obtained when the cocatalyst was added. The 2-furanyl- and cyclohexyl-substituted imines **1c** and **1d** were also converted into the desired products **4i**–**l**.

The utility of this transformation is illustrated by a diastereoselective Mannich-type reaction with an iminoester substrate incorporating the Ellman chiral sulfinamide auxiliary (Scheme 4, **1e**).[18] The direct Mannich-type reaction of **1e** offers an efficient route to enantiomerically enriched β-carbonyl α-amino ester derivatives. The possibility of the chromatographic separation of stereoisomers is another advantage (versus enantioselective catalysis). Indeed, a range of pronucleophiles led to the corresponding α-amino ester products **5a**–**h** with d.r. > 20:1–3:1.[19] β-Substituted amino esters **5b**–**d**, which are inaccessible by transition-



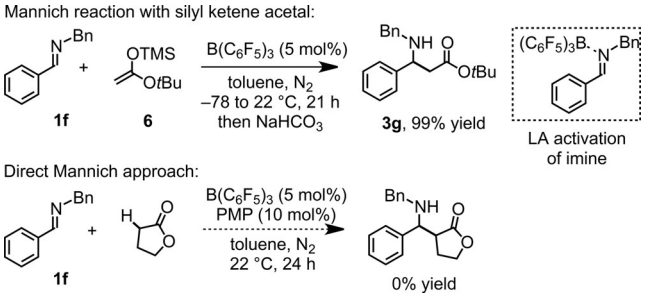
Scheme 3. Mannich-type reactions of *N*-tosylaldimines. Reaction conditions: imine (0.3 mmol), $B(C_6F_5)_3$ (10 mol%), base (20 mol%), pronucleophile (0.33 mmol), toluene (0.6 mL), hexanes (0.3 mL), N_2 atmosphere, 22°C, 12 h. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. The relative configuration of the major diastereomer was assigned as *anti* (see the Supporting Information). For **4a–d**, **4h**, **4i**, **4k**, and **4l**, PMP was used as the base. For **4e–g** and **4j**, DBU was used as the base. [a] Yield determined by ^{1}H NMR analysis of the crude product with mesitylene as the internal standard. [b] Yield of the isolated product. [c] Copper(I) triflate (CuOTf, 5 mol%) was added as a cocatalyst.



Scheme 4. Diastereoselective Mannich-type reactions. Reaction conditions: imine (0.3 mmol), $B(C_6F_5)_3$ (10 mol%), base (20 mol%), pronucleophile (0.33 mmol), toluene (1.0 mL), N_2 atmosphere, 22°C, 12 h. Yields are for the isolated product. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude product. The structure and absolute configuration of **5d** were established by X-ray crystallography, and the configuration of all other products was assigned by analogy. For **5a–e** and **5h**, PMP was used as the base. For **5f** and **5g**, DBU was used as the base.

metal-catalyzed asymmetric hydrogenation, were readily synthesized. A versatile Weinreb amide could be converted into **5g**. No epimerization of **5d** was observed when treated with 1 equivalent of $B(C_6F_5)_3$ and PMP.[20]

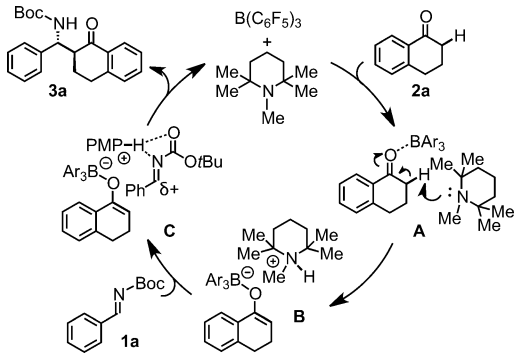
The broad range of compatible pronucleophiles (Tables 2–4) suggests that $B(C_6F_5)_3$/amine pairs are highly efficient catalysts for the enolization of monocarbonyl compounds. However, a lack of intrinsic electrophilicity and instability of the imines appear to be the reasons for decreased efficiency. This observation is somewhat unexpected because the $B(C_6F_5)_3$-catalyzed Mannich-type reaction of less electrophilic *N*-benzylbenzaldimine (**1f**) and silyl ketene acetal (**6**) is known (Scheme 5); the reaction is



Scheme 5. Mannich-type reactions of *N*-benzylbenzaldimine (**1f**). TMS = trimethylsilyl.

proposed to proceed through the activation of **1f** by $B(C_6F_5)_3$.[21] Still, in our direct Mannich-type reactions, **1f** failed to react with any of the evaluated pronucleophiles, thus implying that another species may be involved in imine activation instead of $B(C_6F_5)_3$.[22]

A possible pathway involving $B(C_6F_5)_3$/PMP activation of *N*-(*tert*-butoxycarbonyl)benzaldimine (**1a**) and α-tetralone (**2a**) is outlined in Scheme 6. $B(C_6F_5)_3$-activated **2a** possessing



Scheme 6. Possible catalytic cycle.

an acidic α-carbonyl C–H bond (intermediate **A**) is deprotonated by PMP to form an ion pair **B** consisting of a boron enolate and an ammonium ion. The ammonium ion in **B** can serve as a Brønsted acid catalyst to activate the imine toward nucleophilic attack by the boron enolate. The higher reaction efficiency with less polar solvents may support the importance of the ionic or H-bonding interactions.[11] Subsequent C–C

bond formation generates the Mannich-type product **3a** and simultaneously regenerates the catalyst. Further elucidation of the catalyst–substrate interactions is in progress.

In summary, we have developed a $B(C_6F_5)_3$/amine-catalyzed direct Mannich-type reaction that provides access to an assortment of α- and β-amino esters from ketone, ester, amide, and thioester pronucleophiles. This protocol can be used for the diastereoselective synthesis of important α-amino ester derivatives. On the basis of our mechanistic hypothesis, it should be possible to control the stereochemical outcome of these addition reactions through the design of appropriate chiral Lewis acid/Brønsted base catalyst combinations. Investigations along these lines are currently under way and will be reported in due course.

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Keywords: acid–base catalysis · boron · frustrated Lewis pairs · Lewis acids · Mannich-type reactions

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[23] CCDC 1504251 and 1504252 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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