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Organocatalytic Vinyl and Friedel−Crafts Alkylations with Trifluoroborate Salts

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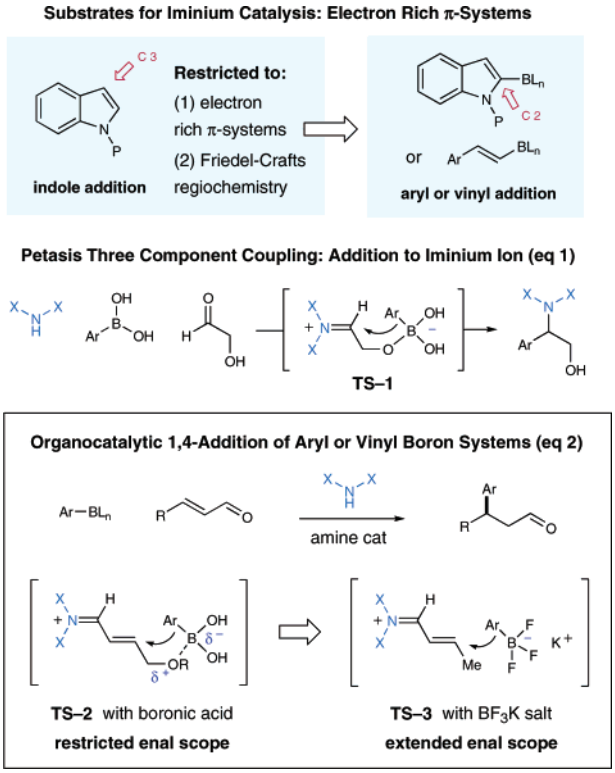
Over the last 8 years, our laboratory has developed the concept of iminium catalysis, a mode of LUMO-lowering activation that has enabled the invention of a large number of enantioselective organocatalytic transformations including Diels−Alder cycloadditions, Friedel−Crafts alkylations, Mukaiyama−Michael additions, hydrogenations, and heteroconjugate additions.[1] Central to the utility of this technology has been the discovery that a wide variety of π-rich aromatics, such as indoles, pyrroles, furans, and aniline rings, readily participate in iminium-catalyzed 1,4-addition with enals, a Friedel−Crafts mechanism that ensures highly rigid regiocontrol with respect to ring functionalization (e.g., indole selective for 3-position, pyrrole 2-position, etc.).[2]



Recently, we hypothesized that the inherent value of iminium catalysis might be greatly expanded via the identification of a traceless activation group that would (i) allow π-neutral or π-deficient substrates to function as suitable nucleophiles for iminium catalysis, while (ii) enabling site-specific alkylation of aromatic nucleophiles outside of the constraints of Friedel−Crafts regioselectivity. Herein we report the first use of vinyl and heteroaryl trifluoroborate salts as viable substrates for amine-catalyzed conjugate additions. While BF_3K salts are routinely employed in transition metal catalysis,[3] to our knowledge, this is the first use of this activation group for organic catalysis or Friedel−Crafts alkylations.[4]

Design Plan. The seminal work of Petasis[5] has established that boronic acids can be utilized as a robust π-activation group that enables aryl and vinyl moieties to readily undergo 1,2-iminium addition as part of a powerful three-component coupling protocol (eq 1, **TS-1**).[6] With this mechanism in mind, we hypothesized that an iminium catalysis platform might be susceptible to boronate conjugate addition, wherein an amine component would now function as a chiral catalyst in lieu of a coupling partner (eq 2). However, direct analogy to the Petasis reaction would require the use of γ-oxy-substituted enals to ensure activation of the boronic acid via formation of a tethered boronate nucleophile (**TS-2**), a structural restriction that would greatly limit the scope of the electrophile. To address this issue, we proposed the use of preformed borate complexes, such as Vedejs−Molander BF_3K salts,[7] to enable intermolecular 1,4-addition without the need for pre-association to an alkoxy group (**TS-3**), a simple modification that we hoped would allow π-neutral or π-deficient nucleophiles to enantioselectively couple with a broad range of enals.

To our delight, exposure of crotonaldehyde to potassium styryltrifluoroborate in the presence of imidazolidinone catalyst **1**·HCl and hydrofluoric acid[8] did indeed provide the desired γ,δ-unsaturated aldehyde product with enantioinduction and good levels of reaction efficiency (Table 1, entry 1, 94% yield, 56% ee). Further evaluation revealed that the tryptophan-derived imidazolidinone catalyst **2**·HCl exhibited optimal conversion and enantiocontrol in solvents such as 1,2-dimethoxyethane (DME) or toluene (entries 5 and 6, 87% ee). The superior levels of induction and efficiency exhibited by catalyst **2**·HCl in DME prompted us to select these conditions for further exploration.

The scope of the organo(trifluoro)borate nucleophile was next examined (Table 2). Styryltrifluoroborate salts, with varied substitution on the aromatic ring, were successful reaction partners (entries 1−3, 70−96% yield, 87−95% ee). Extension of this protocol to electron-deficient heteroaromatics[9] that are traditionally inert to iminium catalysis reveals that 2-formyl furans, benzofurans, and *N*-Boc-indoles become excellent π-nucleophiles upon incorporation of a BF_3K moiety (entries 4−7, 79−94% yield, 91−97% ee). Perhaps, most important, these salts can indeed provide nontraditional regiocontrol as part of a Friedel−Crafts pathway. As revealed in entry 7, site-specific alkylation of an electron-deficient indole at the 2-position was accomplished without any loss in enantioselectivity (79% yield, 91% ee).[10] We anticipate that the discovery that BF_3K salts can direct the regioselectivity of aromatic alkylations will likely find broad application throughout the larger realm of electrophilic aromatic substitution chemistry.

A diverse and representative scope of α,β-unsaturated aldehydes is well tolerated in this process (Table 3), inclusive of both alkyl (entries 1 and 2, 90−97% yield, 93−97% ee) and aryl substituents (entry 5, 69% yield, 92% ee). Additionally, significant electronic variation of the olefin substituent from a methyl ester group to a protected alcohol has little effect on enantiocontrol (entries 3 and 4, ≥88% ee).

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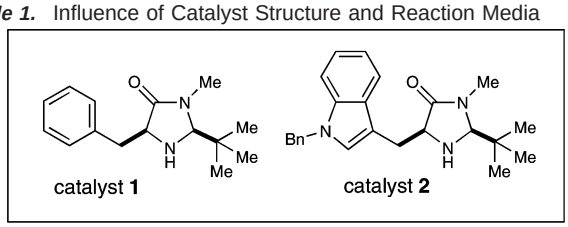
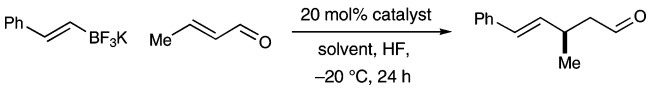
Table 1. Influence of Catalyst Structure and Reaction Media

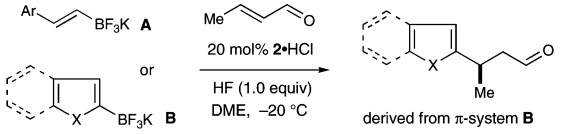


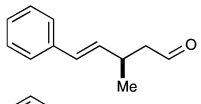
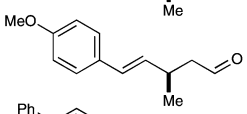
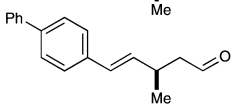
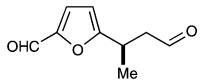
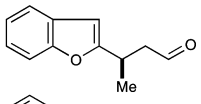
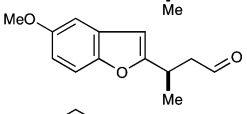
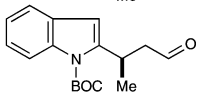


entry	catalyst	solvent	% yield[a]	% ee[b]
1	**1**·HCl	CH_2Cl_2	94	56
2	**2**·HCl	CH_2Cl_2	100	72
3	**2**·HCl	MeCN	28	64
4	**2**·HCl	EtOAc	92	78
5	**2**·HCl	toluene	100	87
6	**2**·HCl	DME	100	87

[a] Determined by GC analysis relative to an internal standard. [b] Enantioselectivity determined by chiral SFC analysis.

Table 2. Scope of Trifluoroborate Activated π-Nucleophiles

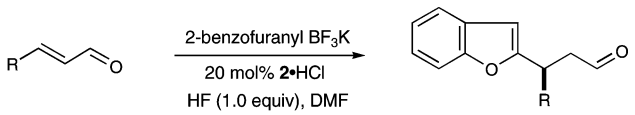


entry	product	time (h)	% yield[a]	% ee[b]
1		24	96	87
2		20	70	88
3		24	91	95
4		24	85	95
5		20	90	97
6		24	94	92
7		24	79	91

[a] Absolute stereochemistry assigned by chemical correlation, X-ray analysis or by analogy. [b] Enantioselectivity determined by chiral SFC analysis.

In accord with our design plan, we found that heteroaryl and vinyl boronic acids will participate in conjugate addition with 4-benzyloxy-2-butenal[11] yet are chemically inert to iminium systems derived from unfunctionalized enals (eq 3). Given our mechanistic proposal, we considered that the addition of boronic acids to β-alkyl-substituted enals might be accomplished via in situ formation of a boronate species, a hypothesis that was validated with the addition of hydrofluoric acid to enable benzofuran addition with high enantioselectivity (eq 4, 92% ee). Studies to determine the general utility of boronic acids in this catalytic conjugate addition are now underway.

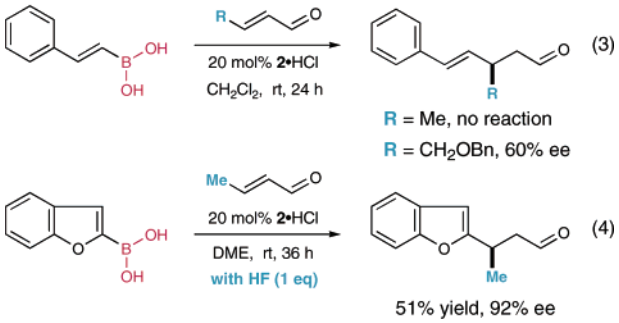
Table 3. Survey of Enal Scope with BF_3K-Activated π-Systems



entry	R	*T* (°C)	time (h)	% yield	% ee[a]
1	Me	−20	24	90	97
2	*n*-Pr	+4	12	97	93
3	MeO_2C	−20	20	93	88
4	$BzOCH_2$[b]	−20	23	75	89
5	*p*-NO_2Ph	rt	24	69	92

[a] Enantioselectivity determined by chiral SFC analysis. [b] Bz = 4-NO_2PhC(O).

Organocatalytic Addition of Boronic Acids as Activated π-Systems



In summary, we have described the first enantioselective organocatalytic conjugate addition of trifluoro(organo)borates to α,β-unsaturated aldehydes. Application of this methodology to the total synthesis of (+)-frondosin B will be described shortly.

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Supporting Information Available: Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) HF is necessary for sequestration of the reaction byproduct, boron trifluoride, by forming a BF_4K precipitate as determined by ^{19}F NMR.
(9) On the basis of the conditions shown, we have found that phenyl trifluoroborate salts are not viable π-nucleophiles for this asymmetric conjugate addition.
(10) Friedel−Crafts alkylation of *N*-Boc-indole occurs at the 3-position: Lei, F.; Chen, Y.-J.; Yong, S.; Liu, L.; Wang, D. *Synlett* **2003**, *8*, 1160.
(11) Equation 3, R = CH_2OBn, 60% yield. The addition of 2-benzofuranyl boronic acid to 4-benzyloxy-2-butenal also proceeds with high levels of enantioselectivity (82% ee).

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