

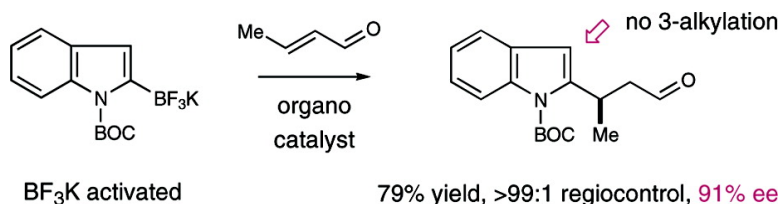
Communication

Organocatalytic Vinyl and Friedel–Crafts Alkylations with Trifluoroborate Salts

Sandra Lee, and David W. C. MacMillan

J. Am. Chem. Soc., **2007**, 129 (50), 15438-15439 • DOI: 10.1021/ja0767480

Downloaded from <http://pubs.acs.org> on February 9, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 12 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



ACS Publications
 High quality. High impact.

Organocatalytic Vinyl and Friedel–Crafts Alkylations with Trifluoroborate Salts

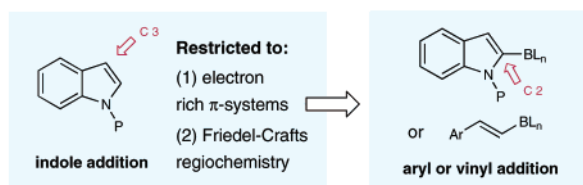
Sandra Lee and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544, and Division of Chemistry, California Institute of Technology, Pasadena, California 91125

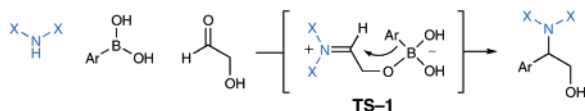
Received September 6, 2007; E-mail: dmacmill@princeton.edu

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

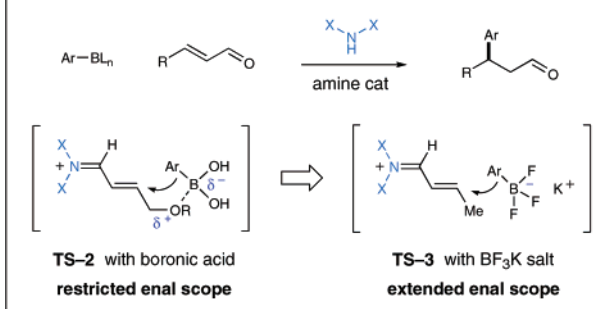
Substrates for Iminium Catalysis: Electron Rich π -Systems



Petasis Three Component Coupling: Addition to Iminium Ion (eq 1)



Organocatalytic 1,4-Addition of Aryl or Vinyl Boron Systems (eq 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 Petasis⁵ 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 styryl-trifluoroborate in the presence of imidazolidinone catalyst **1**·HCl and hydrofluoric acid⁸ 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 heteroaromatics⁹ 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, $\geq 88\%$ ee).

Table 1. Influence of Catalyst Structure and Reaction Media

entry	catalyst	solvent	% yield ^a	% ee ^b
1	1 ·HCl	CH ₂ Cl ₂	94	56
2	2 ·HCl	CH ₂ Cl 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-butenal¹¹ 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

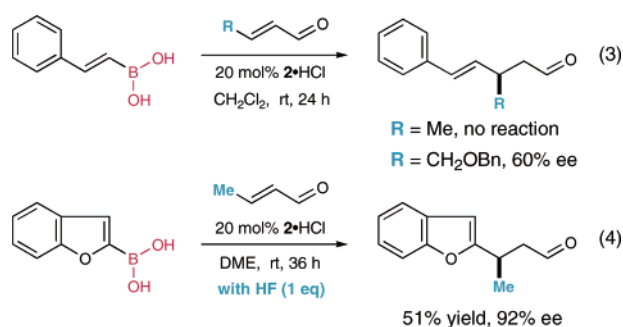
Table 3. Survey of Enal Scope with BF₃K-Activated π -Systems

entry	R	T (°C)	time (h)	% yield	% ee ^a
1	Me	-20	24	90	97
2	<i>n</i> -Pr	+4	12	97	93
3	MeO ₂ C	-20	20	93	88
4	BzOCH ₂ ^b	-20	23	75	89
5	<i>p</i> -NO ₂ Ph	rt	24	69	92

^a Enantioselectivity determined by chiral SFC analysis. ^b Bz = 4-NO₂PhC(O).

utility of boronic acids in this catalytic conjugate addition are now underway.

Organocatalytic Addition of Boronic Acids as Activated π -Systems



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

Acknowledgment. Financial support was provided by the NIHGM5 (R01 GM078201-01-01) and kind gifts from Merck. S.L. is grateful for a NPSC fellowship with Amgen.

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>.

References

- (1) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79 and references therein.
- (2) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: Chichester, UK, 1976; pp 33–85.
- (3) For excellent reviews on potassium organotrifluoroborates, see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, *22*, 4313.
- (4) Use of aryl boronic acids in asymmetric catalysis: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908. (c) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.
- (5) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
- (6) (a) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567.
- (7) Organotrifluoroborate salts are commercially or readily available: (a) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743. (b) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.
- (8) HF is necessary for sequestration of the reaction byproduct, boron trifluoride, by forming a BF₃K precipitate as determined by ¹⁹F 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 = CH₂OBn, 60% yield. The addition of 2-benzofuranyl boronic acid to 4-benzyloxy-2-butenal also proceeds with high levels of enantioselectivity (82% ee).

JA0767480