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A General Method for the Enantioselective Synthesis of α-Chiral Heterocycles

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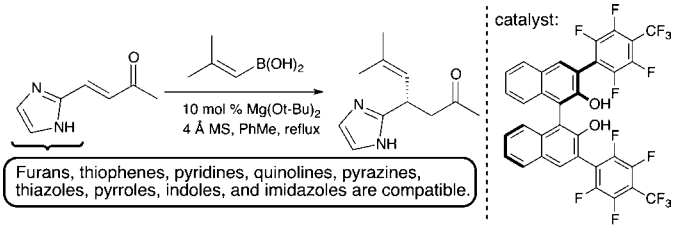
ABSTRACT



The enantioselective formation of stereocenters proximal to unprotected heterocycles has been accomplished. Thus, vinyl boronic acids are added to heterocycle-appended enones via a modified-BINOL catalyst. Catalyst design was key to enable a general reaction. High yields and useful er's are observed for a host of common heteroaryls.

Methods to functionalize heterocycles are of utmost importance to natural product synthesis and to pharmaceutical development.[1] However, enantioselective synthesis in the presence of heterocycles, especially without the use of protecting groups, is still a formidable challenge. In particular, forming stereocenters adjacent to heteroaryls is problematic due to facile stereocenter epimerization, the likelihood of the heterocycle interacting with reagents and disrupting bond formation, and their propensity to undergo deleterious side reactions in the presence of acid, base, oxygen, and/or light.[2] One of the few methods to generate such stereocenters includes conjugate addition of heteroaryls to β-functionalized enones and enals.[3] There, stereocenter substituents in the products may be alkyl, aryl, or an ester, but not vinyl or alkynyl. Also, the resulting heterocyclic substitution is generally limited to Friedel–Crafts-like regioselectivity. A complementary method for the enantioselective formation of α-chiral heterocycles would be conjugate addition to α,β-unsaturated carbonyls **1** with heterocycles attached to the β-position (Figure 1). This strategy would overcome the above-mentioned limitations by taking advantage of enones **1**, with the heterocycle functionalized at any position, and the ability to generate stereocenters rapidly with vinyl and alkynyl groups through variation of the nucleophile. Recently, we initiated such a transformation in the context of β-indoloenones.[4] Herein we report on the design of a next generation catalyst that exhibits significant rate acceleration and allows the conjugate addition to function with a diverse set of heterocycles.

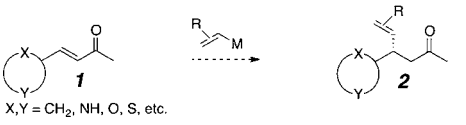


Figure 1. Underutilized strategy for α-chiral heterocycles.

[†] These authors contributed equally.

(1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461. (c) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (d) de Sa Alves, F. R.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (e) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; John Wiley & Sons: West Sussex, U.K., 2010. (b) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 5752.

(3) (a) Jensen, K.; Thorhauge, J.; Hazell, R.; Jorgensen, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (d) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438. (e) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040. (f) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464. (g) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339.

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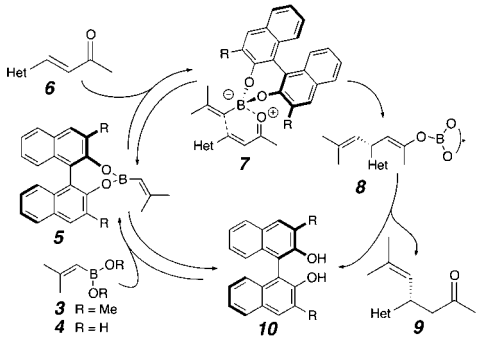
Earlier work demonstrated that diol catalysts derived from BINOL can promote the conjugate addition of alkenyl, alkynyl, and arylboronate esters to β-arylenones.[5] However, with heteroaryl-appended enones, less than a 2% yield of product was seen under those conditions.[4] To accommodate heterocyclic substrates, the mechanism of the transformation was examined to identify the sources of the problems (Scheme 1). Briefly, the catalyst generates Lewis acidic boronate ester **5**, which coordinates to the enone **6** to form **7**. The involvement of both BINOL hydroxyls in **5** is supported by studies in which a monoalkylated BINOL reacts sluggishly and with poor stereoselectivity.[6] Intramolecular C−C bond formation occurs from **7** to form boron enolate **8**, which is then protonolyzed to release the catalyst **10**.[7]

Scheme 1. Putative Reaction Mechanism

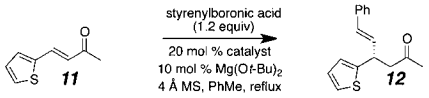


Two pressing problems with this reaction required solving: (1) difficulties arising from the use of low molecular weight vinyl boronate esters **3**,[5] which are volatile, hygroscopic, and hydrolytically unstable, and (2) the sluggish reactivity of heteroaryl-appended substrates. The first was avoided by the use of boronic acids **4**,[4] which are relatively air-stable crystalline solids. Additionally, many more boronic acids are commercially available than boronate esters. Either *t*-BuOH or Mg(O*t*-Bu)$_2$ could be used to accelerate the reaction.[6] In most cases, the latter gave a slightly higher product yield than the former. These additives are postulated to be acting as proton transfer agents to protonolyze enolate **8**.

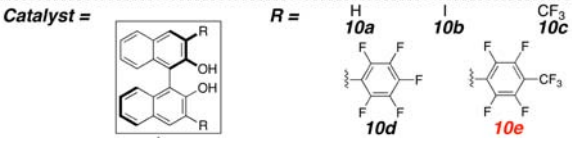
To address the continued lack of reactivity of the substrates, new catalysts were synthesized. The BINOL 3,3′ substituents have a significant impact on vinyl boronate ester addition to chalcones.[7,8] Experimental and theoretical evidence suggests that electron-withdrawing substitution is needed on the catalyst to promote the formation of zwitterionic intermediate **7** (Scheme 1).[7,8] In developing a more efficient catalyst system to effect the conjugate addition of vinyl boronic acids to β-heteroarylenones, effort was focused on increasing the fluorination of the ortho substituents on BINOL to improve catalyst efficiency.[9] We postulated that doing so would increase the Lewis acidity of BINOL boronate ester **5** and/or allow the R substituents in **7** to stabilize the buildup of anionic charge in that mechanistic intermediate.

A direct comparison of known and new catalysts was made with thiophene substrate **11** (Table 1). A small background reaction was observed in the absence of catalyst (entry 1). BINOL (**10a**) slightly increased the reaction rate and showed some enantioinduction (entry 2). The catalysts **10b** and **10c** showed a significant increase in performance and enantiocontrol (entries 3 and 4). Our first generation bisperfluorophenyl catalyst **10d** performed even better (entry 5). None of these BINOL derivatives were nearly as active as the bisperfluorotoluene **10e**, however, which gave an 87% yield of product and a 92% ee in only 4 h. The seemingly minor change of an additional CF_3 is reasoned to increase the electron deficiency of the fluorinated phenyl.[10]

Table 1. Comparison of Catalysts



entry	catalyst	time	yield[a]	er[b]
1	none	6 h	<5%	50:50
2	**10a**	6 h	15%	73:27
3	**10b**	6 h	40%	96:4
4	**10c**	6 h	44%	95:5
5	**10d**	6 h	58%	97:3
6	**10e**	4 h	87%	96:4



[a] Isolated yields. [b] Determined via HPLC with chiral stationary phase.

The rate and selectivity improvements given by catalyst **10e** can be seen for a variety of substrates. Comparable yields and enantioselectivities were sometimes obtained in less than 20% of the time relative to catalyst **10d** (compare entries 1/2 and 9/10, Table 2). Both 2- and 3-substituted furans worked well (entries 1 and 4, Table 2). Diverse nucleophiles are available for the

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(6) See Supporting Information for details.

(7) (a) Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3116. (b) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *J. Org. Chem.* **2008**, *73*, 5078.

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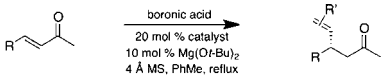
(9) In the case of ketone and aldehyde allylations, catalyst release appears to be rate determining: Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679.

(10) Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 5419.

reaction (entries 4–6 and 9–16). Furan **17** is the product of selective 1,4-addition to a conjugated dienone (entry 8). No 1,2- or 1,6-addition was observed in the reaction, which is consistent with intramolecular nucleophile delivery via transition state **7**.

Pyridine-, quinoline-, and pyrazine-appended enones show varying reactivity (Table 3). For the pyridines, reaction times increased as the point of ring substitution was moved further from the pyridine nitrogen. Thus, the addition of dimethylvinyl boronic acid to a 2-pyridyl enone finished in 3 h, a 3-pyridyl enone took 15 h, and a 4-pyridyl enone required 21 h for complete conversion (compare entries 1, 4, and 5). Additionally, products **20** and **22** were formed with a lower er than **21**. Apparently the benzylic protons in the former examples are more acidic than in the latter. Indeed, the enantioenriched 2- and 4-pyridyl products **20** and **22** racemize when resubjected to the reaction conditions, with **20** epimerizing at a faster rate.[6] This difficulty illustrates the complexity of working with heterocyclic compounds. The best results were obtained when catalyst **10e** was used (entries 2 and 3). Then, a high yield was obtained and the er was improved. Quinoline and pyrazine rings also nicely provided products (entries 7–10).

Table 2. Furans and Thiophenes

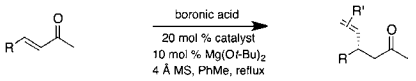


entry	product	catalyst	time	yield[a]	er[b]
	13a R = Ph				
1		**10d**	24 h	93%	96:4
2		**10e**	4 h	99%	95:5
	13b R = p-F-C_6H_4				
3		**10d**	24 h	86%	99:1
4	**14**	**10d**	24 h	95%	99:1
5	**15**	**10d**[c]	36 h	89%	94:6
6	**16**	**10d**[d]	36 h	99%	95:5
7	**17**	**10d**	72 h	74%	98:2
8		**10e**	36 h	75%	97:3
9	**18**	**10d**	17 h	72%	90:10
10		**10e**	2 h	99%	96:4
	12 R = Ph				
11		**10d**	24 h	96%	94:6
12		**10e**	22 h	98%	97:3
	19a R = p-MeO-C_6H_4				
13		**10d**[e]	16 h	64%	92:8
14		**10e**[f]	24 h	90%	97:3
	19b R = p-F-C_6H_4				
15		**10d**	24 h	80%	94:6
16		**10e**	22 h	92%	98:2

[a] Isolated yields. [b] Determined via HPLC with chiral stationary phase. [c] PhCl as solvent at 80 °C. [d] Boronate ester used. [e] Reaction run at 90 °C. [f] Reaction run at 70 °C.

Thiazole and benzothiazole products also epimerize slowly under the reaction conditions in a similar manner to the 2- and 4-pyridyl products, resulting in nonoptimal er's (Table 4). Again, the new catalyst significantly increased the reaction rate, generally allowing higher stereoselectivity in the α-chiral heterocyclic products.

Table 3. Pyridines, Quinoline, and Pyrazine



entry	product	catalyst	time	yield[a]	er[b]
1	**20**	**10d**	3 h	71%	86:14
2		**10e**[c]	16 h	95%	94:6
3		**10e**	75 min	92%	93:7
4	**21**	**10d**	15 h	87%	98:2
5	**22**	**10d**	21 h	92%	91:9
6		**10e**	22 h	91%	95:5
7	**23**	**10d**	1 h	85%	88:12
8		**10e**[c]	5 h	94%	96:4
9	**24**	**10d**	4 h	95%	92:8
10		**10e**[c]	8 h	99%	95:5

[a] Isolated yields. [b] Determined via HPLC with chiral stationary phase. [c] Reaction run at 70 °C.

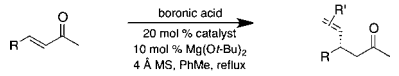
These reaction conditions are even compatible with unprotected pyrroles and imidazoles (Table 5), though alkylation of the ring nitrogen does improve product formation (compare entries 1 to 3 and 8 to 10). Unprotected indoles are tolerated and give excellent yields (entry 7).[5] Free-NH 2- and 4-substituted imidazoles give products **31** and **32** (R = H) in good yields and with useful enantioselectivity. As before, the new catalyst **10e** accelerates the reactions and improves stereoselectivity. These products would surely be difficult to efficiently obtain by other strategies,[11] demonstrating the advantages of this organocatalytic system.

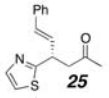
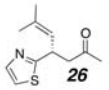
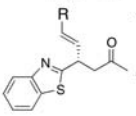
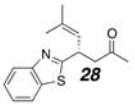
Lastly, the reaction was performed with enone **33**, since electron-rich enones appear to be excellent substrates in the above conjugate addition (Scheme 2). A comparison of product formation was made to one of the most common methods for performing 1,4-additions to enones, though very few examples exist of nucleophilic conjugate additions of carbon nucleophiles to triply oxygenated β-arylenones such as **33**.[12,13] Divinyl cuprate provided **34** in only a moderate yield despite the rapid consumption of the starting material. With the

(11) (a) Makida, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4122. (b) Yoshida, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 11896.

(12) Muraoka, O.; Sawada, T.; Morimoto, E.; Tanabe, G. *Chem. Pharm. Bull.* **1993**, *41*, 772.

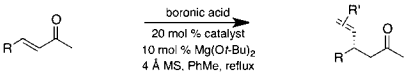
Table 4. Thiazoles and Benzothiazoles

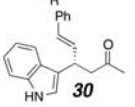
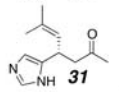


entry	product	catalyst	time	yield[a]	er[b]
1		**10d**	24 h	89%	88:12
2		**10e**	15 h	87%	84:16
3		**10e**[c]	4 h	82%	84:16
4		**10d**	20 h	64%	82:18
5		**10e**	2 h	92%	84:16
6	 **27a R = Ph**	**10d**	60 h	53%	76:24
7		**10e**	36 h	69%	80:20
8	**27b R = p-OMe-C$_6$H$_4$**	**10d**	42 h	77%	89:11
9		**10e**	7 h	85%	92:8
10	**27c R = p-F-C$_6$H$_4$**	**10d**	60 h	47%	74:26
11		**10e**	24 h	84%	87:13
12		**10d**	16 h	88%	80:20
13		**10e**	4 h	91%	86:14

[a] Isolated yields. [b] Determined via HPLC with chiral stationary phase. [c] PhCl, reflux.

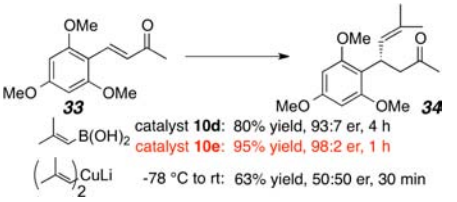
Table 5. Pyrroles and Imidazoles



entry	product	catalyst	time	yield[a]	er[b]
1	**29a R = H**	**10d**[c]	48 h	23%	92:8
2		**10e**[c]	24 h	39%	96:4
3	**29b R = Me**	**10d**	24 h	63%	97:3
4		**10e**	2 h	90%	96:4
7		**10d**	18 h	87%	98:2
5		**10d**	72 h	83%	81:19
6		**10e**	36 h	88%	87:13
8	**32a R = H**	**10d**	32 h	76%	83:17
9		**10e**	15 h	83%	91:9
10	**32b R = Me**	**10d**	12 h	92%	96:4

[a] Isolated yields. [b] Determined via HPLC with chiral stationary phase. [c] Reaction run at 70 °C.

Scheme 2. Addition to an Electron-Rich Enone[6]



electron-deficient catalysts **10d** and **10e**, **34** is easily isolated in excellent yield and enantiopurity, showing the substrate orthogonality of this organocatalytic system relative to traditional methods.

In almost every comparison between catalysts, the second-generation catalyst **10e** provides product more rapidly, in a higher yield, and with a higher er. It more ably outcompetes both boronic acid decomposition and a racemic background reaction (Table 1, entry 1) while allowing less time for product epimerization. Determination of the rate-limiting step for this reaction is underway to help identify the source of the acceleration.

In conclusion, a difficult transformation has been achieved for the formation of allylic and propargylic stereocenters adjacent to a variety of unprotected heterocycles. Improved yields and er's are a result of catalyst design, where increased fluorination improves the reaction rate and stereoselectivity. These products represent an enantioenriched library of novel structures. Additional functionalization of the olefins and alkynes on the stereotopic carbon is available to generate even more complex structures.

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Supporting Information Available. Additional optimization data, experimental procedures, and characterization data for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) For references with doubly oxygenated aromatics, see: (a) Skytte, D. M.; Nielsen, S. F.; Chen, M.; Zhai, L.; Olsen, C. E.; Christensen, S. B. *J. Med. Chem.* **2006**, *49*, 436. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, *349*, 1759. (c) Kobayashi, K.; Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1019. (d) Frost, C.; Edwards, H.; Penrose, S.; Gleave, R. *Synthesis* **2010**, 3243.