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Enantioselective Conjugate Addition of Alkenylboronic Acids to Indole-Appended Enones

Brian J. Lundy, Santa Jansone-Popova, and Jeremy A. May*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States

jmay@uh.edu

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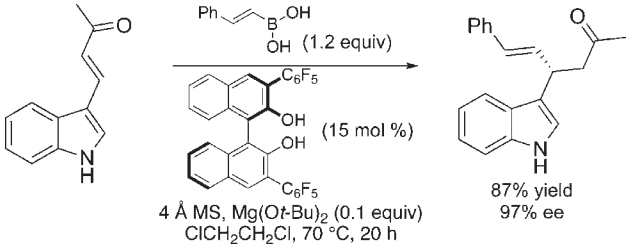
ABSTRACT



An enantioselective addition of alkenylboronic acids and alkynylboronic esters to unprotected indole-appended enones is reported. This transformation proceeds with high enantioselectivity and high product yields via the use of catalytic amounts of 3,3′-bis(pentafluorophenyl)-BINOL and Mg(Ot-Bu)$_2$. A range of α-branched indole derivatives are available from the transformation.

Indoles are important and essential active structural components in many biologically active small molecules.[1] Many of these compounds have stereocenters at the carbon adjacent to the indole. However, the difficulty in stereoselectively forming such centers is illustrated by the relative lack of compounds not derived[2] from natural sources.[3] Only recently have approaches been explored to create stereocenters adjacent to indoles enantioselectively,[4] and of these approaches, many are not viable with unprotected indoles. The conjugate addition[5] of a vinyl or alkynyl nucleophile to an indole-appended enone potentially provides a direct route to create the stereocenter in ketoindoles such as **B** (Scheme 1).[6] However, very few examples exist of conjugate additions performed on enones appended at the β-position with an unprotected indole (e.g., **A**).[7] Moreover, none of these examples are enantioselective.[8] To address the lack of such

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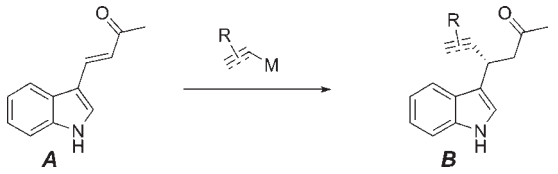
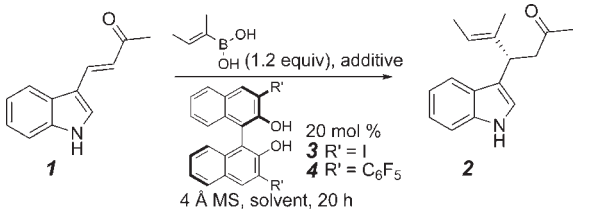
Scheme 1. Formation of an α-Branched Indole



methods, we have developed a catalytic enantioselective addition of vinyl nucleophiles to indolo enones.

As unprotected indolo enones are generally incompatible with strongly basic organometallic agents,[9] we chose to investigate neutral organocatalytic 1,4-addition conditions to access ketones such as **B** stereoselectively. This approach was inspired by work described by A. Suzuki[10] and H. C. Brown[11] and later elaborated by others for asymmetric transformations.[12–14] However, existing conditions afforded at best ~2% yield when an unprotected indole was present in the enone.[15] The use of low molecular weight boronic esters was problematic for reasons of volatility, hydrolytic instability, and loss of purity during storage. Additionally, the unreactive indole substrate **1** (Table 1) required long reaction times that led to the production of various side products.

Table 1. Optimization of the BINOL-Catalyzed Conjugate Addition of 2-*cis*-Butenylboronic Acid



entry	R′	additive	solvent	yield (SM)[a]	ee[b]
1	I	none	CH_2Cl_2, 25 °C	<2% (85%)	n.d.[c]
2	I	none	THF, reflux	<2% (96%)	n.d.[c]
3	I	none	$ClCH_2CH_2Cl$, 70 °C	21% (77%)	n.d.[c]
4	C_6F_5	none	$ClCH_2CH_2Cl$, 70 °C	32% (63%)	98%
5	C_6F_5	Cs_2CO_3 (0.1 equiv)	$ClCH_2CH_2Cl$, 70 °C	11% (81%)	n.d.[c]
6	C_6F_5	LiCl (0.1 equiv)	$ClCH_2CH_2Cl$, 70 °C	38% (54%)	99%
7	C_6F_5	Mg(O*t*-Bu)$_2$ (0.1 equiv)	$ClCH_2CH_2Cl$, 70 °C	48% (51%)	99%
8	C_6F_5	Mg(O*t*-Bu)$_2$ (0.1 equiv)	$ClCH_2CH_2Cl$, reflux	49% (36%)	98%

[a] Yields determined by comparison of NMR peaks to an internal standard.[15] [b] Determined for the purified product via analytical HPLC. [c] ee's were not determined.

To address the first of these issues, we looked to use readily available, easily purified, and conveniently handled boronic acids or their dehydrated congeners, boroxines.[16] We reasoned that boroxines could act as reactive surrogates for boronic esters for the initial formation of BINOL-boronic esters **5** (Figure 1).[17,18] Importantly, these vinyl nucleophiles are usually more easily accessed, functionalized, and stored than their zinc, copper, aluminum, or magnesium congeners. The use of a boronic acid did not initially fare well with enone **1** and the known catalyst **3** (entry 1, Table 1). However, when elevated temperatures and a nonpolar solvent were used, some product formation occurred (entry 3).

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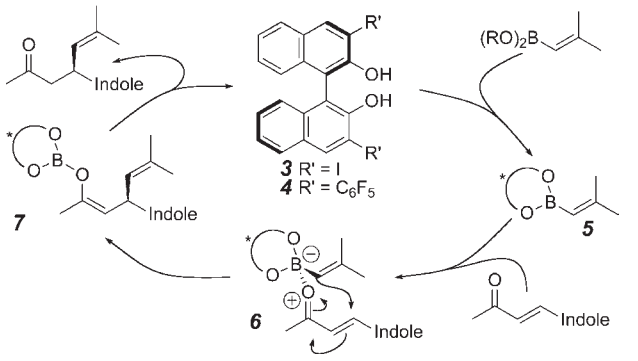


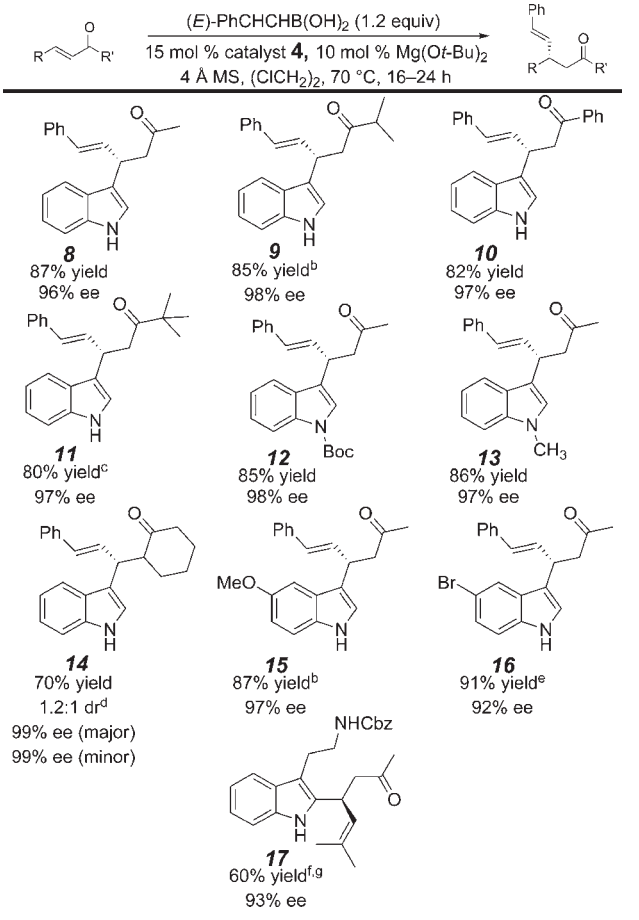
Figure 1. Proposed mechanism for the conjugate addition.[18,19]

To compensate for the unreactive substrate, a more reactive catalyst was needed. The literature suggested a potential correlation between reaction conversion for chalcone substrates and the strength of the electron-withdrawing group at the 3 and 3′ positions of a BINOL catalyst.[12,13] This effect could be due to an increase in formation of the ate complex **6** postulated in Pellegrinet and Goodman's proposed mechanism for boronic ester nucleophiles shown in Figure 1 (R = Me).[18,19] Next, the transformation would proceed via an intramolecular alkenyl transfer from the boron ate complex in the *s-cis* conformation[10,11] to form the enol borate **7**. If the formation of complex **6** was the slow step in the transformation, then a more Lewis acidic boronic ester **5** would accelerate the reaction. However, if the alkyl transfer is slowest, then a more Lewis acidic boronic ester **5** would stabilize ate complex **6** and consequently slow the reaction.

The possibility that the formation of ate complex **6** is the reaction's slow step prompted the synthesis of (*R*)-3,3′-bis(pentafluoro-phenyl)-BINOL (**4**, Table 1).[20] When added to the enone **1** and 2-*cis*-butenylboronic acid, the bispentafluorophenyl derivative showed a reproducible increase in product formation with excellent enantiomeric excess (Table 1, entries 3 and 4). Although steric or conformational effects cannot be excluded, we view the increase in product formation as a partial validation of the above hypothesis. While acidic additives inhibited the reaction and neutral salts had little effect, Mg(O*t*-Bu)$_2$ improved the reaction (entry 7). Whether this is due to catalyst activation by deprotonation or due to the presence of *t*-BuOH as a proton shuttle is now under investigation.

Examples of successfully treating indole-appended enones with *trans*-2-phenylvinylboronic acid and 15 mol % of (*R*)-3,3′-bis(pentafluorophenyl)-BINOL (**4**) are shown in Scheme 2. With these conditions, the ketone substituent could be a methyl (**8**), isopropyl (**9**), or phenyl (**10**). A *tert*-butyl group (**11**) is tolerated, though it causes the reaction to be sluggish. An unprotected indole is not necessary for the reaction, as both Boc- (**12**) and methyl-protected (**13**) indoles reacted well. Cyclic ketones (**14**) are also competent, as long as the enone can adopt an *s-cis* configuration.[10,11] In this case, a 1.2:1 mixture of diastereomers was observed in the product, likely due to an unselective protonation of the enol borate **7**. Both diastereomers were found in high enantiomeric excess, which indicates that the carbon–carbon bond formation occurred with high enantioselectivity. Neither electron-donating

Scheme 2. 1,4-Addition Products of β-Indolo Enones[a]



[a] Isolated yields averaged over 2–3 reactions. [b] Recycled catalyst used. [c] Reaction time 48 h. [d] Determined through integration of NMR peaks for the crude mixture. [e] Reaction time 36 h. [f] 20% catalyst **3** used with 3 equiv of 2,2-dimethylvinylboronic acid. [g] Yield based on recovered starting material.[22]

(15) See Supporting Information for detailed optimization trails, experimental conditions, and compound data.

(16) A different approach uses the dibutyl ester for stability: Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337–4340.

(17) A control experiment in $CDCl_3$ without catalyst or substrate showed that the boroxine was substantially generated in situ from the boronic acid. Also: (a) Storgaard, M.; Ellman, J. A. *Org. Synth.* **2009**, 360–373. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752.

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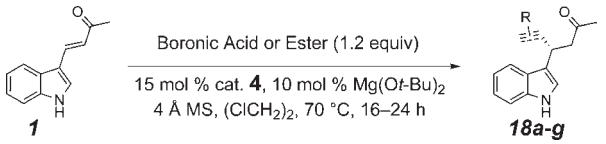
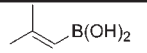
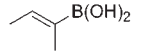
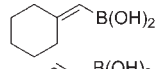
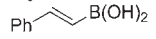
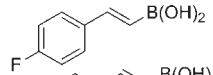
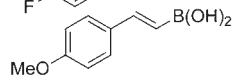
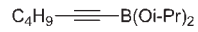
nor electron-withdrawing groups on the indole ring affected reactivity (see **15** and **16**). Importantly, the catalyst could be recovered during purification and recycled. The yields and enantioselectivity reported for ketoindoles **9** and **15** were obtained using recycled catalyst. Finally, the enone could be in either the 3- or 2-position of the indole (compare **8** and **17**), though the significantly hindered substrate in the latter case was more reactive with (*R*)-3,3′-bisiodo-BINOL. This catalyst bears smaller groups than that with bis-pentafluorophenyl substitution, likely lowering steric repulsion.

Table 2. Alkenyl and Alkynyl Nucleophiles[a]



entry	boronic acid	product	yield	ee
1		18a	90%[b]	89%
2		18b	82%[c]	96%
3		18c	74%	87%
4		18d	87%	96%
5		18e	86%	96%
6		18f	85%	94%
7		18g	71%[b,d]	98%

[a] All yields are isolated yields averaged over 2–3 reactions. [b] 3 equiv of boronic acid or ester.[22] [c] PhMe was used as solvent at 115 °C in a sealed tube. [d] $Mg(Ot\text{-}Bu)_2$ omitted.

Next, enone **1** was treated with a range of boronic acids (Table 2). Both alkylvinylboronic acids (entries 1–3) and arylvinylboronic acids (entries 4–6) proved amenable to the reaction conditions, giving products **18** in respectable yields and with good to excellent enantioselectivity. 1-Substituted vinylboronic acids are almost as reactive as their less-hindered counterparts (compare entries 1 and 2). Electron-withdrawing groups (entry 5) and electron-donating groups (entry 6) are well tolerated and produce no drop in reactivity or selectivity. While alkynylboronic acids were found to be too unstable for convenient handling, the diisopropyl ester[21] could be used effectively with excellent enantioselectivity (entry 7).

In conclusion, the use of (*R*)-3,3′-bis(pentafluorophenyl)-BINOL has enabled the conjugate addition of alkenylboronic acids and alkynylboronic esters to indole-appended enones in good yields and with excellent enantioselectivity. Both 2- and 3-functionalized indoles are tolerated, and additional indole substitution or altered indole electronics are compatible. In addition, alkenyl or alkynyl nucleophiles both work well and have a variety of substitutions. The resulting enantioenriched α-branched indoles have an alkene or alkyne at the stereocenter to facilitate further synthetic transformations.

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

(21) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.

(22) Because of decomposition, 1.2 equiv of hexynylboronic ester gave the product **21g** in 58% yield and 96% ee.