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Asymmetric Conjugate Alkenylation of Enones Catalyzed by Chiral Diols

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The asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds has been studied for many years, but it is only relatively recently that reliable catalytic methods have been developed.[1] Of these, the phosphoramidite copper-catalyzed addition of organozincs is particularly noteworthy.[2] Other copper-catalyzed processes are currently being intensively scrutinized.[3] In parallel, the rhodium-catalyzed asymmetric addition of alkenyl- and arylboronic acids has been developed as an excellent complementary method.[4,5] Palladium catalysts are also effective.[6] Common to these methods is the use of chiral metal complexes as catalysts.

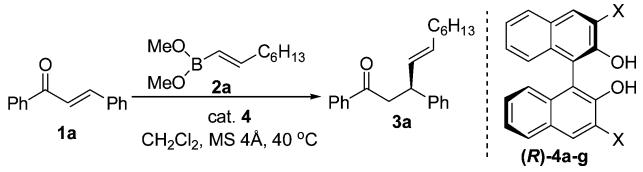
In conjugate additions to enones using alkenylboronic acids and chiral rhodium catalysts, high selectivities are often observed partly because the alkenylboronic acids, on their own, are unreactive toward enones and thus there is no nonselective background reaction. Rhodium catalysts have also been used in asymmetric transfers of alkenyl groups from Si,[7] Sn,[8] and Zr[9] derivatives. A recurring theme in these and related reactions[10] is that activation occurs via transmetalation to a (chiral) alkenylrhodium species. We reasoned that esterification of boronic acids with suitable chiral diols might be an alternative method of activation.[11] Furthermore, if the diol could be turned over during the reaction, one would be able to develop a catalytic asymmetric alkenylation process which does not depend on a heavy metal catalyst.[12,13] We now report for the first time that such a process is possible.

After some experimentation, it was found that 1,4-alkenylation of chalcone (**1a**) using dimethyl boronate **2a** could be achieved using catalytic amounts of binaphthols (**4**) (Table 1). All of the 3,3′-disubstituted binaphthols examined were able to catalyze the addition to produce **3a** with high enantioselectivity. In fact, **3a** was formed with an er of ∼98:2 regardless of the size or electronic nature of the substituent. Higher reaction rates were observed with ligands bearing electron-withdrawing substituents (entries 3, 6, and 7). Reactions were initially screened using 20 mol % of catalyst, but as little as 3 mol % could be used with no diminution in yield or selectivity, albeit the reaction was considerably slower (entry 9).

No alkenylation product **3a** was observed in the absence of added binaphthols. Alkyl diols, such as diisopropyl tartrate, did not catalyze the alkenylation. Also, the addition of water or methanol inhibits the reaction. These observations are consistent with a proposed mechanism wherein catalysis of the reaction arises from transesterification of boronate **1a** with binaphthols to produce more Lewis acidic, and hence more reactive, boronates (Scheme 1). Practically, the deleterious effects of water and alcohols could be alleviated easily by the addition of molecular sieves to the reaction.

Further investigation of this new reaction showed that high selectivities could be obtained for virtually all enones studied (Table 2). Thus heating a mixture of boronate **2a** and an enone in CH_2Cl_2 with a catalytic amount of diol **4g** afforded the desired 1,4-addition product in high yield with enantioselectivities ranging from 97:3 to >99.5:<0.5. Highest selectivities were observed for enones with

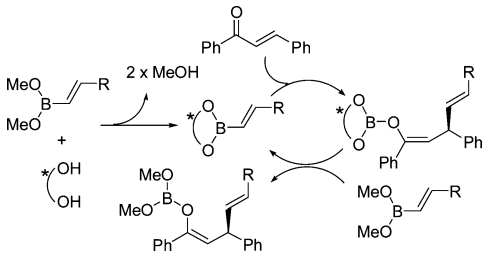
Table 1. Effect on Diols on the Alkenylation of Chalcone with Boronate **2a**



entry	X (ligand)	catalyst loading (mol %)	time (h)	yield (%)[a]	er[b]
1	H (**4a**)	20	24	<20[c]	93:7
2	Me (**4b**)	20	36	25[c]	98.6:1.4
3	CF_3 (**4c**)	20	12	90	98.6:1.4
4	Ph (**4d**)	20	36	75[c]	97.1:2.9
5	Ar[d] (**4e**)	20	36	>95[c]	98.7:1.3
6	Br (**4f**)	20	12	92	98:2
7	I (**4g**)	20	12	92	98.7:1.3
8	I (**4g**)	10	36	93	98.6:1.4
9	I (**4g**)	3	72	91	98.4:1.6

[a] Isolated yields after chromatography. [b] Determined by chiral HPLC analysis. [c] Conversion by ^{1}H NMR analysis. [d] Ar = 3,5-$(CF_3)_2C_6H_3$.

Scheme 1. Proposed Catalytic Cycle



relatively large aryl groups in the β-position (entries 5 and 6), but any aryl group gave high selectivity.

With conjugated dienones, only 1,4-addition products were observed, also with high selectivities (entries 8 and 9). With alkyl groups in the β-position, selectivities were still consistently high (entries 10−12), regardless of whether the group is a methyl, *n*-alkyl, or branched. Also noteworthy is that an enone containing a carbomethoxy group in the β-position reacted smoothly to provide a single regioisomer with good enantioselectivity (entry 13).

The high selectivities observed and the sense of asymmetric induction may be rationalized, albeit very naively, by invoking the involvement of six-membered chair-like transition states (Figure 1). Of the two possible transition states where the β-substituent of the enone is pseudo-equatorial, one is destabilized by a steric interaction of the alkenyl group with the binaphthol. Reaction via the favored transition state leads to the observed enantiomer.

Different boronates were also examined to probe the scope of the alkenylation (Table 3). A diisopropyl boronate gave the same selectivity as the corresponding dimethyl boronate, but the reaction

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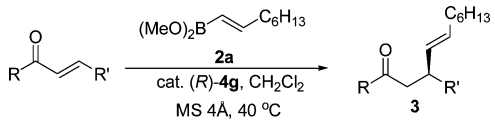
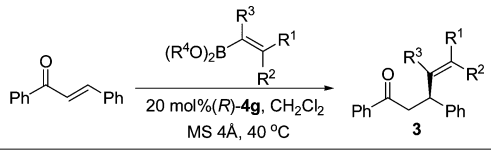
Table 2. Alkenylation of Enones with Boronate **2a**



entry	R′[a]	catalyst (mol %)	time (h)	yield, % (prod)[b]	er[c]
1	Ph	10	36	93 (**3a**)	98.6:1.4
2	4-ClC_6H_4	10	36	96 (**3b**)	99.2:0.8
3	4-$MeOC_6H_4$	10	48	86 (**3c**)	99:1
4	4-MeC_6H_4	10	48	95 (**3d**)	99.4:0.6
5	2-MeC_6H_4	10	48	90 (**3e**)	>99.5:0.5
6	1-naphthyl	10	36	98 (**3f**)	>99.5:0.5
7	2-furyl	20	72	94 (**3g**)	98.5:1.5
8	PhCH=CH	20	72	84 (**3h**)	99:1
9	PhCH=CMe	10	60	94 (**3i**)	99.2:0.8
10	Me	20	72	95 (**3j**)	98:2
11	*n*-hexyl	20	72	94 (**3k**)	99.2:0.8
12	*i*-Pr	20	72	92 (**3l**)	97:3
13	COOMe	25	96	84 (**3m**)	98.4:1.6
14	Ph[d]	20	48	89 (**3n**)	99.5:0.5
15	Ph[e]	20	72	81 (**3o**)	99.1:0.9

[a] R = Ph unless otherwise noted. [b] Isolated yields after chromatography. [c] Determined by chiral HPLC analysis. ">99.5:0.5" denotes that none of the other isomer was detected. [d] R = 2,4-$(MeO)_2C_6H_3$. [e] R = Me. Absolute configuration of product based on rotation.[9]

Table 3. Alkenylation of Chalcone with Alkenylboronates



entry	boronate	time (h)	yield,% (prod)[a]	er[b]
1	C_6H_{13}, $B(OMe)_2$	12	92 (**3a**)	98.7:1.3
2	C_6H_{13}, $B(O\text{-}i\text{-}Pr)_2$	36	92 (**3a**)	98.8:1.2
3	C_6H_{13}, $B(OH)_2$	48	86 (**3a**)	95.6:4.4
4	Ph, $B(OMe)_2$	12	97 (**3p**)	99.3:0.7
5	$BnOCH_2$, $B(OMe)_2$	72	83 (**3q**)	98.6:1.4
6	C_6H_{13}, $B(OMe)_2$	18	91 (**3r**)	95.5:4.5
7	Bu, Br, $B(OMe)_2$	12	85 (**3s**)	91:9
8	Bu, Bu, $B(OMe)_2$	18	93 (**3t**)	96.3:3.7
9	Bu, $B(OMe)_2$, Br	24	94 (**3u**)	95:5
10	Et, $B(OMe)_2$, Et	36[c]	57 (**3v**)	65:35

[a] Isolated yields after chromatography. [b] Determined by chiral HPLC analysis. [c] Done in CH_2Cl_2/CF_3Ph 3:1 at 55 °C.

was much slower. The corresponding boronic acid was even slower and the selectivity diminished slightly. All dimethyl (*E*)-alkenylboronates investigated gave selectivities of ~99:1.

Other substitution patterns gave lower selectivities, but, in general, synthetically useful selectivities were usually observed. Thus a (*Z*)-boronate and a 2,2-disubstituted systems still gave enantioselectivities of >90:10 (with retention of configuration of the alkenyl unit). Only in the case of a 1,2-disubstituted alkenylboronate was poor (er = ~2:1) selectivity observed. Arylboronates were unreactive under similar reaction conditions.

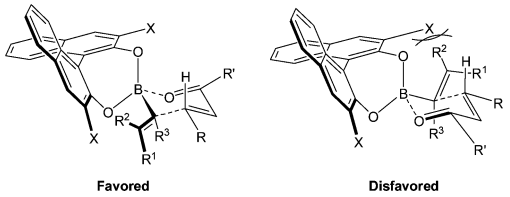


Figure 1. Possible transition states.

Operationally, these reactions are very simple to carry out. Dimethyl boronates are prepared by esterification of boronic acids[14] and can be used without isolation or purification. After the reaction, the chiral ligand is readily recovered by precipitation with hexane or column chromatography.

In summary, we have developed the first catalytic asymmetric conjugate alkenylation methodology that does not rely on a heavy metal. The alkenylboronates used are readily accessible as are the binaphthol catalysts.[15] Enantioselectivities are uniformly high for a wide range of enones and alkenyl groups. Efforts are underway to expand the scope of these reactions.

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Supporting Information Available: Procedures for preparations of alkenylboronates and alkenylation reactions, and spectroscopic data for alkenylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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