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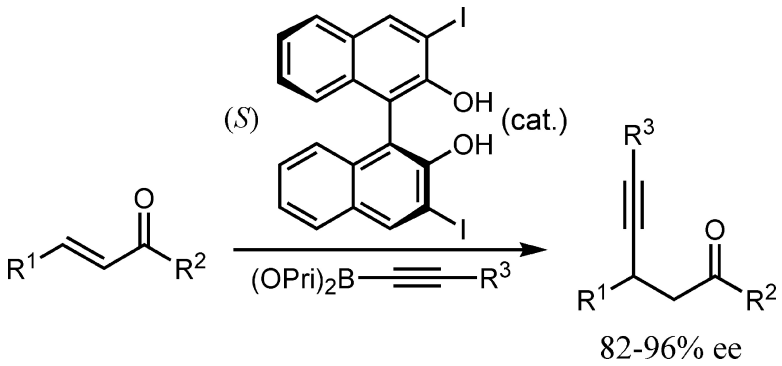


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# Ligand-Catalyzed Asymmetric Alkynylboration of Enones: A New Paradigm for Asymmetric Synthesis Using Organoboranes

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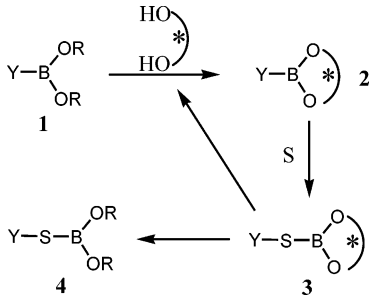
Boron has played an important role in the development of modern asymmetric synthesis.[1] In fact, the first nonenzymatic asymmetric synthesis exhibiting high levels of stereoselectivity was the hydroboration of *cis*-2-butene with diisopinocampheylborane, reported by Brown and Zwiefel over 40 years ago.[2] Since then, boron has been exploited for the development of many useful asymmetric processes, including asymmetric reductions,[3] aldol reactions using boron enolates,[4] allyl- and crotylborations,[5] and α-halo boronic ester chemistry.[6]

The efficacy of boron in many asymmetric processes can be rationalized in part by its relatively small size, which allows any chiral ligands on it to exert more influence on transition-state energies than with other systems. While various boron complexes, particularly oxazaborolidines, have been used as catalysts in asymmetric reactions,[7] one area of boron chemistry that appears to be completely unexplored is the possibility of using a catalytic amount of an "exchangeable" chiral ligand on the boron to promote an asymmetric transformation.[8] The use of only catalytic amounts of ligand has obvious economic and practical advantages. We envisaged a scenario wherein an achiral boronate **1** could undergo transesterification with a chiral diol to form a chiral boronate **2**, which might undergo reaction with a substrate S to generate an intermediate **3**, wherein a group Y has been transferred to the substrate (Scheme 1). If the chiral ligand could then be freed from

***Scheme 1***

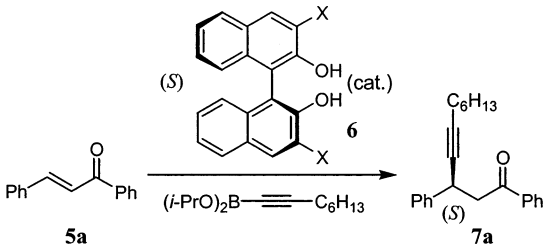



intermediate **3**, it could react with more **1** to generate more boronate **2** and hence complete a catalytic cycle. We now report the first example wherein such a scheme appears to be operative.

In order for Scheme 1 to be effective for asymmetric synthesis, achiral boronate **1** must be much less reactive than boronate **2** toward the substrate. On the basis of our previous work with asymmetric conjugate alkynylations,[9] we knew that alkynylboronates such as **1** (Y = 1-alkynyl, OR = O*i*Pr) are unreactive toward enones. Thus, we chose to investigate whether this reaction could be rendered catalytic in ligand. Initial results are shown in Table 1.

While *B*-1-octynyldiisopropylboronate did not provide detectable amounts of alkyne **7a** from chalcone (**5a**), addition of 20 mol % binaphthol **6a** gave encouraging results in that >20% conversion was observed; however, the reaction did not proceed to completion. Use of other binaphthols, particularly ones with electron-withdrawing groups in the 3,3′-positions, allowed the reaction to proceed to completion. Especially striking were results obtained with 3,3′-diiodobinaphthol **6e**, which provided a 95% isolated yield of alkyne **7a** with enantioselectivity identical to that observed for the corresponding stoichiometric reaction.

***Table 1.*** Binaphthol-Catalyzed Alkynylations of Chalcone[a]




X = H = **6a**; Ph = **6b**; 3,5-$(CF_3)_2C_6H_3$ = **6c**; $CF_3$ = **6d**; I = **6e**.

| entry | ligand | X (mol %) | time (h) | yield of **7a** (%)[b] | % ee[c] |
|---|---|---|---|---|---|
| 1 | none | − (0) | 96 | 0 | − |
| 2 | **6a** | H (20) | 96 | <50[d] | nd[e] |
| 3 | **6b** | Ph (20) | 120 | 60[d] | 83 (85) |
| 4 | **6c** | $(CF_3)_2C_6H_3$ (20) | 96 | 80 | 83 (82) |
| 5 | **6d** | $CF_3$ (20) | 96 | 90 | 83 (83) |
| 6 | **6e** | I (20) | 96 | 95 | 87 (86) |
| 7 | **6e** | I (20)[f] | 24 | 94 | 86 (86) |
| 8 | **6e** | I (10)[f] | 48 | 91 | 85 (86) |
| 9 | **6e** | I (5)[f] | 72 | 90 | 85 (86) |
| 10 | **6e** | I (2)[f] | 72 | 70[d] | 85 (86) |

[a] Reactions were carried out in $CH_2Cl_2$ at 25 °C unless otherwise noted. [b] % isolated yields of chromatographed products. [c] Determined by HPLC analysis on a chiral column; values in parentheses are for reactions using stoichiometric amounts of binaphthol-modified alkynylboronates.[10] [d] Estimated conversion based on $^1$H NMR analysis. [e] Not determined. [f] Reaction warmed to reflux.

Further probing of this reaction revealed that warming to 40 °C (refluxing $CH_2Cl_2$) decreased the reaction time substantially, with essentially no change in yield or enantioselectivity. Decreasing the amount of binaphthol **6e** to 5 mol % affected the reaction time but not the yield or selectivity. A further decrease to 2 mol % resulted in incomplete reaction, but selectivity remained high.

These results suggest that this reaction represents an example of a ligand-accelerated asymmetric process (Scheme 2). In other words, it seems that the rate of reaction of achiral reagent **8** with **5** is much slower than the reaction of chiral reagent **9** with **5**. In fact, since the enantioselectivity of the reaction is essentially invariant with the catalyst loading and is high even when the reaction does not proceed to completion, the rate of reaction of **8** with **5** must be negligibly low. Ligand-accelerated reactions are relatively rare, with only a handful of very successful systems


10.1021/ja043001q CCC: $30.25 

***Scheme 2***

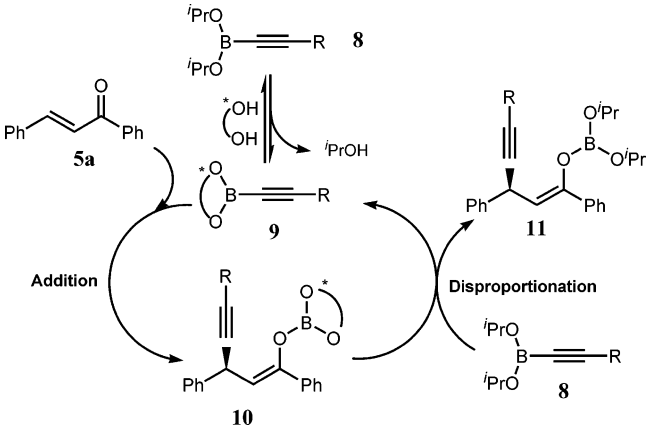
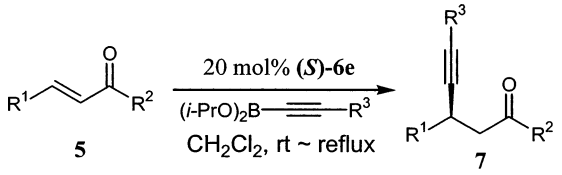



***Table 2.*** Alkynylations of Enones Using Catalytic Amounts of **6e**[a]




**5a**: $R^1$ = Ph, $R^2$ = Ph; **5b**: $R^1$ = 1-naphthyl, $R^2$ = Ph
**5c**: $R^1$ = 2-furyl, $R^2$ = Ph; **5d**: $R^1$ = Ph, $R^2$ = Me

| entry | enone | $R^3$ | time (h) | product | yield (%)[b] | % ee[c] |
|---|---|---|---|---|---|---|
| 1 | **5a** | *n*-$C_6H_{13}$ | 24 | **7a** | 94 | 86 (86) |
| 2 | **5b** | *n*-$C_6H_{13}$ | 12 | **7b** | 93 | 96 (96) |
| 3 | **5c** | *n*-$C_6H_{13}$ | 36 | **7c** | 78 | 88 (88) |
| 4 | **5d** | *n*-$C_6H_{13}$ | 48 | **7d** | 89 | 94 (96) |
| 5[d] | **5a** | Ph | 24 | **7e** | 95 | 82 (84) |
| 6[d] | **5b** | Ph | 24 | **7f** | 97 | 90 (92) |
| 7[d] | **5a** | $CH_2OBn$ | 24 | **7g** | 91 | 86 (87) |
| 8[d] | **5b** | $CH_2OBn$ | 24 | **7h** | 94 | 95 (96) |

[a] 3 equiv of *B*-1-alkynyldiisopropylboronate was used. [b] % isolated yields of chromatographed products. [c] Determined by HPLC analysis on a chiral column; values in parentheses are for reactions using stoichiometric amounts of binaphthol-modified alkynyl boronates. [d] A one-pot procedure starting from a 1-alkyne was used. See text for details.

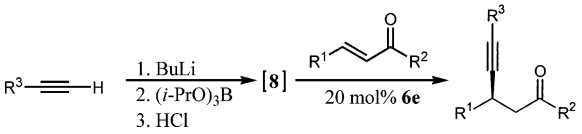
known (e.g., tartrate-accelerated epoxidations,[11] cinchona alkaloid-catalyzed dihydroxylations,[12] amino alcohol-catalyzed organozinc reactions).[13] This appears to be the first example of ligand-accelerated catalysis using organoboronates.

It is noteworthy that this reaction can be catalytic in binaphthol only if the binaphthol can be liberated from intermediate **10**. We speculate that this liberation occurs by ligand exchange/disproportionation with reagent **8** to regenerate more reagent **9** along with intermediate **11**, which upon protonation affords the desired product.

NMR studies have shown that an equilibrium between boronates **8** and **9** is established rapidly at room temperature. Thus, either the addition or disproportionation step must be the rate-determining step (RDS). Since the overall reaction rate is dependent on the $\beta$-substituent of the enone (Table 2, entries 1−3) and the rate of disproportionation should not be affected by this substituent, it is likely that the RDS is the addition step.

Diols other than binaphthols were also examined. Simple aliphatic diols such as ethylene glycol and pinacol gave no product, while diisopropyl tartrate, a ligand used very effectively in allylborations, catalyzed the reaction (88% yield of **7a**) but gave racemic product. Other bidentate ligands, such as *N*-tosyl α-amino acids, also catalyzed the reaction but have thus far afforded only low (<45% ee) selectivities.

Use of 3,3′-diiodobinaphthol **6e** in other catalytic alkynylations gave consistently excellent results (Table 2). High yields of products were obtained in all cases, and the enantioselectivity was essentially the same as that obtained in stoichiometric reactions. Other than the obvious advantage of using less ligand, this new catalytic alkynylation has other benefits. For example, substrate **5d** (and other enones where $R^2$ = alkyl rather than aryl) reacts very sluggishly under the previous stoichiometric conditions and only mediocre (∼50%) yields were obtained; here, the reaction is slow but a significantly higher yield (89%) is observed. Also, it is no longer necessary to pre-make reagent **9**, as it can be generated in situ. Thus, a one-pot procedure starting with a 1-alkyne can be used to effect asymmetric conjugate alkynylation in an operationally simple manner (eq 1). In general, in situ generation could be very useful, particularly if the desired reagent is too reactive or too unstable to be isolated.




(1)

In summary, we have shown that asymmetric alkynylation of enones can be carried out very efficiently using catalytic amounts of binaphthol ligands. This constitutes a major advance over the previous stoichiometric reaction in terms of preparative simplicity and economy. More importantly, we have demonstrated a "proof of principle" that ligand exchange with boronates can be sufficiently fast that catalytic amounts of chiral ligands can be used to effect high levels of stereoselectivity. Efforts are underway to exploit this finding to develop other catalytic asymmetric processes, such as hydroborations,[14] conjugate reductions,[15] and allylborations.[5]

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**Supporting Information Available:** Experimental procedures and spectral data for compounds **7a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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