Asymmetric Conjugate Addition of Alkynylboronates to Enones

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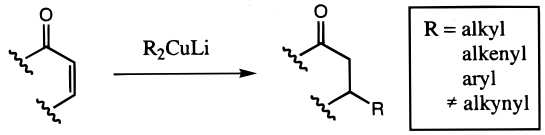
Michael addition of organometallics, particularly organocoppers[1] and organozincs,[2] to α,β-unsaturated carbonyl compounds is a well-established method for the formation of carbon−carbon bonds. Over the past two decades, asymmetric versions of these reactions, particularly with copper reagents, have been developed which can be highly selective.[3,4] However, one important limitation of organocopper reagents is that they do not efficiently transfer alkynyl groups to organic substrates (Scheme 1).[5] Since alkynyl groups may be readily manipulated into many other functionalities,[6] we were interested in filling this void by developing reactions which could stereoselectively add alkynyl groups in a Michael fashion to α,β-unsaturated carbonyl compounds. We now report the first examples of enantioselective conjugate additions of alkynyl groups to enones.[7]

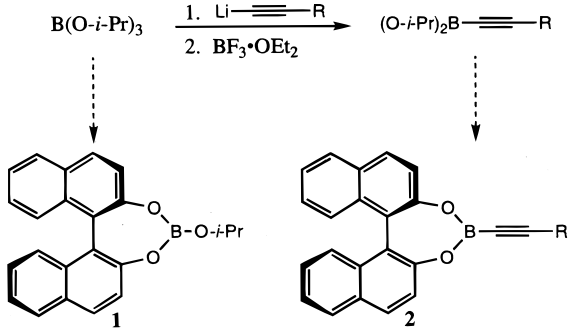
Conjugate alkynyl group transfer using achiral reagents had been achieved with alkynylboron[8] and aluminum[9] reagents. However, it appears that no asymmetric versions of these reactions have been reported.

We reasoned that an alkynylboronate derivative of a chiral diol might be an asymmetric conjugate alkynylation reagent.[10−12] 1,1′-Bi-2-naphthol has been used as a very effective chiral auxiliary in many asymmetric transformations[13] so we directed our initial efforts to prepare reagents of general structure **2** (Scheme 2). It has previously been shown[14] that alkynylboronates may be prepared by reaction of an alkynyllithium with a borate followed by treatment of the resulting adduct with HCl or $BF_3{\cdot}OEt_2$. Since it is known that transesterification of *B*-1-alkynylboronates is not an effective reaction,[14a] the most straightforward route to boronates **2** would be to add alkynyllithiums to a mixed borate such as binaphthyl isopropyl borate (**1**).[14] However, we were unable to prepare compounds such as **1**.[15,16]

Scheme 1



Scheme 2



Eventually it was found that reaction of binaphthol (**3a**) with lithium *B*-1-octynyltriisopropylborate (**4a**) (with removal of *i*-PrOH) provided borate **5a** (Scheme 3).[17] As expected, this complex was unreactive toward enones. However, it was anticipated that, in analogy with previous work,[14a] addition of acid (e.g. HCl or $BF_3{\cdot}OEt_2$) would generate the reactive trivalent boronate **2a**.[18] Indeed, treatment of **5a** and chalcone in CH_2Cl_2 at room temperature with HCl or $BF_3{\cdot}OEt_2$ provided the expected 1,4-addition product cleanly in high yield. The observed enantioselectivity (31% ee) was disappointingly low but showed that enantioselective conjugate alkynylation using this type of chemistry is possible.

It was gratifying to find that when 3,3′-diphenylbinaphthol **3b**[19] was used in place of the parent binaphthol **3a**, addition to chalcone was considerably more selective (Table 1). In general, reactions gave high yields of 1,4-addition products with no detectable side-products. In all cases, reactions using the 3,3′-diphenylbinaphthol reagent were much more selective than those with the unsubstituted binaphthol. In fact, with aryl groups in the β-position, enantioselectivities were uniformly high, ranging from 85 to

(1) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.
(2) Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741−742.
(3) Reviews: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. (b) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283−285.
(4) Organozincs: Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869−7872 and references therein.
(5) It has recently been shown that alkynylcuprates will add to enones in the presence of trialkylsilyl triflates or TMSI: (a) Kim, S.; Park, J. H.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 783−786. (b) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182−187.
(6) Hudrlik, P. F.; Hudrlik, A. M. Applications of Acetylenes in Organic Synthesis. In *The Chemistry of the Carbon−Carbon Triple Bond*; Patai, S., Ed.; John Wiley and Sons: Chichester, 1978; Part 1, pp 199−273.
(7) An account of preliminary work was presented at the 81st Canadian Society for Chemistry Conference and Exhibition, Whistler, BC, Canada, May 31−June 4, 1998, abstract No. 297.
(8) (a) Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954−956. (b) Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* **1992**, 695−698.
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(11) Asymmetric conjugate addition of aryl- and alkenylboronic acids has been described: Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580.
(12) Alkynylboranes have been used in asymmetric alkynylations of aldehydes: Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.
(13) (a) Rosini, S.; Franzini, L.; Rafaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517. (b) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264−3265. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (d) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.
(14) Unsymmetric borates of general structure $(R'O)_2BOR$ have been used to prepare alkynylboronates: (a) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631−2634. (b) Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871−6873.
(15) It has been suggested that reaction of binaphthol with triphenylborate generates the "expected" mixed borate but it has not been isolated or spectrocopically characterized: refs 13b and 13c.
(16) Many attempts to prepare mixed alkyl binaphthyl borates gave a boron bridged trimer of binaphthol: Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545−546.
(17) Borate **4a** was easily prepared by addition of 1-octynyllithium to triisopropyl borate. The formation of **5a** could be assayed by the position of the isopropyl methine signal in the ^1H NMR ($CDCl_3$/DMSO-d_6) spectra: **4a**, δ 3.98; **5a**, δ 4.41.
(18) Attempts to isolate boronate **2a** were only partially successful. Treatment of borate **5a** with $BF_3{\cdot}OEt_2$ followed by removal of volatiles in vacuo gave a white solid which exhibited ^1H and ^{13}C NMR spectra consistent with **2a** but containing signals for other related compounds as well. The intensities of these other signals increased with time, suggesting slow decomposition of boronate **2a**.
(19) Addition of substituents in the 3,3′-positions of binaphthol can dramatically increase enantioselectivities: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510−3512. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310−312. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930.

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Scheme 3

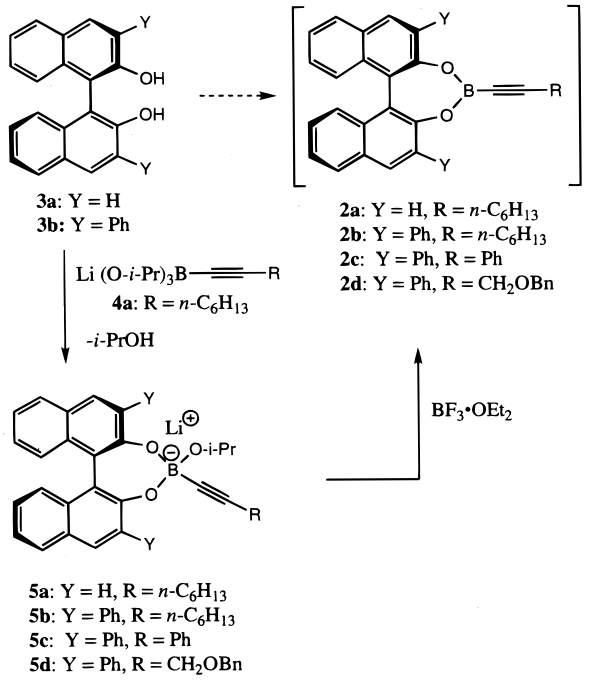
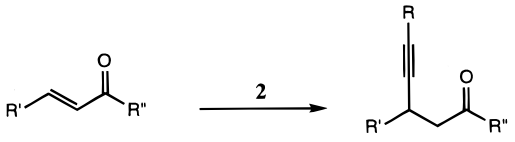


Table 1. Enantioselective Conjugate Addition of Alkynyl Groups to Enones[a]



a: R' = R" = Ph
b: R' = Ph, R" = Me
c: R' = *i*-Pr, R" = Ph
d: R' = *n*-C_6H_{13}, R" = Ph
e: R' = *t*-Bu, R" = Ph
f: R' = *E*-CH_3CH=CH, R" = Ph
g: R' = 2-furyl, R" = Ph
h: R' = 1-naphthyl, R" = Ph
i: R' = R" = *p*-BrC_6H_4

7: R = *n*-C_6H_{13}
8: R = Ph
9: R = $BnOCH_2$

enone	reagent	product	yield[b]	% ee[c]	enone	reagent	product	yield[b]	% ee[c]
6a	**2a**	**7a**	90	31	**6f**	**2b**	**7f**	82	74
6b	**2a**	**7b**	38	31	**6g**	**2b**	**7g**	91	>98[d]
6c	**2a**	**7c**	90	3	**6h**	**2b**	**7h**	91	95
6a	**2b**	**7a**	88	85	**6i**	**2b**	**7i**	93	75
6b	**2b**	**7b**	50	85	**6a**	**2c**	**8a**	90	90
6d	**2b**	**7d**	80	16	**6h**	**2c**	**8h**	99	98
6c	**2b**	**7c**	85	41	**6i**	**2c**	**8i**	87	90
6e	**2b**	**7e**	87	82	**6h**	**2d**	**9h**	81	>98[d]

[a] Reactions run at room temperature as described in ref 23. [b] Isolated yields of chromatographed material. [c] Determined by HPLC using a Chiralcel OD column. [d] Minor isomer not detected by HPLC analysis.

>98% ee. With alkyl groups in the β-position, there was a pronounced steric effect wherein selectivities increased with the size of the substituent. There was also an increase in selectivity when the size of the aryl group in the β-position was increased. Overall, it seems that alkynylboronates **2** efficiently transfer alkynyl groups to enones; an aryl group directly attached to the carbonyl carbon of the enone is important for high reactivity while both the size and electronic character of the β-substituent are important for selectivity. Best selectivities were observed with β-substituents which have electron-rich π-systems.

Since it is known that alkynyl 9-BBN reagents add only to enones capable of achieving an *s*-cis conformation,[8a] it was not surprising to find that **2b** did not react with 2-cyclohexenone. Similarly, no reaction was observed with a β,β-disubstituted enone (dypnone). Reactions of *Z* enones gave essentially the same selectivities as their *E* counterparts.[20]

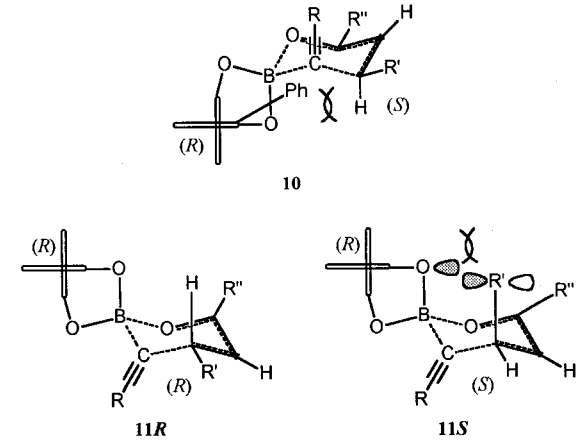


Figure 1. Cyclic 6-membered chair-transition states.

The adducts **7i** and **8i** were prepared particularly to shed some light on the absolute configuration of the addition products. Using *R* binaphthol **3b** produced alkynyl ketones **7i** and **8i** with *R* stereochemistry (X-ray). This stereochemistry is the stereochemistry predicted based on a cyclic six-membered transition state similar to that proposed by Brown for additions of alkynyl 9-BBN reagents to enones[8a] and also by Noyori for the asymmetric reduction of alkyl aryl ketones with BINAL-H (Figure 1).[21] This model is also consistent with the enhanced selectivity observed with 3,3′-substituents. Thus, of the two possible types (based on the diastereotopicity of the binaphthoxy oxygens) of chair-transition states **10** and **11**, structure **10** is disfavored due to steric interactions. With structures such as **11**, there would be two possible diastereomeric transition states with **11*R*** favored over **11*S***. This model fits well with the observed dependence of enantioselectivity on both the size and electronic nature of the β-substituent on the enone.[22]

In conclusion, we have found that alkynylboronates **2** can transfer alkynyl groups regioselectively and enantioselectively to enones.[23] These represent the first enantioselective conjugate alkynylations. We are currently investigating the effects of other diol ligands on this reaction and will report these results in due course.

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Supporting Information Available: Experimental details and spectroscopic data for the preparation of binaphthol **3b**, boronates **4a**, **5a**, and **5b**, enones **6c**−**i**, and adducts **7a**−**i**, **8a**, **8h**, **8i**, and **9h**; X-ray structural information on **7i** and **8i** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) When **2b** was allowed to react with ***Z*-6a** and ***Z*-6d**, **7a** and **7d** were produced in 90% and 4% ee, respectively. In both cases, the major isomer was the same as that produced using the *E* enone, suggesting isomerization to the *E* isomer occurred under the reaction conditions.

(21) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

(22) The absolute configurations of the other adducts in Table 1 are unknown at this time, but it is expected that they will also be consistent with our working model.

(23) Representative preparative procedures follow. Borate **5b**: To a cooled (0 °C) mixture of binaphthol **3b** (0.416 mmol) and **4a** (0.345 mmol) under Ar was added THF (15 mL). The mixture was stirred at 0 °C for 1 h, then at room temperature for 3 h. The solvent was removed and the resulting white solid was dried in vacuo overnight to give compound **5b** in quantitative yield. Alkynylation: To a mixture of adduct **5b** (0.345 mmol), an enone (0.232 mmol), and CH_2Cl_2 (15 mL) was added BF_3•OEt_2 (58 μL, 0.461 mmol). After reaction was complete (or no further change by TLC, 1−24 h), saturated NH_4Cl (2 mL) and water (2 mL) were added to quench the reaction. Standard aqueous workup afforded the 1,4-addition product (see Table 1 for yields) and **3b** (>95% recovery).