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Asymmetric Propargylation of Ketones Using Allenylboronates Catalyzed by Chiral Biphenols

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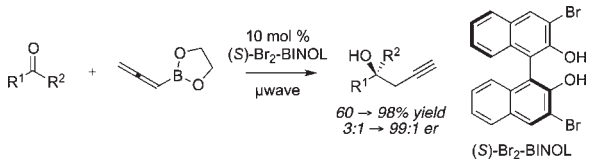
ABSTRACT



Chiral biphenols catalyze the enantioselective asymmetric propargylation of ketones using allenylboronates. The reaction uses 10 mol % of 3, 3′-Br_2-BINOL as the catalyst and allenyldioxoborolane as the nucleophile, in the absence of solvent, and under microwave irradiation to afford the homopropargylic alcohol. The reaction products are obtained in good yields (60−98%) and high enantiomeric ratios (3:1−99:1). Diastereoselective propargylations using chiral racemic allenylboronates result in good diastereoselectivities (dr >86:14) and enantioselectivities (er >92:8) under the catalytic conditions.

Homopropargyl alcohols are versatile building blocks for use in synthesis[1] possessing divergent options for synthetic transformations in comparison to the analogous homoallylic alcohol reagents.[2] However, few methods exist to prepare them in enantioenriched form. Chiral allenyl metal reagents have proven effective,[3,4] and recently described catalytic approaches[5−7] are notable alternatives for accessing these chiral synthetic intermediates. As a reagent for propargylation reactions, allenylboronates are attractive starting materials due to the ease of preparation and predictable reactivity patterns.[4a,b,8] Chiral diols are capable of activating boronates as chiral nucleophiles under catalytic conditions,[9] and we postulated that chiral biphenols could function as effective promoters of the asymmetric propargylation of ketones. Herein we describe the development of an operationally simple addition of allenyl boronates to ketones catalyzed by chiral biphenols under microwave irradiation.

Insight we garnered during our investigations of the asymmetric allylboration of ketones employing cyclic boronate reagents and chiral biphenols as catalysts[9g] proved valuable in expanding the scope of diol activated reagents to include allenyl boronates. We envisaged conditions that activate more stable, easier to handle, cyclic boronates could be ascertained for propargylation reactions. We began by investigating the reaction of allenyldioxaborinane **1** with acetophenone **3** using **5a** as the catalyst (Table 1). At room temperature, in the absence of solvent (Table 1, entry 1), no reaction was observed after three days. However, under gentle heating at 65 °C, homopropargyl alcohol **4** was isolated in 80% yield after 15 h in an enantiomeric ratio (er) of 93:7 (Table 1, entry 3). Temperature had little effect on the reaction, and the reaction time could be

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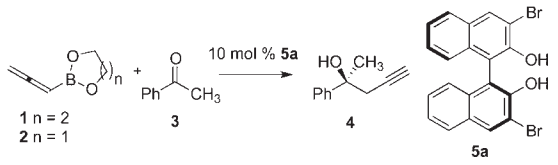
Table 1. Progargylation of Ketones[a]



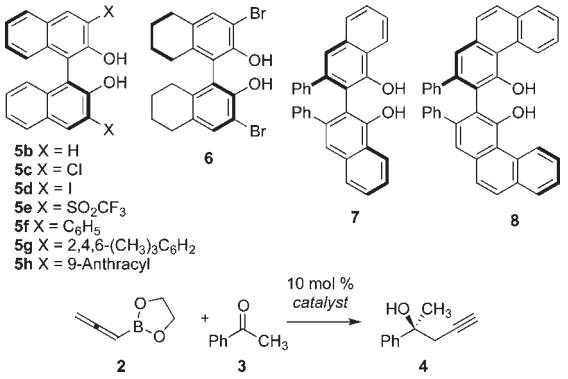
entry	boronate	method[a]	temp (°C)	time (h)	yield (%)[b]	er[c]
1	**1**	a	20	72	0	–
2	**1**	b	65	1	5	4:1
3	**1**	b	65	15	80	93:7
4	**1**	b	105	1	60	93:7
5	**1**	c	105	1	77	93:7
6	**2**	a	20	72	75	3:1
7	**2**	b	65	15	80	97:3
8	**2**	b	65	1	64	97:3
9	**2**	c	60	1	85	97:3

[a] Catalyst (0.05 mmol) was dissolved in boronate (0.75 mmol) and then added ketone (0.5 mmol) using the following methods: (a) stirred at room temp. (b) conventional heating (c) microwave reactor held at 10 W. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

lowered substantially by the use of microwave irradiation (entries 4–7).

We proposed the use of allenyldioxaborolane **2** as the nucleophile with the expectation that the greater ring strain in the cyclic boronate would result in a better exchange partner for the biphenol catalyst leading to a faster reaction. Indeed, the use of boronate **2** resulted in an increase in the rate of reaction, 64% yield after 1 h at 65 °C (Table 1, entry 8) compared to a 5% yield with boronate **1** (Table 1, entry 2), with an increase in enantioselectivity. Boronate **2** also demonstrated greater reactivity at room temperature (Table 1, entry 6) over boronate **1**. While a higher rate of the racemic background reaction is expected for boronate **2**, upon heating, the rate of the BINOL/boronate exchange reaction and entry into the catalytic pathway appears to exceed the uncatalyzed pathway (entries 7 and 8). Ultimately, the microwave-promoted reaction at a powermax setting of 10 W for 1 h afforded the product in excellent yield and enantioselectivity (Table 1, entry 9).

Table 2. Catalyst Dependence on Enantioselective Propargylation[a]



entry	catalyst	yield (%)[b]	er[c]
1	**5b**	81	52:48
2	**5c**	82	92.5:7.5
3	**5d**	79	93:7
4	**5e**	65	92.5:7.5
5	**5f**	70	94:6
6	**5g**	55	97:3
7	**6**	58	92:8
8	**7**	80	96:4
9	**8**	84	89:11

[a] Reactions run with 10 mol % catalyst (0.05 mmol) that was dissolved in boronate (0.75 mmol) and then added ketone (0.5 mmol) and submitted directly to the microwave at 10 W for 60 min. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

We next investigated the dependence of catalyst structure on enantioselectivity in the propargylation reaction (Table 2). Although 3,3′-Br_2-BINOL **5a** afforded the product in excellent yield and selectivity, other related structures may be equally effective and that insight could prove useful when investigating the reaction substrate scope. The 3,3′-substitution on the BINOL appeared crucial (entry 1 vs entries 2–6) for enantioselectivity, and the aryl substituted BINOLs **5f**[10] and **5g**[11] gave comparable results to **5a**. Biphenols **6**[12] and **7**[13] were also suitable catalysts (entries 7 and 8) while the use of VAPOL **8**[13]

(3) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett*. **2006**, *8*, 4089.

(4) (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc*. **1982**, *104*, 7667. (b) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc*. **1986**, *108*, 483. (c) Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3697. (d) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc*. **1990**, *112*, 878. (e) Marshall, J. A.; Wang, X.-J. *J. Org. Chem*. **1991**, *56*, 3211. (f) Marshall, J. A.; Adams, N. D. *J. Org. Chem*. **1999**, *64*, 5201. (g) Loh, T.; Lin, M.; Tan, K. *Tetrahedron Lett*. **2003**, *44*, 507. (h) Lai, C.; Soderquist, J. A. *Org. Lett*. **2005**, *7*, 799. (i) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett*. **2006**, *47*, 5173. (j) Brawn, R. A.; Panek, J. S. *Org. Lett*. **2007**, *9*, 2689.

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(6) (a) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal*. **2009**, *351*, 2295. (b) Shi, S.; Xu, L.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2010**, *132*, 6638.

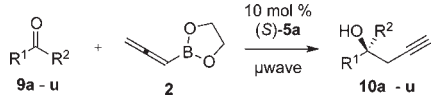
(7) (a) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun*. **1993**, 1468. (b) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett*. **1994**, *35*, 8323. (c) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Chem. Commun*. **1997**, *8*, 763. (d) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed*. **1998**, *37*, 2392. (e) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc*. **2001**, *123*, 12095. (f) Denmark, S. E.; Wynn, T. J. *J. Am. Chem. Soc*. **2001**, *123*, 6199. (g) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1063. (h) Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2449. (i) Konishi, S.; Hanawa, H.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1603. (j) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem.—Eur. J*. **2003**, *9*, 4405. (k) Inoue, M.; Nakada, M. *Org. Lett*. **2004**, *6*, 2977. (l) Liu, S.; Kim, J. T.; Dong, C.; Kishi, Y. *Org. Lett*. **2009**, *11*, 4520. (m) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc*. **2010**, *132*, 7600. (n) Usanov, D. L.; Yamamoto, H. *Angew. Chem., Int. Ed*. **2010**, *49*, 8169. (o) Trost, B. M.; Ngai, M.-Y.; Dong, G. *Org. Lett*. **2011**, *13*, 1900. (p) Chen, J.; Captain, B.; Takenaka, N. *Org. Lett*. **2011**, *13*, 1654.

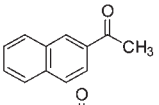
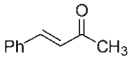
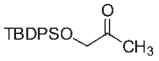
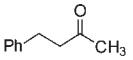
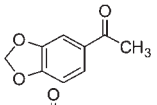
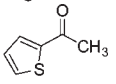
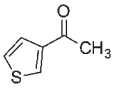
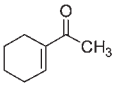
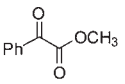
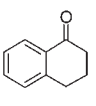
resulted in lower enantioselectivity (entry 9). Based on the accessibility and ease of synthesis, biphenol **5a** was chosen for use in the assessment of the substrate scope.

The scope of the propargylation reaction using boronate **2** was determined using a selection of ketones that varied in both electronic and steric properties (Table 3). Aromatic substrates were generally good substrates with notably better selectivities when R^1 = aromatic and R^2 = alkyl chain (entries 3–4). Conversely, lower enantioselectivities are observed when the steric bias is reduced as is the case for ketones **9g**, **9h**, and **9i**. However, the use of 3,3′-Mes_2-BINOL **5g** in the reaction of **9g** with **2** resulted in an improvement of the selectivity to 95:5 er (from 85:15 with **5a**) in good yield. In addition, 3,3′-9-anthracyl-BINOL enhanced selectivities of ketone **9h** to 90:10 er (from 60:40 er with **5a**). In general, the reaction catalyzed by **5a** possessed good substrate scope affording the products in high enantioselectivities and good yields (Table 3, entries 10–21).

Diastereoselective propargylation reactions using racemic boronates offered intriguing possibilities for reaction development. The successful addition reaction in high enantioselectivities would be the result of a chiral boronate kinetic resolution process.[14]

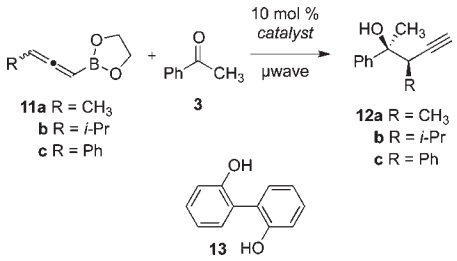
Table 3. Propargylation of Ketones Catalyzed by Chiral Biphenols[a]



entry	ketone	product	yield (%)[b]	er[c]
1	**3** R^1 = Ph, R^2 = CH_3	**4**	85	97:3
2	**9a** R^1 = Ph, R^2 = CH_2CH_3	**10a**	87	98:2
3	**9b** R^1 = Ph, R^2 = $(CH_2)_2CH_3$	**10b**	85	99:1
4	**9c** R^1 = Ph, R^2 = $(CH_2)_2Cl$	**10c**	96	98:2
5	**9d** R^1 = Ph, R^2 = $(CH_2)_3Cl$	**10d**	97	99:1
6	**9e** R^1 = Ph, R^2 = CH_2Ph	**10e**	98	98:2
7	**9f** 	**10f**	86	97:3
8[d]	**9g** 	**10g**	91	95:5
9[e]	**9h** 	**10h**	96	90:10
10[d]	**9i** 	**10i**	86	79:21
11	**9j** R^1 = *p*-Br-C_6H_4, R^2 = CH_3	**10j**	88	96:4
12	**9k** R^1 = *m*-Br-C_6H_4, R^2 = CH_3	**10k**	83	97:3
13	**9l** R^1 = *p*-NO_2-C_6H_4, R^2 = CH_3	**10l**	91	95:5
14	**9m** R^1 = *m*-CF_3-C_6H_4, R^2 = CH_3	**10m**	83	96:4
15	**9n** R^1 = *p*-CH_3O-C_6H_4, R^2 = CH_3	**10n**	88	97:3
16	**9o** R^1 = *p*-CH_3-C_6H_4, R^2 = CH_3	**10o**	87	98:2
17	**9p** 	**10p**	88	97:3
18	**9q** 	**10q**	83	96:4
19	**9r** 	**10r**	85	96:4
20	**9s** 	**10s**	68	96:4
21[f]	**9t** 	**10t**	93	90:10
22[g]	**9u** 	**10u**	60	97:3

[a] Catalyst (0.05 mmol) was dissolved in boronate (0.75 mmol) and then added ketone (0.5 mmol) and submitted directly to the microwave. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction run with 10 mol % **5g**. [e] Reaction run with 10 mol % **5h**. [f] Ketone was added to mixture of **2** and **5a** previously heated to 70 °C and stirred for 30 min. [g] Reaction run in 0.5 mL of toluene and heated to 65 °C overnight.

Table 4. Diastereoselective Propargylations[a]



entry	boronate	cat.	prod	yield[b]	er[c]	dr[c]
1	**11a**	**5a**	**12a**	93	92:8 (major) 98:2 (minor)	86:14
2[d]	**11a**	**5a**	**12a**	76	76:24 (major) 98:2 (minor)	3:1
3	**11a**	**13**	**±12a**	70	1:1	91:9
4	**11b**	**5a**	**12b**	82	94:6 (major)	>25:1
5	**11c**	**5a**	**12c**	98	93:7 (major) 96:4 (minor)	87:13

[a] Catalyst (0.05 mmol) was dissolved in boronate (1.25 mmol) and then added ketone (0.5 mmol) and submitted directly to the microwave. [b] Combined isolated yield. [c] Determined by chiral HPLC analysis. [d] Acetophenone was used in excess (0.55 mmol) with respect to boronate **11a** (0.5 mmol), and microwave time was extended to 5 h.

A mixture of enantiomers would, upon exchange with the chiral biphenol, form a set of diastereomers that would disproportionately react with the electrophile to give one diastereomer preferentially. Under the optimized conditions, (±)-methyl-allenylboronate **11a** afforded the *syn*-methylpropargyl product **12a** in 93% yield and in a 86:14 diasteromeric ratio (dr) (Table 4, entry 1). Preference for the *syn* diastereomer has been reported using aluminum reagents generated from 3-substituted propargylic bromides and $PbCl_2$ as a catalyst resulting in the formation of ±**12a** in 85% yield and 89:11 dr.[15]

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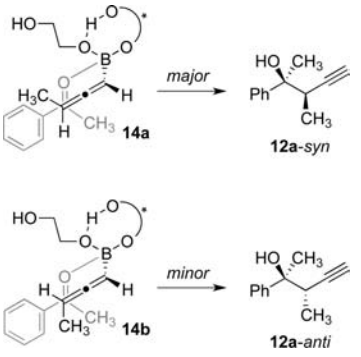

Figure 1. Methylpropargylation diastereoselectivity.

Preference for the *syn* diastereomer can be rationalized *via* a model with the methyl groups on acetophenone and boronate **11a** aligned antiperiplanar to each other (Figure 1) giving rise to the *syn* product.[15] Conversely, the alternative reacting diastereomer possesses a disfavored gauche interaction with both the methyl and phenyl groups of acetophenone. Both diastereomers were obtained in good enantioselectivities with major *syn* diastereomer 92:8 er and the minor *anti* diastereomer in 98:2 er. For comparison, the reaction using achiral biphenol **13** as the catalyst resulted in a greater preference for the formation of **12a**-*syn*, providing evidence that the catalyst structure influences the diastereomeric preference (Table 4, entry 3).

We reasoned that a greater degree of diastereoselectivity could be achieved using allenes possessing larger substituents at the γ-position.[15] This was indeed the case, as a significantly greater degree of selectivity was observed upon using the isopropyl-allenylboronate **11c** as a nucleophile, yielding **12c** as essentially one diastereomer in 94:6 er (Table 4, entry 4). Finally, phenyl-allenylboronate **11b** also afforded the addition product **12b** in good yields and selectivities (Table 4, entry 5).

In summary, we have developed a ketone propargylation reaction using allenylboronate reagents and biphenol catalysts, expanding the scope of enantioselective diol-catalyzed boronate reactions. The reaction is run in the absence of solvent, and the use of microwave irradiation enhances the reaction yields without loss of selectivity. The catalytic reaction conditions are also effective at promoting the diastereoselective addition of chiral racemic allenyl boronates to ketones. Continued investigations will seek to expand the type of reaction partners promoted by this mode of catalysis.

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Supporting Information Available. Synthetic procedures, chiral HPLC analysis, together with characterization and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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