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Chiral Boronate Derivatives via Catalytic Enantioselective Conjugate Addition of Grignard Reagents on 3-Boronyl Unsaturated Esters and Thioesters

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The growing importance of boronic acids and their derivatives as synthetic intermediates[1] has recently spurred the development of new methods to prepare chiral organoboronate derivatives in optically pure form.[2] These intermediates may be employed in cross-coupling chemistry or can be used as precursors for alcohols and amines following a B−C bond oxidation. In this regard, the boronate group may be viewed as a surrogate for oxygen-containing nucleophiles in conjugate addition reactions. Oxy-Michael reactions are notoriously difficult,[3] thus borylative conjugate additions[4] as recently demonstrated by the groups of Yun,[5] Fernandéz,[6] Hoveyda,[7] Shibasaki,[8] and Nishiyama[9] provide an attractive alternative. Herein, we present a complementary conceptual approach where the boronate group is preinstalled on a universal α,β-unsaturated ester substrate and used in a catalytic asymmetric conjugate addition with unstabilized carbanions (Figure 1). This versatile approach avoids the preparation of a different 3-substituted enoate for each new alkylboronate product.

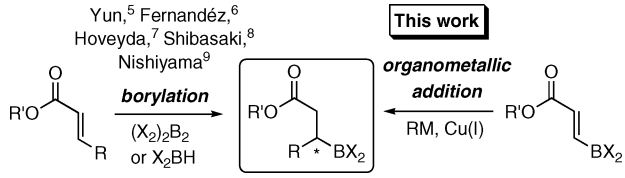
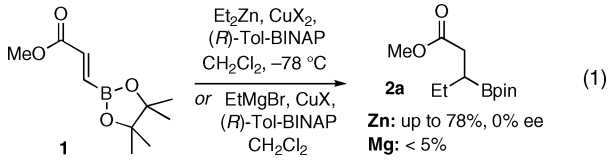


Figure 1. Possible conjugate addition approaches to chiral boronates.

To the best of our knowledge, there are no examples of catalytic conjugate addition on β-borylated α,β-unsaturated carbonyl compounds.[10] We anticipated that the chemical compatibility of the boronate substituent could be a major challenge in these reactions. Possible undesired pathways include nucleophilic attack onto the boronate substituent (giving a borinic ester) and insertion into the B−C bond leading to deboronative processes. The first round of optimization examined traditional organometallic agents such as organozinc and organomagnesium reagents under copper catalysis.[11] Because pinacol boronates are known to tolerate many reaction conditions, substrate **1**[12] was attempted first. Under all conditions, however, only a low yield of desired product **2a** was observed with Grignard reagents under Cu(I) catalysis (eq 1). Although the use of a dialkyl zinc reagent led to a good yield of **2a**, it was obtained in a racemic form.



(1)

Because we suspected that in these reactions the pinB−C bond may be susceptible to a competing insertion with the transition metal catalysts, leading to side reactions, we considered adducts that were recently shown to suppress the normal reactivity of boronic acids (Figure 2). Thus, we prepared[12] the *N*-methyldiaminoacetic acid (MIDA) adduct **3**,[13] the trifluoroborate salt **4**,[14] and the 1,8-diaminonaphthalene (dan) derivative **5**[15] and evaluated their use in the Cu(I)-catalyzed addition of EtMgBr using Loh's conditions for β-alkyl α,β-unsaturated esters with Tol-BINAP as the chiral ligand.[16] Substrate **3** was found to be insoluble in most reaction solvents, and borate salt **4** gave incomplete conversion to a complex mixture. The dan adduct **5**, however, gave very promising results at −40 °C in dichloromethane, with a 60% yield of product **6a** in 72% ee (Table 1, entry 1).

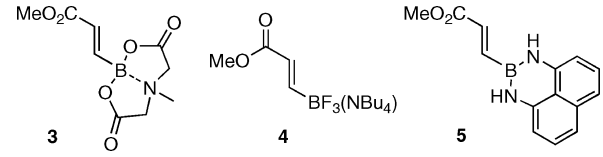
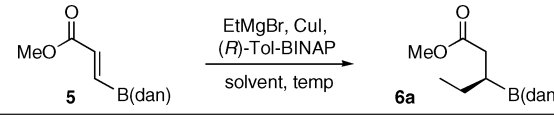


Figure 2. Boronate derivatives attempted in catalytic conjugate additions.

Table 1. Optimization of Reactions Parameters between **5** and EtMgBr[a]



entry	solvent	temp (°C)	equiv of EtMgBr	yield %[b]	ee (%)[c]
1	CH_2Cl_2	−40	5.0	60	72
2	2-MeTHF	−78	5.0	<5	nd
3	Et_2O	−78	5.0	62	93
4	Et_2O	−78	1.2	64	97
5	*t*-BuOMe	−78	1.2	<5	nd
6	Et_2O	−78	2.5	75	97
7	CH_2Cl_2	−78	2.5	92	95.5

[a] Reaction conditions: to a solution of the ligand and CuI at room temperature was added 0.5 mmol of **5** at 0.0625 M (8 mL of solvent). The solution was then cooled at the indicated temperature, and the Grignard reagent was added dropwise. See Supporting Information (SI) for detailed procedures. [b] Isolated yields. [c] Measured by chiral HPLC. Configuration assigned by comparison of optical rotation with the known, corresponding alcohol following the sequence of eq 2 (see SI for details).

For practical reasons, we favored a modification of the literature procedure[16] where the Grignard reagent is added last. Further optimization of this reaction focused on the reagent stoichiometry and the solvent, which led to the conditions of entry 7 (2.5 equiv of EtMgBr in dichloromethane at −78 °C) that strike an optimal compromise of product yield and ee. The examination of a small number of other popular chiral biphosphines confirmed that Tol-BINAP was the most suitable one. Likewise, CuI was the most effective source of copper.

A study of scope for the Grignard reagent is summarized in Table 2. With the exception of methyl, unbranched aliphatic reagents

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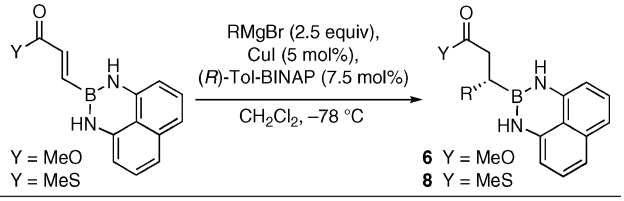
provided high yields of product **6** with ee's over 95% (entries 1−7) and slightly lower selectivities for branched ones (entries 8−9). It is known that thioester derivatives are more reactive and can provide improvements of yields and selectivities with less reactive organomagnesium reagents.[17] In the event, the methyl thioester derivative **7** led to a substantial improvement of both yields and enantioselectivity with MeMgBr and PhMgBr (entries 11−12). Except for hindered ones (entry 14), aromatic Grignard reagents fared very well (entries 13−17). These excellent results are in stark contrast with the use of nonboronated unsaturated esters, which are notoriously unsuccessful with aromatic Grignard reagents.[18] A hindered alkenyl reagent produced **8h** unselectively (entry 18).

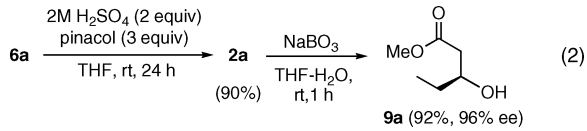
Table 2. Study of Scope for the Grignard Reagent[a]



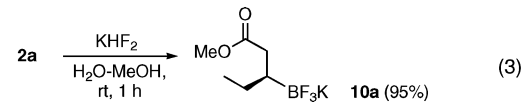
entry	substr.	R	time (h)	product	yield %[b]	ee (%)[c]
1	**5**	CH_3CH_2	0.5	**6a**	92	95
2	**5**	CH_3	0.5	**6b**	<10	nd
3	**5**	$CH_3(CH_2)_3$	0.5	**6c**	94	95
4	**5**	$CH_3(CH_2)_4$	0.5	**6d**	81	95
5	**5**	$CH_2{=}CH(CH_2)_2$	0.5	**6e**	87	98
6	**5**	$CH_2{=}CH(CH_2)_3$	0.5	**6f**	88	96
7	**5**	$Ph(CH_2)_3$	0.5	**6g**	88	98.5
8	**5**	$(CH_3)_2CH$	0.5	**6h**	89	91
9	**5**	*c*-C_6H_{11}	0.5	**6i**	81	91
10	**5**	Ph	2.0	**6j**	31	89
11	**7**	CH_3	0.5	**8a**	82	98
12	**7**	Ph	0.5	**8b**	80	91
13	**7**	*p*-MeC_6H_4	1.0	**8c**	62	82
14	**7**	*o*-MeC_6H_4	12	**8d**	46	0
15	**7**	*p*-F-C_6H_4	12	**8e**	80	95
16	**7**	*p*-Cl-C_6H_4	12	**8f**	65	91
17	**7**	*p*-CF_3-C_6H_4	12	**8g**	50	92.5
18	**7**	$CH_2{=}C(Me)$	0.5	**8h**	54	0

[a] Reaction conditions: see footnote a in Table 1 and SI for detailed procedures. [b] Isolated yields. [c] Measured by chiral HPLC (see SI for details).

The potential utility of chiral boronate derivatives **6** and **8** relies on the ability to transform the 1,8-diaminonaphthalene unit into other useful adducts. Using **6a** as a model substrate, we optimized the hydrolysis to the corresponding boronic acid followed by in situ formation of pinacolate ester **2a** (eq 2).



(2)



(3)

The latter was mildly oxidized in high yield into the corresponding alcohol **9a**. This approach to chiral secondary β-hydroxy esters is complementary to asymmetric acetate aldol and Reformatsky methodologies, which tend to be less effective on aliphatic substrates.[19] Pinacolate **2a** was also transformed into the potassium trifluoroborate salt **10a** (eq 3), which belongs to a class of boronate surrogates with great utility in cross-coupling chemistry.[14]

In conclusion, we have developed an efficient catalytic enantioselective conjugate addition methodology for the preparation of chiral alkylboronate derivatives in high yields and up to 98% ee. This method extends the realm of chemical reactions compatible with useful boron-containing substrates. Applications and extensions of this chemistry are underway in our laboratory.

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Supporting Information Available: Full experimentals and NMR spectral reproductions for substrates and new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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