DOI: 10.1002/chem.201002361

Conjugate Boration of β,β-Disubstituted Unsaturated Esters: Asymmetric Synthesis of Functionalized Chiral Tertiary Organoboronic Esters

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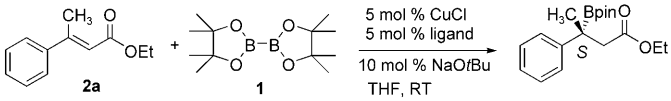
Catalytic conjugate addition of a boron nucleophile (M-B) to unsaturated carbonyl substrates[1] has emerged as a novel synthetic tool to afford β-boryl carbonyl compounds,[2] an important class of organoboron compounds. While several important and efficient methodologies for conjugate boration have been developed,[3] the asymmetric conjugate boration of β,β-disubstituted α,β-unsaturated esters is especially challenging because of the low reactivity and poor enantioselectivity exhibited by these substrates. The lower reactivity of β,β-disubstituted α,β-unsaturated esters, compared to enones[1b,j] and β-monosubstituted substrates, is due to the inherently lower electrophilicity and greater steric bulkiness at the reaction site. As is often practiced with catalysts to address this type of challenge, the development of a more efficient catalytic system to enhance reactivity and enantioselectivity is required. In this communication, we describe a highly efficient catalytic system for the asymmetric conjugate boration of β,β-disubstituted α,β-unsaturated esters that produces tertiary organoboron compounds with a quaternary boron-substituted carbon center[4] and ester functional group. We also report the successful application of these organoboranes as carbon nucleophiles in a rhodium-catalyzed addition reaction.

Recently, Shibasaki and co-workers reported an efficient copper-catalyzed asymmetric conjugate boration of β-substituted cyclic enones in DMSO solvent.[5] However, in light of a major difficulty, the keto⇄enol isomerization of β-borylated C-bound Cu ester enolate intermediates in copper-catalyzed borations, compared with enones,[6] we predicted and observed that β,β-disubstituted α,β-unsaturated esters would not be efficiently converted to products under the same conditions ($CuPF_6(CH_3CN)_4$, LiO*t*Bu, (*R*,*R*)-QuinoxP, DMSO, RT).[7] Inclusion of proton accelerators[1c] seemed necessary to promote the conversion of the enolate intermediate to borylated product. Since we have observed greatly enhanced catalytic activity of copper-mediated nucleophiles through coordination with select ligands,[1c,8] we started our investigation of the conjugate boration of β,β-disubstituted α,β-unsaturated esters with diboron (**1**) by screening ligands and proton sources. For the initial screening, we chose (*E*)-ethyl-3-phenylbut-2-enoate (**2a**) as a model substrate (Table 1).

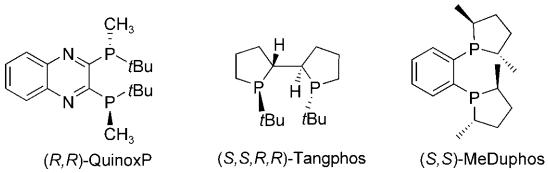
A large difference in catalytic activity was observed depending on the chiral ligand employed. Josiphos and BINAP led to very poor conversions, while chiral phosphine ligands with a short tether between the two phosphines showed comparable reaction conversions (entries 3–5). The optimal ligand was determined to be MeDuphos, which resulted in complete conversion to the product with excellent

Table 1. Optimization conditions.[a]



Entry	Ligand	Additive (2 equiv)	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*R*,*S*)-Josiphos	MeOH	15	0	–
2	(*S*)-BINAP	MeOH	24	5	–
3	(*R*,*R*)-QuinoxP	MeOH	24	83	93 (*R*)
4	(*S*,*S*,*R*,*R*)-Tangphos	MeOH	24	91	60 (*R*)
5	(*S*,*S*)-MeDuphos	MeOH	20	100[d]	93 (*S*)
6	(*S*,*S*)-MeDuphos	–	24	8	–
7	(*S*,*S*)-MeDuphos	PhOH	20	14	92 (*S*)
8	(*S*,*S*)-MeDuphos	AcOH	20	10	–

[a] RT = 17–18 °C. [b] Determined by GC analysis with an internal standard. [c] Determined by chiral HPLC analysis. [d] Isolated yield = 91 %.



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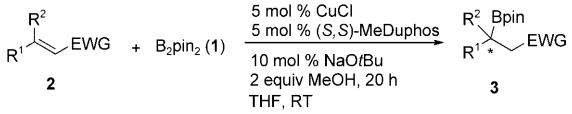
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002361.

enantioselectivity (entry 5). However, reactions without methanol or with other proton sources, such as phenol or acetic acid proceeded in low conversion, even in the presence of the Duphos ligand (entries 6–8). The optimized conditions were determined to be a combination of CuCl/NaO*t*Bu[9] and MeDuphos in the presence of MeOH as an additive.

Various β,β-disubstituted α,β-unsaturated substrates were then investigated via optimized catalytic conditions (Table 2). In general, β-aryl-β-alkyl-substituted unsaturated esters (**2b**, **2e**–**g**) afforded borylated products with high enantioselectivity. The electronic nature of substituents on the aryl group did not affect the yield nor enantioselectivity (entries 4–5). However, when the conjugated EWG group is a bulkier *tert*-butyl ester or nitrile group, lower enantioselectivities were observed for the borylated products (entries 2–3). β-Ethyl-substituted cinnamate required a slightly higher reaction temperature for completion, and 5–9% of the protodeboronated byproduct was formed (entry 6). β,β-Dialkyl-substituted esters gave good to modest asymmetric inductions (entries 7–9). In the case of primary alkyl and methyl-substituted cases (**2i** and **2j**), the smaller steric difference between the substituents at the β-position is reflected, giving lower *ee* values, compared to β-aryl-β-alkyl-substituted substrates. In addition, the heteroaromatic thiophene-substituted substrate **2k** was smoothly borylated, with a high level of enantioselectivity at a slightly elevated reaction temperature (entry 10).

Table 2. Asymmetric conjugate boration of β,β-disubstituted α,β-unsaturated esters.

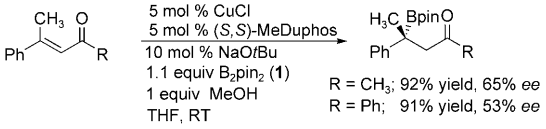


2 3

Entry	Substrate (**2**)	Yield [%][a]	*ee* [%][b]
1	**2b**: R^1 = Ph, R^2 = CH_3, EWG = C(O)OMe	91	94 (*S*)
2	**2c**: R^1 = Ph, R^2 = CH_3, EWG = C(O)O*t*Bu	85[c]	88 (*S*)
3	**2d**: R^1 = Ph, R^2 = CH_3, EWG = CN	90	84 (*S*)
4	**2e**: R^1 = *p*-$MeOC_6H_4$, R^2 = CH_3, EWG = C(O)OEt	97	94
5	**2f**: R^1 = *p*-FC_6H_4, R^2 = CH_3, EWG = C(O)OEt	95	94
6[d,e]	**2g**: R^1 = Ph, R^2 = CH_2CH_3, EWG = C(O)OEt	85	91 (*S*)
7[f]	**2h**: R^1 = cyclohexyl, R^2 = CH_3, EWG = C(O)OEt	88	92
8	**2i**: R^1 = $PhCH_2$, R^2 = CH_3, EWG = C(O)OEt	90	84
9	**2j**: R^1 = $PhOCH_2$, R^2 = CH_3, EWG = C(O)OEt	95	69
10[d]	**2k**: R^1 = 2-thienyl, R^2 = CH_3, EWG = C(O)OEt	91	92

[a] Yield of the isolated product. [b] Determined by Chiral HPLC analysis. [c] 91% conversion. [d] 15 mol% NaO*t*Bu was used and the reaction temperature was 30°C. [e] 5–9% of protodeboronated product was obtained. [f] 15 mol% NaO*t*Bu was used. 96% conversion.

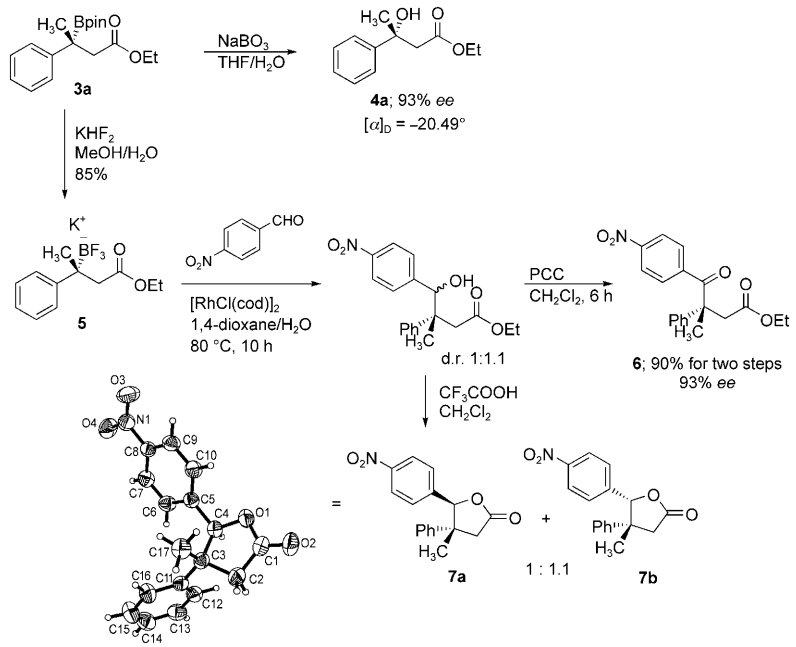
Next, the conjugate boration of acyclic β,β-disubstituted α,β-unsaturated ketones were briefly investigated using the same catalytic conditions (Scheme 1). The borylated products, however, were formed with moderate levels of enantiomeric excess. These results and the data (entries 1–3) in Table 2 indicate that the current copper–Duphos ligand catalytic system is more sensitive to the size and nature of the electron-withdrawing group than our previous conditions[3a,b] for β-monosubstituted unsaturated compounds.



Scheme 1. Asymmetric conjugate boration of β,β-disubstituted α,β-unsaturated ketones.

Organoboron derivatives are important synthetic intermediates in organic synthesis, due to their versatility in various transformations and low toxicity.[10] Along with alkenyl boron derivatives, the use of alkyl boron derivatives as sp^3-hybridized carbon nucleophiles has recently increased,[11] and notable examples of stereoretentive coupling reactions of chiral alkyl boron derivatives have recently been reported by Crudden[12] and Aggarwal.[13] In this regard, the feasibility of using our chiral tertiary organoboron product **3a** as a carbon nucleophile possessing an ester functionality was tested for the first time in a rhodium-catalyzed addition reaction under Aggarwal's conditions (Scheme 2). The boronic ester **3a** was successfully converted to the corresponding trifluoroborate salt **5** with 85% yield.[14] The reaction of **5** with *p*-nitrobenzaldehyde with a rhodium catalyst gave the addition products (d.r. 1:1.1),[15] which were then oxidized to the corresponding ketone. The keto-ester product **6** was obtained in 90% yield over the two steps and was measured to be 93% *ee* by chiral HPLC analysis, proving the addition occurred with complete transfer of chirality. Notably, the fragile stereogenic center of the new organoboronic compound was preserved without erosion of chirality, and the all-carbon quaternary center was made successfully without interruption of β-hydride elimination or protodeboronation using this protocol.

In conclusion, we have developed a catalytic enantioselective conjugate boration system for β,β-disubstituted α,β-unsaturated esters to afford chiral tertiary organoboronic esters. The utility of the organoboron reagents prepared by this protocol as carbon nucleophiles was demonstrated by a rhodium-catalyzed coupling reaction with aldehydes to produce all carbon quaternary centers.



Scheme 2. Synthesis of a chiral tertiary potassium trifluoroborate salt and its use in the Rh-catalyzed addition to aldehyde.

Experimental Section

General procedure: A mixture of CuCl (0.025 mmol, 2.5 mg), NaO*t*Bu (0.05 mmol, 5.0 mg), and (*S*,*S*)-MeDuphos (0.025 mmol, 7.7 mg) in anhydrous THF (0.4 mL) was stirred for 30 min in a Schlenk tube under an atmosphere of nitrogen. Bis(pinacolato)diboron (0.55 mmol, 140.0 mg) was added to the reaction mixture and stirred for 10 min at room temperature. Starting material (0.5 mmol) including tetradecane (0.25 mmol) as an internal standard was added, followed by MeOH (1 mmol, 40 μL). The reaction tube was washed with another THF (0.3 mL), sealed, and the reaction was monitored by TLC and GC. The reaction mixture was filtered through a pad of Celite and concentrated. The product was purified by flash silica gel chromatography.

Acknowledgements

This work was supported by the Mid-career Researcher Program through a National Research Foundation (NRF) grant funded by the Ministry of Education, Science and Technology, Republic of Korea (No. R01-2008-000-20332-0). We thank Professor S. Lee and Y.-M. Jung for X-ray analysis.

Keywords: asymmetric synthesis · boron · conjugate addition · enantioselectivity · quaternary stereocenters

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[15] Treatment of the addition products with CF_3COOH afforded the cyclized lactone products **7**. CCDC-784215 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: July 14, 2010
Published online: November 4, 2010

