ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 6701–6703

www.rsc.org/chemcomm

COMMUNICATION

Catalytic asymmetric conjugate boration of α,β-unsaturated sulfones†

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Received 6th April 2011, Accepted 26th April 2011
DOI: 10.1039/c1cc11949d

The α,β-unsaturated sulfones are suitable activated olefins in catalytic asymmetric conjugate β-boration. These substrates undergo smooth conjugate addition of bis(pinacolato)diboron [$B_2(pin)_2$] catalyzed by nonracemic Cu^I-diphosphine complexes to provide, upon subsequent oxidation, β-hydroxy sulfones in good yields and high enantiocontrol.

Organoboronic acids and their derivatives exhibit remarkable versatility due to their functional group tolerance and the ability of the boron atom to be readily converted into a wide variety of functionalities in a stereospecific manner and under mild reaction conditions.[1] Therefore, the development of novel protocols for the enantioselective construction of chiral organoboronates is of growing importance in asymmetric synthesis.[2] The asymmetric Cu^I-catalyzed boration of electron-deficient alkenes with $B_2(pin)_2$ *via* catalytic generation of chiral Cu–B species as "formal boryl nucleophiles" has recently emerged as a powerful synthetic tool to provide functionalized chiral boronates.[3–5] Stunning progress in this area has been achieved mainly through two approaches: γ-boration of allylic or propargylic carbonates[3] and β-boration of electron-deficient alkenes.[4] The pioneering racemic work on Cu-catalyzed conjugate addition of B_2pin_2 to α,β-enones, independently reported by Hosomi *et al.*[6] and Miyaura *et al.*,[7] spurred the development of the catalytic asymmetric variant of this reaction and its application to a variety of activated olefins including α,β-unsaturated cyclic[4h,j] and acyclic[4i,o,q] ketones, acyclic esters[4e–g,n–p] and lactones,[4j,k] amides[4l,m] and nitriles,[4d,e,n] as well as imines,[4r] to afford optically active β-boryl carbonyl derivatives and nitriles.[8] However, despite the great versatility of sulfones in organic synthesis,[9] α,β-unsaturated sulfones remain yet to be incorporated into the arsenal of activated olefins with general application in Cu-catalyzed asymmetric direct β-boration. We describe herein a novel procedure for such asymmetric transformation affording, upon oxidation, enantioenriched β-hydroxy sulfones[10] in good yields and high enantiocontrol.

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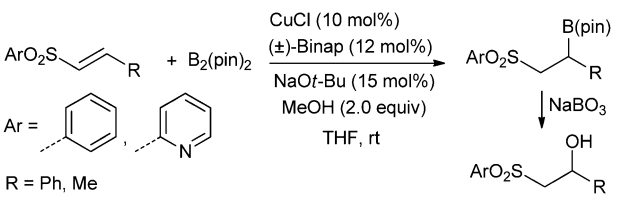
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds, copies of NMR spectra, and X-ray crystallography data. CCDC 818353. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11949d

The reactivity of α,β-unsaturated sulfones was first investigated by running model reactions of a small set of representative aryl 1-alkenyl sulfones. To test the influence of the nature of the arylsulfonyl group and the aromatic/aliphatic nature of the substituent at the β-position, substrates **1a–b** and **2a–b** were subjected to the reaction with $B_2(pin)_2$ (1.1 equiv.) following typical conditions reported using (±)-Binap as the diphosphine ligand: CuCl/(±)-Binap (10 mol%), NaO*t*-Bu (15 mol%), MeOH (2 equiv.) in THF at room temperature (Table 1). The isolation of the resulting β-boryl sulfone intermediate was not successful because of its instability during chromatography. Therefore, it was quantitatively transformed into the corresponding β-hydroxy sulfone by oxidation with $NaBO_3$ of the crude reaction mixture.

In accordance with previous findings,[4a–c] the very low conversion observed in the absence of MeOH confirmed its important role for catalytic turnover in this reaction (entry 1). However, even in the presence of this additive the reactivity of **1a** was very low to be practical (57% conversion after 72 h, entry 2), showing the reluctance of vinyl sulfones to undergo conjugate boration compared to other activated olefins.

Table 1 Reactivity of α,β-unsaturated sulfones in the Cu-catalyzed conjugate boration



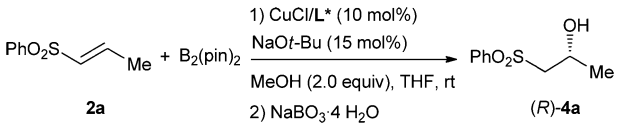
Entry[a]	Ar	R (substrate)	Method[b]	*T*/h	Product	Yield[c] (%)
1[d]	Ph	Ph (**1a**)	A	72	**3a**	28
2	Ph	Ph (**1a**)	A	72	**3a**	57
3	Ph	Ph (**1a**)	B	2	**3a**	82
4	Ph	Me (**2a**)	A	0.75	**4a**	52
5	Ph	Me (**2a**)	B	0.75	**4a**	100 (85)
6	2-Py	Ph (**1b**)	B	2	**3b**	33
7	2-Py	Me (**2b**)	B	0.75	**4b**	100 (87)

[a] Conditions: substrate **1** or **2** (0.2 mmol), B_2pin_2 (0.22 mmol, 1.1 equiv.), CuCl (10 mol%), (±)-Binap (12 mol%), NaO*t*-Bu (15 mol%), MeOH (2 equiv.), THF (0.4 mL), rt. [b] Method A: copper salt, ligand and base were aged for 30 min before addition of B_2pin_2 and then, after 10 min, addition of substrate and MeOH; Method B: MeOH was added dropwise to a solution of copper salt, ligand, base, substrate and B_2pin_2 in THF at rt. [c] Conversion yield. In parentheses, isolated yield after chromatography. [d] Reaction performed in the absence of MeOH.

A survey of reaction conditions led us to find that a change in the mode of addition of the reagents produced a dramatic increase of reactivity (Method B, entry 3). Thus, 82% conversion after just 2 h was observed when MeOH was directly added to the solution containing all the species (copper salt, base, ligand, substrate, and diborane) in THF at room temperature (Method B), rather than the typical reported procedure consisting of aging the copper source, the base and the ligand for 30 min before the addition of the $B_2(pin)_2$ and then, after further stirring for 10 min, the addition of the olefin and the MeOH (Method A). This enhancement of reactivity when using the mode of addition B was also observed in the case of the methyl-substituted sulfone **2a** (compare entries 4 and 5). Interestingly, this substrate **2a** showed higher reactivity than the phenyl-substituted substrate **1a** (complete conversion after 45 min at room temperature, entry 5). Heteroarylsulfones such as **1b** and **2b**, both bearing a (2-pyridyl)sulfonyl group, were also suitable substrates, providing comparable reactivity in the case of the β-methyl-substituted substrate **2b** (entry 7).[11] However, the lower reactivity associated to aromatic substituents at the β-position of the α,β-unsaturated sulfone moiety observed in the couple **1a**/**2a** was even more pronounced in the case of the substrate **1b** (R = Ph, 33% conversion after 2 h, entry 6).[11]

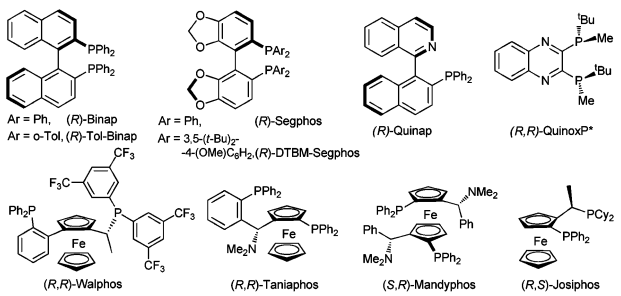
With the optimized conditions for the racemic reaction in hand, a broad survey of chiral phosphines was undertaken to realize an enantioselective variant of the conjugate boration of the model substrate **2a** (Table 2). The nature of the ligand

Table 2 Enantioselective Cu^I-catalyzed β-boration of vinyl sulfone **2a**



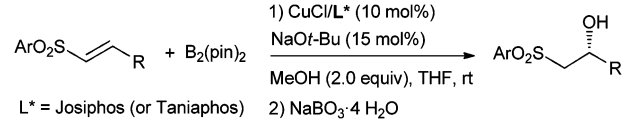
2a (*R*)-**4a**

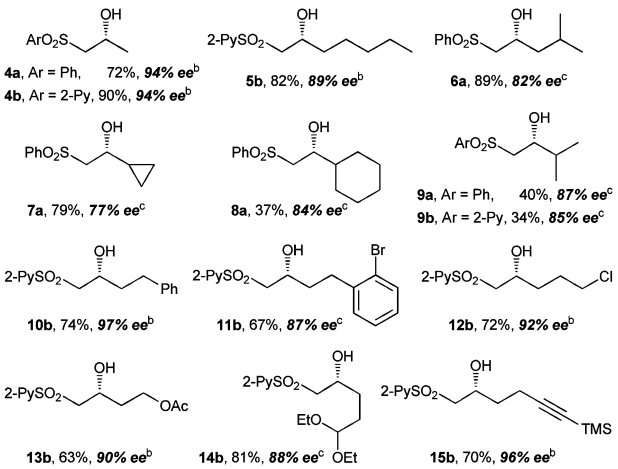
Entry	Ligand[a] (L*)	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
1	Binap	100	85	60
2	Tol-Binap	90	—	53
3	Segphos	100	80	60
4	DTBM-Segphos	100	82	86
5	Quinox	100	—	33
6	Quinap	89	—	40
7	Mandyphos	100	—	1
8	Walphos	76	—	40
9	Josiphos	100 (100)[e]	90 (81)[e]	91 (91)[e]
10	Taniaphos	100 (90)[e]	72 (62)[e]	94 (94)[e]



[a] See ESI† for the complete ligand screening (16 ligands tested). [b] Determined by ^1H NMR on the crude reaction mixture. [c] In pure product after chromatography. [d] Determined by HPLC on a chiral stationary phase. [e] In parentheses, values for the reaction performed with 5 mol% of catalyst loading (CuCl/L*) and 7.5 mol% of NaO*t*-Bu.

Table 3 Catalytic enantioselective conjugate boration of β-alkyl-substituted α,β-unsaturated sulfones[a]

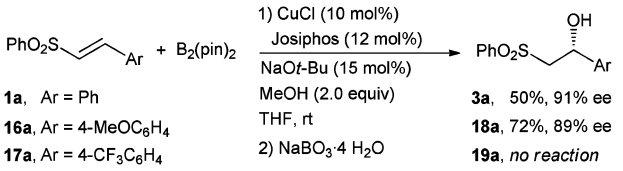




[a] Conditions: sulfone (0.2 mmol), B_2pin_2 (0.22 mmol, 1.1 equiv.), CuCl (10 mol%), Taniaphos or Josiphos (12 mol%), NaO*t*-Bu (15 mol%), MeOH (2 equiv.), THF (0.4 mL), rt. [b] Using Taniaphos as the chiral ligand. [c] Using Josiphos as the chiral ligand.

slightly influenced the reactivity (90–100% conversion in most cases), compared with the deep impact observed in enantiocontrol. The ferrocene-based (*R*,*R*)-Josiphos and (*R*,*S*)-Taniaphos provided the alcohol (*R*)-**4a**[12] with excellent values of asymmetric induction (>90% ee, entries 9 and 10), and were chosen as optimal chiral ligands. Catalyst loading and the amount of base were reduced to 5 mol% and 7.5 mol%, respectively, without affecting enantioselectivity, although the chemical yield was slightly lower (entries 9 and 10).

We next investigated the substrate scope under the optimized conditions. As shown in Table 3, the reaction tolerates a series of β-alkyl substituents, which furnished the corresponding β-hydroxy sulfones of (*R*)-configuration[12] generally in good yields and enantiocontrol. Substrates with linear alkyl chain substituents displayed high reactivity and enantioselectivity (products **4a–b** and **5b**, 89–94% ee), regardless of the nature of the sulfonyl group. Side chains branched at the β-position were also well tolerated (product **6a**), while branching at the α-position (*e.g.*, cyclohexyl or *i*-Pr) had a strong detrimental impact on the reactivity (products **8a**, **9a** and **9b**, 34–40% yield), yet maintaining a good asymmetric induction (84–87% ee). On the other hand, the less sterically encumbered cyclopropyl group did not affect the reactivity (product **7a**, 79% yield), albeit it produced slightly lower enantioselectivity (77% ee). Substrates containing several functional groups such as bromoaryl (product **11b**), chloride (**12b**), acetoxy (**13b**), acetal (**14b**) and alkynes (**15b**) also behaved very well in this transformation (87–97% ee), highlighting the wide functional tolerance of this method, as well as opening attractive possibilities for further functionalization.



Scheme 1 Catalytic asymmetric β-boration of β-aryl-substituted α,β-unsaturated sulfones.

Despite β-aryl-substituted α,β-unsaturated sulfones showing poorer reactivity in the model β-boration reaction of **1a**, and especially **1b**, with the catalyst system CuCl/(±)-Binap, we briefly explored the reactivity of this type of substrates under the enantioselective version conditions (Scheme 1). The negative influence of aromatic substituents at the β-position on the reactivity was confirmed in the reaction of **1a** with the Cu^{I}/Josiphos (10 mol%) catalyst system. The product (*R*)-**3a** was isolated in moderate yield (50%) due to incomplete conversion (70%), but with high asymmetric induction (91% ee). Noteworthily, electron-rich aromatic substituents at the β-position tend to give higher yields, while maintaining the high enantiocontrol, as exemplified by the substrate **16a** bearing a 4-methoxyphenyl group (product **18a**, 72% yield, 89% ee). In contrast, electron-poor aromatic substituents such as a 4-trifluoromethylphenyl group (substrate **17a**) seem to make the substrate inert in this reaction (product **19a**, not detected).

In conclusion, this work provides the first methodology for the asymmetric β-boration of α,β-unsaturated sulfones *via* conjugate addition of bis(pinacolato)diboron catalyzed by Cu^{I}/Josiphos complexes. Upon *in situ* oxidation of the boronate, the corresponding β-hydroxy sulfones are produced in good yields and high enantioselectivities (typically in the range 85–95% ee). Broad structural scope and wide functional group tolerance have been demonstrated, especially with β-alkyl-substituted substrates. Novel applications and extension of this chemistry are currently underway in our laboratory.

We thank the *Ministerio de Ciencia e Innovación* (*MICINN*, CTQ2009-07791) and the *Consejería de Educación de la Comunidad de Madrid* (programme AVANCAT, S2009/PPQ-1634) for financial support. A.L.M. thanks the *UAM* for a predoctoral fellowship. We thank Solvias AG (Dr H.-U. Blaser and Dr B. Pugin, Solvias ligand-kit) and Takasago (Dr T. Touge, Segphos and DTBM-Segphos) for generous loans of chiral ligands.

Notes and references

1 For recent general reviews, see: (*a*) *Contemporary Boron Chemistry*, ed. M. Davidson, A. K. Hughes, T. B. Marder and K. Wade, RSC, Cambridge, 2000; (*b*) C. M. Crudden, B. W. Glasspoole and C. J. Lata, *Chem. Commun.*, 2009, 6704.

2 For examples on recent applications of chiral boronates: (*a*) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024; (*b*) S. Nave, R. P. Sonawane, T. G. Elford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2010, **132**, 17096; (*c*) S. M. Winbush and W. R. Roush, *Org. Lett.*, 2010, **12**, 4344; (*d*) J. Chang, H. Lee and D. G. Hall, *J. Am. Chem. Soc.*, 2010, **132**, 5544.

3 Recent examples: (*a*) H. Ito, T. Okura, K. Matsuura and M. Sawamura, *Angew. Chem., Int. Ed.*, 2010, **49**, 560; (*b*) H. Ito, S. Kunii and M. Sawamura, *Nat. Chem.*, 2010, **2**, 972; (*c*) J. K. Park, H. H. Lackey, B. A. Ondrusek and D. T. McQuade, *J. Am. Chem. Soc.*, 2011, **133**, 2410.

4 For reviews, see: (*a*) J. A. Schiffner, K. Müther and M. Oestreich, *Angew. Chem., Int. Ed.*, 2010, **49**, 1194; (*b*) A. Bonet, C. Sole, H. Gulyas and E. Fernández, *Curr. Org. Chem.*, 2010, **14**, 2531; (*c*) L. Mantini and C. Mazet, *ChemCatChem*, 2010, **2**, 501. For catalytic asymmetric conjugate borations, see: ; (*d*) S. Mun, J.-E. Lee and J. Yun, *Org. Lett.*, 2006, **8**, 4887; (*e*) J.-E. Lee and J. Yun, *Angew. Chem., Int. Ed.*, 2008, **47**, 145; (*f*) W. J. Fleming, H. Müller-Bunz, V. Lillo, E. Fernández and P. J. Guiry, *Org. Biomol. Chem.*, 2009, **7**, 2520; (*g*) V. Lillo, A. Prieto, A. Bonet, M. M. Díaz-Requejo, J. Ramírez, P. J. Pérez and E. Fernández, *Organometallics*, 2009, **28**, 659; (*h*) I.-H. Chen, L. Yin, W. Itano, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 11664; (*i*) H.-S. Sim, X. Feng and J. Yun, *Chem.–Eur. J.*, 2009, **15**, 1939; (*j*) X. Feng and J. Yun, *Chem. Commun.*, 2009, 6577; (*k*) H. Chea, H.-S. Sim and J. Yun, *Adv. Synth. Catal.*, 2009, **351**, 855; (*l*) H. Kim and J. Yun, *Adv. Synth. Catal.*, 2010, **352**, 1881; (*m*) D. Hirsch-Weil, K. A. Abboud and S. Hong, *Chem. Commun.*, 2010, **46**, 7525; (*n*) X. Feng and J. Yun, *Chem.–Eur. J.*, 2010, **16**, 13609; (*o*) J. M. O'Brien, K.-s. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 10630; (*p*) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk and D. T. McQuade, *Org. Lett.*, 2010, **12**, 5008; (*q*) I.-H. Chen, M. Kanai and M. Shibasaki, *Org. Lett.*, 2010, **12**, 4098; (*r*) C. Sole, A. Whiting, H. Gulyas and E. Fernández, *Adv. Synth. Catal.*, 2011, **353**, 376.

5 For NHC-copper-catalyzed boron–copper addition to unactivated olefins and alkynes with B_2pin_2, see, respectively: (*a*) Y. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 3160; (*b*) Y. Lee, H. Jang and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 18234.

6 H. Ito, H. Yamanaka, J.-i. Tateiwa and A. Hosomi, *Tetrahedron Lett.*, 2000, **41**, 6821.

7 (*a*) K. Takahashi, T. Ishiyama and N. Miyaura, *Chem. Lett.*, 2000, 982; (*b*) K. Takahashi, T. Ishiyama and N. Miyaura, *J. Organomet. Chem.*, 2001, **625**, 47.

8 For the rhodium-catalyzed enantioselective β-boration of α,β-unsaturated carbonyl compounds, see: (*a*) T. Shiomi, T. Adachi, K. Toribatake, L. Zhou and H. Nishiyama, *Chem. Commun.*, 2009, 5987. For metal-free catalytic asymmetric β-borations, see: (*b*) A. Bonet, H. Gulyás and E. Fernández, *Angew. Chem., Int. Ed.*, 2010, **49**, 5130.

9 (*a*) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, 1993; (*b*) J. C. Carretero, R. Gómez Arrayás and J. Adrio, in *Sulfones in Asymmetric Catalysis*, ed. T. Toru and C. Bolm, Wiley-VCH, Weinheim, 2008, ch. 9, pp. 291–320.

10 Enantioenriched β-hydroxy sulfones are typically accessed by asymmetric reduction of β-ketosulfones. See for instance: (*a*) B. T. Cho and D. J. Kim, *Tetrahedron: Asymmetry*, 2001, **12**, 2043; (*b*) V. Gotor, F. Rebolledo and R. Liz, *Tetrahedron: Asymmetry*, 2001, **12**, 513; (*c*) G. Zhao, J.-B. Hu, Z.-S. Quian and W.-X. Yin, *Tetrahedron: Asymmetry*, 2002, **13**, 2095; (*d*) H.-L. Zhang, X.-L. Hou, L.-X. Dai and Z.-B. Luo, *Tetrahedron: Asymmetry*, 2007, **18**, 224.

11 A competitive experiment, in which an equimolar mixture of substrates **2a** and **2b** was subjected to the reaction with B_2pin_2 under the optimized conditions with the Cu–Josiphos catalyst system, revealed that the 2-pyridylsulfone **2b** displayed a slightly higher rate than the parent **2a** ($k_{2\text{-PySO}_2}/k_{\text{PhSO}_2}$ = 1.2). In contrast, the opposite tendency was observed when this experiment was performed with an equimolar mixture of the β-phenyl-substituted substrates **1a** and **1b** under identical conditions ($k_{2\text{-PySO}_2}/k_{\text{PhSO}_2}$ = 0.4). These values are in concordance with the results shown in Table 1.

12 The absolute configuration of the β-hydroxy phenyl sulfones was determined by comparison of the $[\alpha]_D$ values with those of known compounds. The same absolute stereochemistry of the 2-pyridyl sulfones was confirmed by X-ray crystallographic analysis of a recrystallized 97% ee sample of compound (*R*)-**10b**. See ESI† for details. CCDC 818353 contains the supplementary crystallographic data for this paper.