

Ni and Pd mediate asymmetric organoboron synthesis with ester functionality at the β -position†

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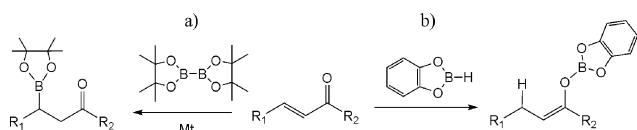
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Catalytic systems based on Ni and Pd complexes modified with chiral P-P ligands can be used in a convenient strategy for enantioselectively adding a boron unit to the β -position of α,β -unsaturated esters.

Introduction

The metal-mediated 1,4-addition reaction of diboron reagents to α,β -unsaturated olefins is a new methodology for preparing β -boryl carbonyl compounds.¹ One boryl unit from the diboron reagent can be catalytically added by Cu,² Pt,³ Rh⁴ and Ni⁵ catalytic systems to the β -position of the substrate, affording the 1,4-hydroborated product after a hydrolytic workup (Scheme 1a). Interestingly, the hydroboration of these substrates does not afford the same product, but the boron enolate instead^{3a} (Scheme 1b). Advantageously, the β -boration originates a stereogenic center at the β -carbon, so induction of enantioselectivity can be achieved with the appropriate chiral catalyst. However, to the best of our knowledge, the successful enantioselective β -boration/oxidation of α,β -unsaturated esters and nitriles has been described in the literature only by Yun and co-workers^{2d,6a} using CuCl and the phosphines (R)-(S)-Josiphos or (R)-(S)-NMe₂-PPh₂-Mandyphos to afford e.e. values up 91%. The same authors have extended this study to α,β -unsaturated ketones and amides.^{6b,c}



Scheme 1

We have also found that complexes containing the (NHC)Cu core, (NHC = N-heterocyclic carbene ligand), catalysed the selective β -boration of α,β -unsaturated α -methyl substituted esters and aldehydes under mild conditions, and the use of chiral NHC ligands induced a certain degree of enantioselectivity in the final products, (*i.e.* up to 73% for isobutyl angelate).⁷

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Results and discussion

Taking advantage of the benefits that nickel and palladium complexes provide for the cross-coupling reaction with organoboron compounds,⁸ we decided to establish a general methodology for using these metals to catalyse the β -boration of α,β -unsaturated esters in an attempt to induce asymmetry on the organoboron product. To this end, we first investigated the potential of Ni(cod)₂ modified with chiral bidentate ligands (Fig. 1), in the β -boration of the model substrate ethyl-*trans*-crotonate (R₁ = Me, R₂ = OEt) with bis(pinacolato)diboron (B₂pin₂) as the boron source.⁹ Table 1 shows that when ligand (R)-(S)-Mandyphos, (R)-Ph-MeOBiphep and (R)-(S)-Josiphos modified the Ni(0) complex, the enantioselectivity was only moderate in the quantitative formation of the β -borylated ester (entries 1–3), while in the presence of the chiral ligand (R)-(R)-Walphos it was low (Table 1, entry 4). Enantioselectivity was also low with the P,N-ligand (R)-Quinap despite the successful asymmetric induction in the Rh-catalysed diboration of alkenes¹⁰ (Table 1, entry 5). However, the use of ligand (R)-(S)-Taniaphos provided very high enantioselectivity on the β -borylated ester with values up to 95% e.e., which was an improvement on those values observed by Yun *et al.* for the same substrate with the catalytic system CuCl/(R)-(S)-Josiphos (e.e. 90%).^{2d,6}

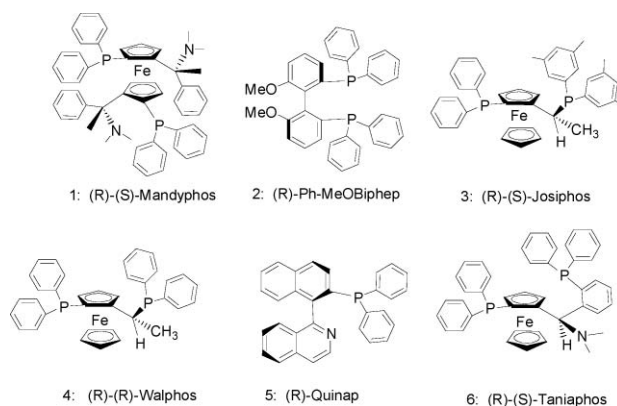


Fig. 1 P,P-ligands and P,N-ligands used in this work.

The presence of the base seemed to have a crucial influence on the catalytic activity of the catalyst, because when a lower amount of Cs₂CO₃ was used, the activity and enantioselectivity observed for the Ni(0)/Taniaphos catalytic system diminished

Table 1 Ni-catalyzed asymmetric 1,4-addition reaction of (B₂pin₂)^a

Entry	Substrate R ₂	L	Conversion (%) ^b	e.e. (%) ^c
1	OEt	1	<50	51
2	OEt	2	98 (83) ^d	63
3	OEt	3	83	65
4	OEt	4	95	10
5	OEt	5	99 (79) ^d	12
6	OEt	6	99 (78) ^d	95
7	OEt	6 ^e	91	90
8	OEt	6 ^f	87	85
9	OMe	6	99 (85) ^d	92 ^g
10	O <i>i</i> Bu	6	99 (81) ^d	98
11	O <i>i</i> Bu	3	97	90
12 ^h	O <i>i</i> Bu	3	91	96
13 ^h	OEt	3	99 (80) ^d	81
14 ^h	OMe	3	91	79

^a Standard conditions: Substrate/Ni(cod)₂ = 0.5/0.025, diphosphine (0.025 mmol), 1.5 eq. Cs₂CO₃, 1.5 eq. of bis(pinacolato)diborane (B₂pin₂), solvent: toluene (5 mL)/MeOH (0.25 mL), T:25 °C, 4 h. Conversions and selectivity values are an average of two reactions. ^b Determined by ¹H NMR. ^c Determined by G. C. on the acylated product. ^d Isolated yields. ^e 1 eq. Cs₂CO₃. ^f 0.5 eq. Cs₂CO₃. ^g Determined by HPLC on the alcohol derivative. ^h NiCl₂.

(Table 1 entries 7–8). The nature of the base is also influential because when NaOH, NaOAc or NaO*i*Bu was used instead of Cs₂CO₃, only a small conversion into the corresponding product was observed. The effect of the base as an activator of diboron has also been observed by Oshima *et al.*¹¹ and our group in the Pd- and Au-catalysed diboration reaction.¹²

With the aim of exploring the scope of the Ni(0)/Taniaphos catalytic system, we carried out a series of experiments with a range of α,β-unsaturated esters under the optimized reaction conditions. Changing the ester moiety from OMe to O*i*Bu, we found that the bulkiest *iso*-butyl-*trans*-crotonate ester was the most effective substrate, as far as the enantioselection induced by the metal center was concerned, with values up to 98% e.e. (Table 1, entries 9–10). These results contrast with the tendency observed by Yun *et al.*,^{24,6} for enantioselectivity to be independent of the nature of the ester moiety when CuCl/(R)-(S)-Josiphos was used as the catalytic system. The β-boration of *iso*-butyl-*trans*-crotonate with Ni(0)/(R)-(S)-Josiphos also provides a significant increase in enantioselectivity with e.e. values up to 90% (Table 1, entry 11). Interestingly, when the nickel source of the catalyst precursor was Ni(II) in NiCl₂/(R)-(S)-Josiphos, the activity and enantioselectivity were slightly better than obtained using Ni(cod)₂/(R)-(S)-Josiphos (Table 1, compare entries 3 and 11 with entries 12–13).

We then checked whether Pd(0) modified with the phosphine ligands could perform the β-boration reaction under identical reaction conditions to those used for Ni(0). We were very pleased to observe that catalyst precursor Pd₂(dba)₃ performed this reaction and became the first example of palladium-mediated β-boration of α,β-unsaturated carbonyl compounds. Table 2 shows how the β-boration of *iso*-butyl-*trans*-crotonate with Pd₂(dba)₃ modified with (R)-(S)-Mandyphos and (R)-Quinap remained unfinished after 4 h of reaction. Enantioselection was low (Table 2, entries 1–2). However, when the chiral ligands involved in the modification of Pd₂(dba)₃ were (R)-Ph-MeOBiphep and (R)-(R)-Walphos, the conversion of the reaction was higher and e.e. values rose to 56% and 75%, respectively (Table 2, entries 3–4). More satisfactory

Table 2 Pd-catalyzed asymmetric 1,4-addition reaction of (B₂pin₂)^a

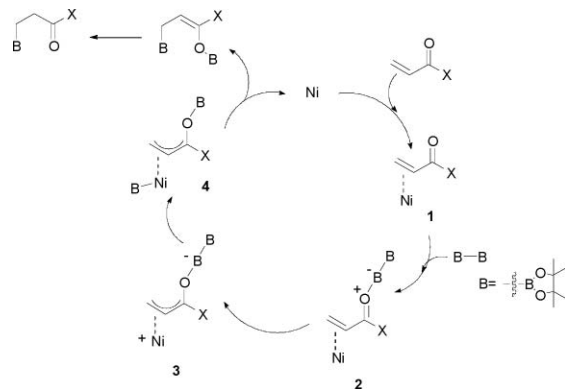
Entry	Substrate R ₂	L	Conversion (%) ^b	e.e. (%) ^c
1	O <i>i</i> Bu	1	29	24
2	O <i>i</i> Bu	5	41	8
3	O <i>i</i> Bu	2	93 (86) ^d	56
4	O <i>i</i> Bu	4	82	75
5	O <i>i</i> Bu	6	31	90
6	O <i>i</i> Bu	3	60	86
7	OEt	3	99 (81) ^d	91
8	OMe	3	99 (79) ^d	87
9 ^e	O <i>i</i> Bu	3	77	13
10 ^e	OEt	3	99	3
11 ^e	OMe	3	90	5

^a Standard conditions: Substrate/Pd₂(dba)₃ = 0.5/0.0125, diphosphine (0.025 mmol), 1.5 eq. Cs₂CO₃, 1.5 eq. of bis(pinacolato)diborane (B₂pin₂), solvent: toluene (5 mL)/MeOH (0.25 mL), T:25 °C, 4 h. Conversions and selectivity values are an average of two reactions. ^b Determined by ¹H NMR. ^c Determined by G. C. ^d Isolated yield. ^e Substrate/Pd(OAc)₂ = 0.5/0.025.

enantioselection was provided by Pd₂(dba)₃/(R)-(S)-Taniaphos (entry 5) and Pd₂(dba)₃/(R)-(S)-Josiphos (entry 6), which afforded enantioselectivity with values of up to 91% e.e., depending on the ester moiety of the substrate (Table 2, entries 6–8). Surprisingly, when Pd(II) was tested as the catalyst precursor in Pd(OAc)₂/(R)-(S)-Josiphos, the conversion was only comparable to that obtained with Pd(0), while the enantioselectivity diminished significantly (Table 2, entries 9–11). This fact could be related to the plausible partial oxidation of the ligands by Pd(OAc)₂.¹³

From a mechanistic point of view, we can assume that the catalytic cycle for Pd(0) is similar to that proposed by Oshima *et al.*,⁵ where Ni(0) species react with substrate α,β-unsaturated esters and amides to generate the η²-coordinated complex, followed by further reactivity with bis(pinacolato)diboron to favour the formation of η³-coordinated boryl-nickel(II) complexes. An eventual reductive elimination provides the boryl enolate product, which is susceptible to protonolysis and affords the β-boryl ester product.

One of the key steps in this proposal is the transformation of the η²-coordinated metal complex to the corresponding η³-complex on reaction with B₂pin₂, (Scheme 2). However, as Kurosawa *et al.*¹⁴ and Morken *et al.*¹⁵ have previously observed, the Lewis acidity of boron could promote this pathway in palladium and nickel-mediated reactions, respectively. We are still considering the role of Ni(II) and Pd(II) complexes as precursors of catalysts in the

**Scheme 2**

catalytic cycle, as they have proved to be as active and selective as Ni(0) and Pd(0).

Conclusions

Although nickel-catalysed reactions with diboron reagents are quite rare,¹⁶ we are pleased to have promoted not only the first Ni-mediated asymmetric boron addition reaction, but also the first described palladium β -boration of α,β -unsaturated esters, inducing asymmetry in the presence of chiral ligands. Further work on the tandem β -boration/cross-coupling reaction with Ni and Pd complexes is currently underway.

Acknowledgements

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Notes and references

- (a) T. B. Marder, *Organomet. Chem.*, 2008, **34**, 46; (b) L. Dang, Z. Lin and T. B. Marder, *Organometallics*, 2008, **27**, 4443.
- (a) H. Ito, H. Yamanaka, J. Tateiwa and A. Hosomi, *Tetrahedron Lett.*, 2000, **41**, 682; (b) K. Takahashi, T. Isiyama and N. Miyaoura, *Chem. Lett.*, 2000, 982; (c) K. Takahashi, T. Isiyama and N. Miyaoura, *J. Organomet. Chem.*, 2001, **625**, 47; (d) S. Mun, J.-E. Lee and J. Yun, *Org. Lett.*, 2006, **8**, 4887; (e) J.-E. Lee, J. Kwon and J. Yun, *Chem. Commun.*, 2008, 733.
- (a) Y. G. Lawson, M. J. G. Lesley, T. B. Marder, N. C. Norman and C. R. Rice, *Chem. Commun.*, 1997, 2051; (b) H. A. Ali, I. Goldberg and M. Srebnik, *Organometallics*, 2001, **20**, 3962; (c) N. J. Bell, A. J. Cox, N. R. Cameron, J. S. O. Evans, T. B. Marder, M. A. Duin, C. J. Elservier, X. Baucherel, A. A. D. Tilloch and R. P. Tooze, *Chem. Commun.*, 2004, 1854.
- G. W. Kabalka, B. C. Das and S. Das, *Tetrahedron Lett.*, 2002, **43**, 2323.
- K. Hirano, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2007, **9**, 5031.
- (a) J.-E. Lee and J. Yun, *Angew. Chem., Int. Ed.*, 2008, **47**, 145; (b) H.-S. Sim, X. Feng and J. Yun, *Chem.-Eur. J.*, 2009, **15**, 1939; (c) H. Chea, H.-S. Sim and J. Yun, *Adv. Synth. Catal.*, 2009, **351**, 855.
- V. Lillo, A. Prieto, A. Bonet, M. M. Díaz Requejo, J. Ramirez, P. J. Pérez and E. Fernández, *Organometallics*, 2009, **28**, 659–662.
- (a) V. V. Grushin and H. Alper, *Chem. Rev.*, 1994, **94**, 1047; (b) V. Percec, J.-Y. Bae and D. H. Hill, *J. Org. Chem.*, 1995, **60**, 1060; (c) S. Saito, M. Sakai and N. Miyaoura, *Tetrahedron Lett.*, 1996, **37**, 2993; (d) S. Saito, S. Oh.tani and N. Miyaoura, *J. Org. Chem.*, 1997, **62**, 8024; (e) A. F. Indolese, *Tetrahedron Lett.*, 1997, **38**, 3513.
- Typical β -boration procedure*: The precursor of the catalyst complex (0.025 mmol of metal) and diphosphine (0.025 mmol) were placed in a schlenck and dissolved with toluene (3 mL) under nitrogen. The suspension was stirred for 10 minutes and Cs_2CO_3 (244 mg, 0.75 mmol) was added. Afterwards, a solution of alkyl (*E*)-crotonate, (0.5 mmol of methyl (*E*)-crotonate, or ethyl (*E*) crotonate or *i*-butyl (*E*)-crotonate) and bis(pinacolato)diboron (191 mg, 0.75 mmol) in toluene (2 mL) was then added. Finally MeOH (0.25 mL) and water (14 mL, 0.75 mmol) were added, and the mixture was allowed to stir at room temperature for 4 h. The resulting mixture was poured into water (10 mL) and the product was extracted with hexane/ethyl acetate (20:1). The combined organic layer was dried over sodium sulfate, and concentrated *in vacuo*. Silica gel column purification (hexane: ethyl acetate = 40:1) gave the alkyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate in 80% for methyl derivative, 75% for ethyl derivative and 77% for *i*-butyl derivative.
- (a) J. B. Morgan, S. P. Miller and J. P. Morken, *J. Am. Chem. Soc.*, 2003, **125**, 8702; (b) S. Trudeau, J. B. Morgan, M. Shrestha and J. P. Morken, *J. Org. Chem.*, 2005, **70**, 9538; (c) J. Ramirez, A. M. Segarra and E. Fernández, *Tetrahedron: Asymmetry*, 2005, **16**, 1289; (d) J. Ramirez, V. Lillo, A. M. Segarra and E. Fernández, *C. R. Chimie*, 2007, **10**, 138.
- (a) K. Hirano, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2005, **7**, 4689; (b) K. Hirano, H. Yorimitsu and K. Oshima, *Adv. Synth. Catal.*, 2006, **348**, 1543; (c) K. Hirano, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2007, **9**, 1541.
- (a) V. Lillo, E. Mas-Marzá, A. M. Segarra, J. J. Carbó, C. Bo, E. Peris and E. Fernández, *Chem. Commun.*, 2007, 3380; (b) J. Ramirez, M. Sanaú and E. Fernández, *Angew. Chem., Int. Ed.*, 2008, **47**, 5194.
- W. J. Marshall and V. V. Grushin, *Organometallics*, 2003, **22**, 555.
- S. Ogoshi, T. Yoshida, T. Nishida, M. Morita and H. Kurosawa, *J. Am. Chem. Soc.*, 2001, **123**, 1944.
- J. D. Sieber, S. Liu and J. P. Morken, *J. Am. Chem. Soc.*, 2007, **129**, 2214.
- (a) I. Beletskaya and C. Moberg, *Chem. Rev.*, 1999, **99**, 3435; (b) C.-M. Yu, J. Youn, S.-K. Yoon and Y.-T. Hong, *Org. Lett.*, 2005, **7**, 4507.