Organocatalysis

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Metal-Free Catalytic Boration at the β-Position of α,β-Unsaturated Compounds: A Challenging Asymmetric Induction**

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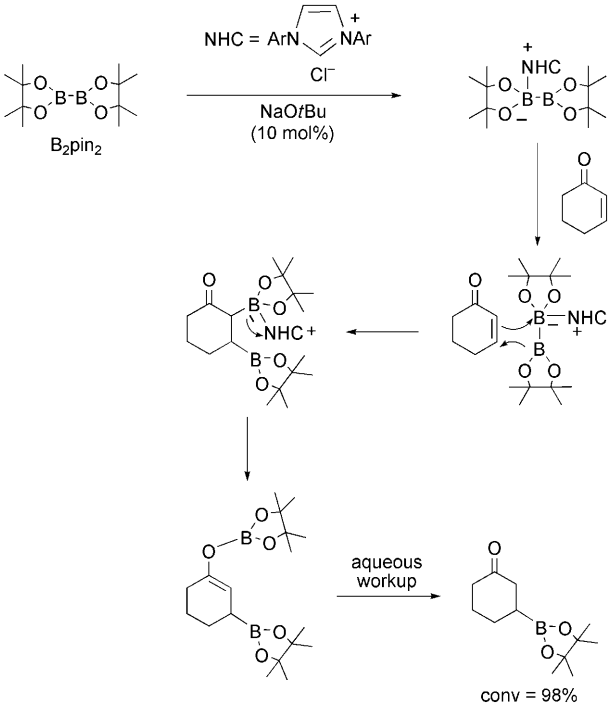
Dedicated in memory of László Gulyás.

Enantioenriched α-chiral boron compounds were first obtained using chiral rhodium–phosphine complexes from the catalytic hydroboration of prochiral alkenes.[1] There are three reasons why metal-mediated asymmetric induction in C–B bond formation is more successful than existing methods involving interactions between the substrate and a chiral borane reagent[2] in the absence of a metal: 1) the low cost/availability of the achiral borane reagent, 2) the milder reaction conditions, and, most importantly, 3) the possibility for optimization and maximization of the asymmetric induction by screening the chiral ligands. Considerable progress has since been made, particularly in relation to the enantioselective metal-mediated hydroboration,[3] diboration,[4] and β-boration[5] of electron-deficient olefins. However, one challenge still remains to be overcome: the development of a metal-free asymmetric boron-addition reaction with achiral boron reagents.

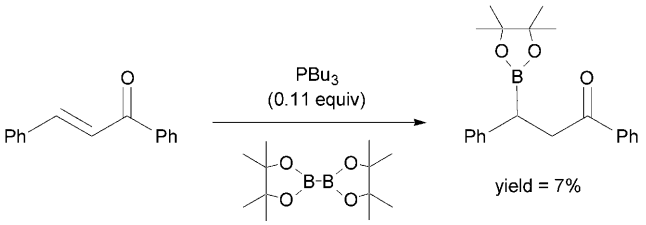
Our group has recently studied metal-mediated asymmetric conjugate borylation reactions in the presence of copper,[5c,d] palladium, [5g] nickel,[5h] and iron[5j] complexes that were modified with either chiral phosphine or carbene ligands. This field has recently been elegantly reviewed by Oestreich and co-workers,[6] and the authors conclude that asymmetric metal-free approaches to conjugate borylation might be the next pioneering step forwards. Hoveyda and co-workers recently reported an efficient metal-free β-boration of cyclic and acyclic α,β-unsaturated carbonyl groups promoted by N-heterocyclic carbenes (NHCs).[7] Mechanistic studies revealed that 10 mol% of carbene alone can activate the diboron reagent, bis(pinacolato)diboron (B_2pin_2), by nucleophilic attack at one of the boron atoms (Scheme 1).



Scheme 1. Mechanism reported by Hoveyda and co-workers for B_2pin_2 activation and conjugate addition to an enone, catalyzed by N-heterocyclc carbenes; see Ref. [7].

After 1,4-addition of the reagent to the substrate the carbene is regenerated, this making the reaction catalytic.

Attempts by Hoveyda and co-workers[7] to promote the β-boration of 2-cyclohexen-1-one with PPh_3 and PCy_3 as nucleophilic reagents in the absence of a metal were unsuccessful. However, an early example by Hosomi and co-workers [8] showed that PBu_3 could induce slight conversion of benzylideneacetophenone into the β-borated ketone in the absence of the catalyst precursor CuOTf (Scheme 2).



Scheme 2. PBu_3-promoted β-boration of benzylideneacetophenone, see Ref. [8].

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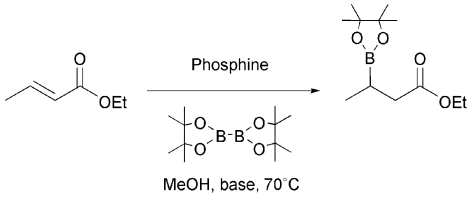
Herein, we describe a method for the synthesis of β-borated carbonyl compounds by reacting B_2pin_2 with either α,β-unsaturated esters or ketones in the presence of chiral phosphine catalysts. The reaction is metal free, and only requires tertiary phosphorus compounds, MeOH, and a base as additives.

We first optimized the reaction conditions using ethylcrotonate as a model substrate, B_2pin_2 as the boron source, and PPh_3 (the most common achiral phosphine) as the catalyst. The reactions were carried out in tetrahydrofuran at 70 °C. Moderate conversions values were observed in the presence of either 4 or 10 mol% phosphine, Cs_2CO_3, and using either MeOH or *i*PrOH as an additive (Table 1,

Table 1: Phosphine-mediated catalytic β-boration of ethylcrotonate with B_2pin_2.[a]



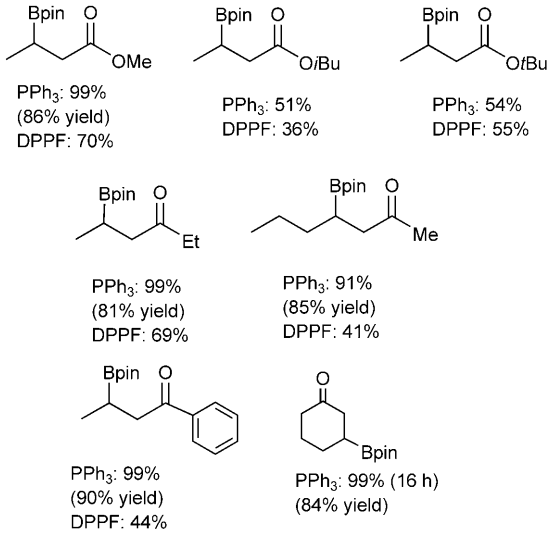
Entry	Phosphine (mol%)	Base	Additive	Conversion [%][b]
1	PPh_3 (4)	–	MeOH	0
2	PPh_3 (4)	Cs_2CO_3	–	12
3	PPh_3 (4)	Cs_2CO_3	MeOH	54
4	PPh_3 (10)	Cs_2CO_3	MeOH	63
5	PPh_3 (20)	Cs_2CO_3	MeOH	99
6	PPh_3 (4)	Cs_2CO_3	*i*PrOH	49
7	$O{=}PPh_3$ (4)	Cs_2CO_3	MeOH	21
8	DTBPMB (4)	Cs_2CO_3	MeOH	32
9	DPPF (4)	Cs_2CO_3	MeOH	39
10	DPPF (4)	NaO*t*Bu	MeOH	42
11	DPPF (4)	K_2CO_3	MeOH	27
12	DPPF (4)	CsF	MeOH	37

[a] Standard conditions: substrate (0.5 mmol), phosphine (4–20 mol%), base (15 mol%), MeOH (2.5 mmol), THF (2 mL), 70 °C, 6 h. [b] Conversion calculated using G.C. analysis and confirmed by ^{1}H NMR spectroscopy.

entries 1—4 and 6). Complete conversion was achieved by using 20% PPh_3 (Table 1, entry 5). The first two experiments also demonstrate that both the base and the alcohol are essential additives for this reaction.

Hoveyda and co-workers found that $O{=}PPh_3$ could also promote moderate β-boration of 2-cyclohexen-1-one, even in the absence of a base.[7] Under our reaction conditions, $O{=}PPh_3$ was much less active than PPh_3 (Table 1, entry 7 versus entry 3). Diphosphines **1** and **2** also catalyzed the β-boration of ethylcrotonate, but less efficiently than PPh_3. Whilst 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) only afforded 32% conversion (Table 1, entry 8), 1,1′-bis(diphenylphosphino)ferrocene (DPPF), a diphosphine containing a ferrocene backbone, resulted in a 39% conversion of the substrate (Table 1, entry 9). The nature of the base was also studied: NaO*t*Bu and CsF were found to be as effective as Cs_2CO_3 (Table 1, entries 10–12). The need for a base has also been observed in the metal-mediated β-boration of electron-deficient olefins with copper (NaO*t*Bu preferred), nickel, palladium, and iron (Cs_2CO_3 preferred), although its role is still a matter of discussion.[5e,9,10] It has been postulated that a base preactivates the transition-metal precursor to facilitate the transmetalation between the complex and the diboron reagent,[11] but the direct interaction of the base with the diboron reagents could facilitate the heterolytic cleavage, and thus the metal–boryl bond formation.[12]

The substrate scope was then investigated under optimized reaction conditions using PPh_3 and DPPF as catalysts (Scheme 3). Structure—activity relationships in the β-bora-

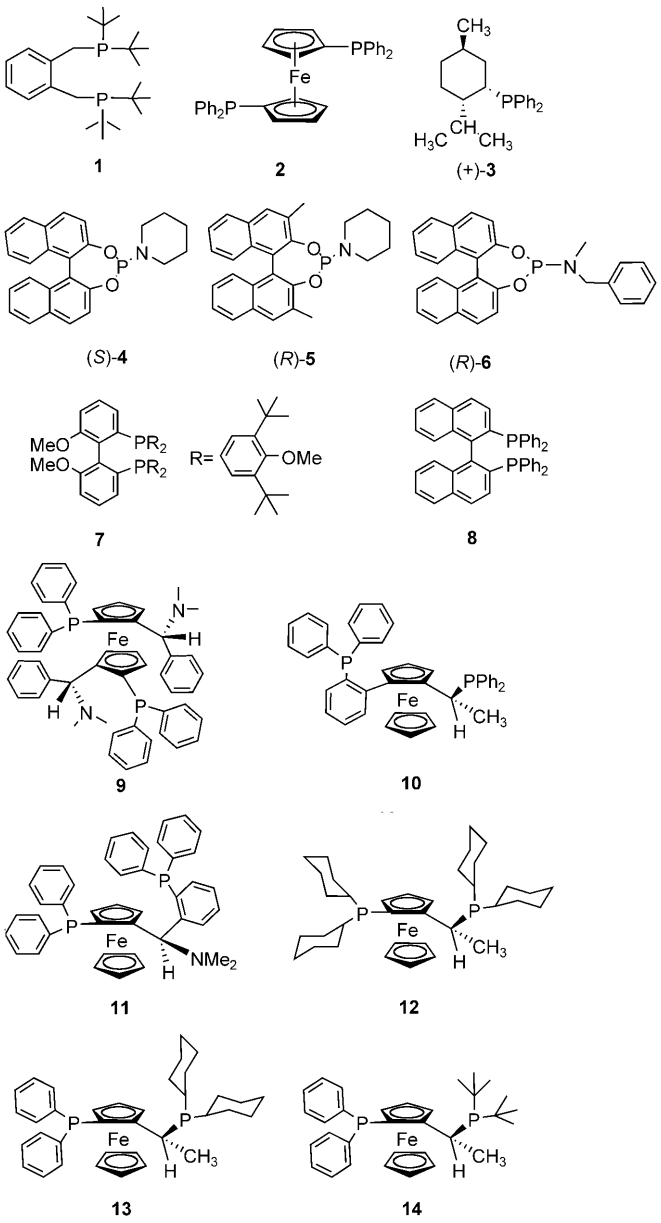


Scheme 3. Substrate scope for the phosphine-mediated β-boration reaction. Conditions: phosphine (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 mmol), THF, 70 °C, 6 h. Yield in parentheses is the yield of isolated product. DPPF = bis(diphenylphosphino)ferrocene.

tion of α,β-unsaturated esters showed a certain trend. Higher conversions were observed when the ester moieties were less sterically hindered. The α,β-unsaturated ketones were less sensitive to structural changes, and they were all readily converted into their corresponding organoboranes with PPh_3.

Having identified the appropriate conditions, we focused our efforts on obtaining asymmetric induction in the model reaction. Chiral monophosphorus compounds, as well as diphosphines, were explored as catalysts at a 4 mol% loading in the β-boration of ethylcrotonate (Scheme 4, Table 2). The fairly basic (+)-neomenthyldiphenylphosphine (**3**) provided good conversion, but no asymmetric induction (Table 2, entry 1). However, to our delight, chiral monodentate phosphoramidite ligands **4**, **5**, and **6** induced a certain degree of enantioselectivity (35% *ee* with **5**, Table 2 entry 3; 31% *ee* with **6**, entry 7), which was considerably higher than the enantioselectivities achieved with the copper(I)–phosphoramidite complexes reported by Yun and co-workers (< 7% *ee*).[5b]

When the reaction was carried out at room temperature, the enantioselectivity increased slightly, whilst the activity decreased (Table 2, entry 4). The influence of the base on the asymmetric induction was also studied. We observed that the



Scheme 4. Chiral and nonchiral phosphorous compounds used in this work.

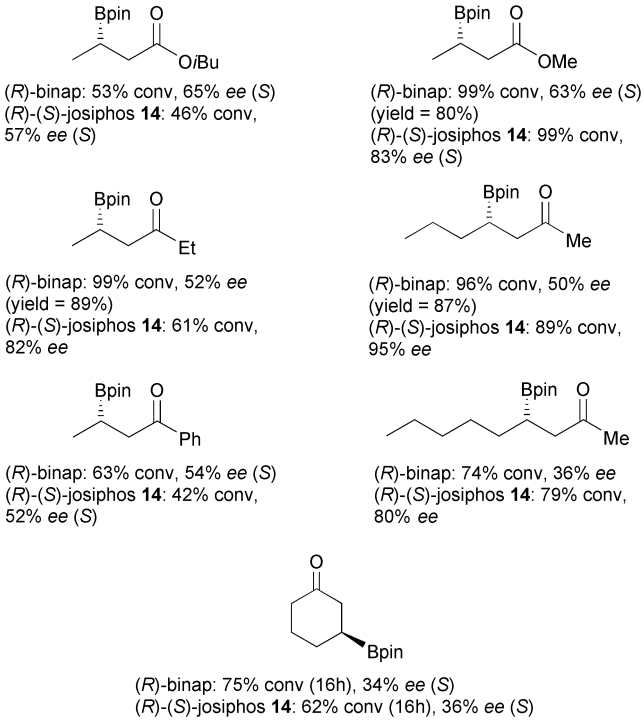
nature of the base was important for optimized asymmetric induction: Cs_2CO_3 was superior to both NaO*t*Bu and CsF (Table 2, entries 3, 5, and 6). Subsequently, bidentate ligands (*R*)-3,5-Bu-4-MeO-MeObiphep (**7**) and (*R*)-binap (**8**) were tested in the model reaction, (Table 2, entries 8 and 9). Whereas diphosphine **7** was a rather poor catalyst, (*R*)-binap provided complete conversion and 77% enantiomeric excess. Notably, (*R*)-binap was used as a modifying ligand in the iron-mediated β-boration of ethylcrotonate under similar reaction conditions, and negligible enantioselectivity was observed (Table 2, entry 10).[5i] Bearing in mind the success of diphosphines containing a ferrocene moiety in their backbone in metal-mediated β-boration reactions,[5] we focused our efforts on exploring chiral ferrocenyl diphosphines. When (*R*)-(*S*)-NMe_2-PPh_2-mandyphos (**9**), (*R*)-(*R*)-walphos-type ligand **10**, and (*R*)-(*S*)-taniaphos-type ligand **11** were used in the β-boration of ethylcrotonate (Table 2, entries 11–13), comparable activities were observed within 6 hours. However, only ligand **11** induced notable stereoselectivity (72% *ee*). Interestingly, (*R*)-(*S*)-josiphos-type ligands **12**, **13**, and **14** all provided much higher activities, but the asymmetric induction was very sensitive to the structure of the substituents of the phosphorus donor atoms (Table 2, entries 14–16). Under the applied conditions, diphosphine **14** was capable of inducing enantioselectivities as high as 88%. Performing the reaction at room temperature afforded a slight increase in the *ee* value (90%), but the activity decreased substantially (Table 2, entry 17). Interestingly, upon applying a smaller amount of base, the *ee* value increased to 93%. Notably, decreasing the amount of base decreased the catalytic activity; in this case, a reaction time of 24 hours was needed to reach a comparable conversion (Table 2, entry 18). Combining phosphine **14** with other bases resulted in less active catalytic systems, but in the case of CsF the stereoselectivity could be maintained (Table 2, entry 16 versus entries 19 and 20). Cu^{I} or Ni^{II} catalysts (4 mol%) that were modified with phosphine **14** only provided moderate asymmetric induction under the standard catalytic conditions (Table 2, entries 21 and 22). The markedly different catalytic performance of **8** and **14** in the presence or absence of transition metals indicates that the mechanisms of the transition-metal catalysis and the organocatalysis must be entirely different.

Table 2: Chiral-phosphine-mediated catalytic β-boration of ethylcrotonate with B_2pin_2.[a]

Entry	Phosphine	Base	Conversion [%][b]	*ee* [%][c]
1	**3**	Cs_2CO_3	74	<5
2	**4**	Cs_2CO_3	53	7(*R*)
3	**5**	Cs_2CO_3	54	35(*S*)
4	**5**[d]	Cs_2CO_3	34	41(*S*)
5	**5**	NaO*t*Bu	67	25(*S*)
6	**5**	CsF	30	8(*S*)
7	**6**	Cs_2CO_3	64	31(*S*)
8	**7**	Cs_2CO_3	32	3(*S*)
9	**8**	Cs_2CO_3	99	77(*S*)
10	$[Fe(acac)_2]$/**8**	Cs_2CO_3	63	<10
11	**9**	Cs_2CO_3	58	<5
12	**10**	Cs_2CO_3	54	23(*R*)
13	**11**	Cs_2CO_3	64	72(*S*)
14	**12**	Cs_2CO_3	89	25(*S*)
15	**13**	Cs_2CO_3	99	75(*S*)
16	**14**	Cs_2CO_3	94	88(*S*)
17	**14**[d]	Cs_2CO_3	17	90(*S*)
18	**14**[e]	Cs_2CO_3	77	93(*S*)
19	**14**	NaO*t*Bu	59	55(*S*)
20	**14**	CsF	72	89(*S*)
21	CuCl/**14**[f]	Cs_2CO_3	97	54(*S*)
22	$NiCl_2$/**14**[f]	Cs_2CO_3	78	58(*S*)

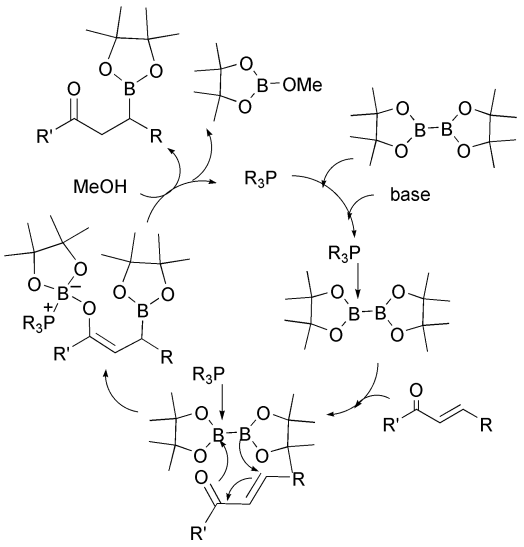
[a] Standard conditions: substrate (0.5 mmol), phosphine (4 mol%), base (15 mol%), MeOH (2.5 mmol), THF (2 mL), 70°C, 6 h. [b] Conversion was calculated by G.C. analysis and confirmed by ^{1}H NMR spectroscopy, (average of three reactions). [c] Enantiomeric excesses were calculated on the acetyl derivative by G.C. methods using a chiral β-cyclodextrin column. [d] 25°C. [e] Run with base (3 mol%) for 24 h. [f] Cu and Ni salt (4 mol%), phosphine (4 mol%). acac = acetylacetonate.

We selected the best-performing phosphines (**8** and **14**) to study the substrate scope in the asymmetric β-boration of α,β-unsaturated carbonyl compounds under the optimized reaction conditions (Scheme 5). The corresponding isobutyl ester was transformed into the β-organoborated product less efficiently than the model substrate, ethylcrotonate. Both the conversion and the stereoselectivity decreased, particularly when phosphine **14** was used. In contrast, the less-bulky methyl ester could be readily converted into the product. The enantioselectivities are comparable to the values we observed for the model substrate. The organocatalysts were also very active for the transformation of α,β-unsaturated ketones, acyclic and cyclic, and we were pleased to see that josiphos-type ligand **14** promoted the β-boration of 3-heptene-2-one with 95% enantioselectivity.



Scheme 5. Substrate scope for the phosphine-mediated asymmetric β-boration reaction. Conditions: phosphine (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 mmol), THF, 70°C, 6 h. Yield in parentheses is the yield of isolated product.

Mechanistic aspects of the metal-mediated conjugate borylation have been recently reviewed,[13] and Marder and co-workers[14] have highlighted the exceptionally strong σ-donor properties of boryl ligands when coordinated to a metal, and their related nucleophilic behavior. The absence of a metal does not seem to diminish the nucleophilicity of one of the boryl moieties when the diboron reagents interact with carbenes, as Hoveyda and co-workers[7] have recently suggested. We postulate a plausible mechanism involving heterolytic cleavage of the B–B bond in the diboron reagent, promoted by the direct interaction of the phosphine with the empty orbital of one of the boron atoms. Upon such interaction, the other boron moiety could act as a nucleophile towards the conjugated electron-deficient substrates (Scheme 6). Various ^{11}B- and $^{31}P\{^1H\}$ NMR spectroscopy experiments have been carried out to study the possible interactions between the reaction partners, and the observations are in accordance with the suggested mechanism. Direct interaction could not be confirmed for the model substrate and PMe_3 (a basic, strongly nucleophilic tertiary phosphine). Thus, a direct nucleophilic attack by the phosphine on the β-carbon atom of the substrate was excluded as a possible step in the catalytic cycle. However, in the presence of the base and MeOH, PMe_3 interacted with B_2pin_2 at 70°C. The $^{31}P\{^1H\}$ resonance of the free phosphine at $\delta = -61.9$ ppm partially shifted to $\delta = -10.5$ ppm, whilst the original ^{11}B signal of B_2pin_2 at $\delta = 31.6$ ppm was partially transformed into two new signals at $\delta = -9.2$ ppm and $\delta = 39.4$ ppm. These resonances could be assigned to the new sp^3–sp^2 hybridized boron centers. Even more interestingly, when ethylcrotonate was added to the mixture and heated at 50°C for 15 hours, the new signals in the ^{11}B NMR and ^{31}P NMR spectra completely disappeared, and a new signal, corresponding to the organoboron product, appeared at about $\delta = 34.9$ ppm in ^{11}B NMR spectrum. The high asymmetric induction observed can be explained by the proximity of the chiral phosphine–boryl intermediate to the substrate in the concerted 1,4-addition of nucleophilic boron atom.



Scheme 6. Plausible mechanism for the phosphine-catalyzed β-boration of α,β-unsaturated carbonyl compound.

In summary, we have found that asymmetric β-boration of α,β-unsaturated esters and ketones can be efficiently carried out by organocatalysis, with tertiary phosphorus compounds as chiral auxiliaries. These results represent the first examples of enantioselection in organoboron synthesis without the application of transition-metal catalysts or chiral boron reagents. The method is particularly advantageous if the borylation reaction needs to be scaled up. Deeper understanding of the mechanism of this novel organocatalytic reaction, and the extension of the approach to other boron addition reactions, are the next challenges to overcome.

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