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COMMUNICATION

Asymmetric synthesis of α-amino boronate esters *via* organocatalytic pinacolboryl addition to tosylaldimines†

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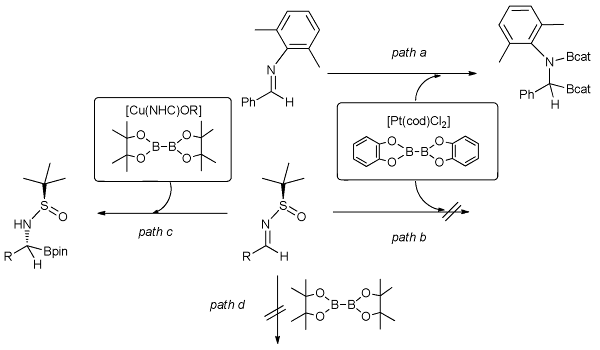
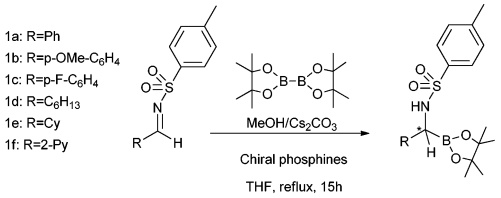
Organocatalytic nucleophilic pinacolboryl addition from *in situ* generated MeO$^-$ → B$_2$pin$_2$ to C═N double bond can be performed enantioselectively with the aid of chiral phosphines, which promote enantiofacial differentiation in the course of the C–B bond formation.

The catalytic addition of diboron reagents to C═N has been attempted using transition metal complexes as catalysts. The activation of bis(catecholato)diboron (B$_2$cat$_2$) by [Pt(cod)Cl$_2$] allowed the diboration of aldimines providing the first synthetic route towards rac-α-aminoboronate esters (Scheme 1, *path a*).[1] However, the same catalytic system was unable to mediate the diboration of *N*-*tert*-butanesulfinyl aldimines (Scheme 1, *path b*).[2] Recently, copper-alkoxide complexes modified with *N*-heterocyclic carbenes have efficiently been used to activate bis(pinacolato)diboron (B$_2$pin$_2$), and to form (NHC)CuBpin complexes, which catalyse the pinacolboryl addition to unsaturated molecules.[3,4] Ellman and co-workers[2] successfully promoted diastereoselective Bpin addition to *N*-*tert*-butanesulfinyl aldimines with the catalytic system (ICy)CuO*t*Bu (ICy = 1,3-dicyclohexylimidazol-2-ylidene) (Scheme 1, *path c*). However, it was also reported that in the absence of transition metal complexes, the *N*-*tert*-butanesulfinyl aldimines could not be transformed into the desired *N*-sulfinyl α-amino pinacolboronate esters (Scheme 1, *path d*).[2]



Scheme 1



Scheme 2

In our ongoing research, we focus on the enantioselective introduction of boryl moieties into unsaturated substrates. Recently, we have found that the methoxide anion activates B$_2$pin$_2$ to promote a nucleophilic boron addition to both activated[5,6] and non-activated olefins.[7] We have also observed that the use of chiral phosphines has been essential to induce asymmetry in the organocatalytic β-boration of α,β-unsaturated carbonyl compounds.[5] Based on the experience we have accumulated in the asymmetric organocatalytic boron addition reactions, we describe here a synthetic route towards α-aminoboronate esters *via* metal-free nucleophilic boryl addition to tosylaldimines. We planned to use the *in situ* formed MeO$^-$ → bis(pinacolato)diboron adduct, and to induce asymmetry with catalytic amounts of chiral phosphines (Scheme 2).

We used *N*-benzylidene-benzenesulfonamide (**1a**) as a model substrate, and we activated B$_2$pin$_2$ with an excess of MeOH and catalytic amount of base to guarantee the *in situ* formation of the MeO$^-$ → B$_2$pin$_2$ adduct.[5–7] Within 15 h, at reflux temperature, 70% of the substrate was transformed into the corresponding α-amino boronate ester (Table 1, entry 1).

The addition of phosphine (PPh$_3$) resulted in higher conversion (up to 91%), but only when base and methanol were also present in the medium, otherwise no activity was observed (Table 1, entries 2–4). The obvious beneficial effect of PPh$_3$ prompted us to complement our catalytic system with the phosphine. To further optimise the methodology, a number of bases and protic additives were screened. We found that MOMe (M = Li, Na, K) could be reasonable alternatives to Cs$_2$CO$_3$ (Table 1, entries 5–10). The nature of the alcohol as additive could be considered to have a more direct influence on the reaction outcome as it is assumed that the alcohol generates the alkoxide ion which interacts with the B$_2$pin$_2$. We examined alcohol additives of different pK_a values and steric properties but none of them could outperform the originally chosen MeOH (Table 1, entries 11–13). It is important

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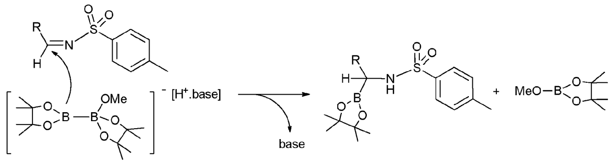
† Dedicated to Prof. Carmen Claver on her 60th birthday.

Table 1 Organocatalytic pinacolboryl addition from B_2pin_2 to *N*-benzylidene-benzenesulfonamide[a]

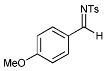
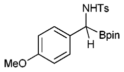
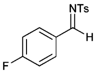
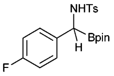
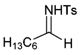
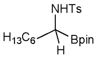
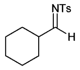
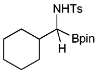
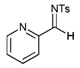
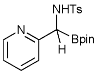
Entry	Base	Phosphine	Additive	Conv[b] (%)
1	Cs_2CO_3	—	MeOH	70
2	Cs_2CO_3	PPh_3	MeOH	91 (78)[c]
3	Cs_2CO_3	PPh_3	—	—
4	—	PPh_3	MeOH	—
5	K_2CO_3	PPh_3	MeOH	83
6	KOH	PPh_3	MeOH	58
7	KOMe	PPh_3	MeOH	88
8	LiOMe	PPh_3	MeOH	89
9	NaOMe	PPh_3	MeOH	88
10	NaOtBu	PPh_3	MeOH	85
11	Cs_2CO_3	PPh_3	PhOH	89
12	Cs_2CO_3	PPh_3	iPrOH	83
13	Cs_2CO_3	PPh_3	BuOH	78

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), phosphine (4 mol%), base (15 mol%), MeOH (2.5 eq.), THF (1 mL), 70 °C, 15 h. [b] Conversion calculated using ^{1}H NMR spectroscopy. [c] Isolated yield from 1 mmol of substrate.



Scheme 3

Table 2 Organocatalytic pinacolboryl addition from B_2pin_2 to tosylaldimines[a]

Entry	Substrate	Product	Time/h	Conv[b] (%)	Yield[c] (%)
1			6/15	80/84	62
2			6/15	95/99	79
3			6/15	99/99	82
4			6/15	31/40	20
5			6/15	61/90	68

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), PPh_3 (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL), 70 °C. [b] Conversion calculated using ^{1}H NMR spectroscopy. [c] Isolated yield from 1 mmol of substrate.

to note at this point that when the (*E*)-*N*-benzylidene-1-phenylmethanamine was used as substrate in the organocatalytic boron addition reaction, the nucleophilic attack of the pinacolboryl, from the $MeO^- \rightarrow B_2pin_2$ adduct, did not take place. The fact that the pinacolboryl addition to the tosylaldimines was efficient might indicate a beneficial electronic influence of the tosyl substituent on N (Scheme 3).

With this hypothesis in mind, we performed organocatalytic pinacolboryl addition to a series of tosylaldimines (**1b–d**), achieving high to quantitative conversions into the corresponding α-amino boronate esters, even within 6 h of reaction time (Table 2). Interestingly, the presence of electron withdrawing substituents on the aryl groups or lack of conjugation in the case of aliphatic tosylaldimines clearly facilitated the nucleophilic addition.

In search of asymmetric induction in the C–B bond formation, we conducted a preliminary study with 2 mol% of the chiral diphosphine Walphos (*R*)-(*R*)W001 (CF_3) (**2**), which allowed the transformation of **1a** into the α-amino boronate ester with 94% of ee at rt (Fig. 1, bar 5). The enantioselectivity slightly decreased at higher temperatures but the activity significantly increased (Fig. 1, bars 3–5). We should also highlight that, under identical reaction conditions, the metal free approach was more enantioselective than the analogous Cu(I)/**2** catalysed reaction (2 mol% loading) which provided only 66% of ee at rt (Fig. 1, bars 1–2). Interestingly, it has been reported that when Cu(I)/**2** mediated the asymmetric boration of α,β-unsaturated β-methyl sulfones, the conversion and ee values were only moderate (76% and 40%, respectively) despite the fact that 10 mol% of copper salt/chiral ligand and 15 mol% of base were required.[8]

To identify alternative chiral catalysts we screened a small library of phosphines and phosphoramidites. Therefore, the enantioselective nucleophilic attack of Bpin from $MeO^- \rightarrow B_2pin_2$ adduct to *N*-benzylidene-benzenesulfonamide (**1a**) could be

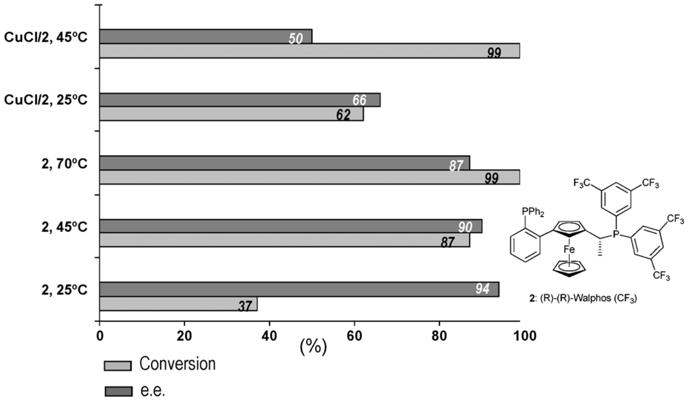
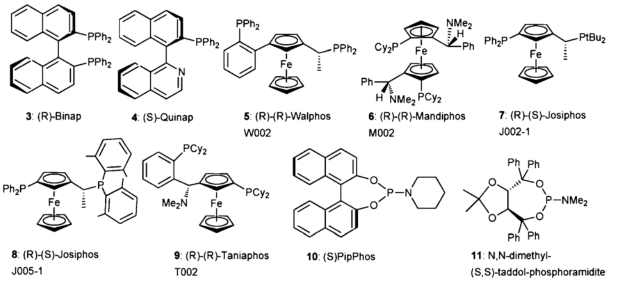


Fig. 1 Enantioselective organocatalytic pinacolboryl addition from B_2pin_2, to **1a** with **2** *versus* the Cu(I)/**2** catalytic reaction. Substrate (0.25 mmol), B_2pin_2 (1.2 eq.), **2** (2 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL), CuCl (2 mol% when required).

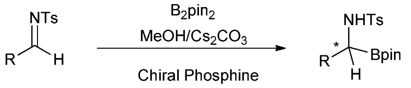
Table 3 Enantioselective organocatalytic pinacolboryl addition to *N*-benzylidene-benzenesulfonamide (**1a**)[a]


3: (R)-Binap; **4**: (S)-Quinap; **5**: (R)-(R)-Walphos W002; **6**: (R)-(R)-Mandiphos M002; **7**: (R)-(S)-Josiphos J002-1; **8**: (R)-(S)-Josiphos J005-1; **9**: (R)-(R)-Taniaphos T002; **10**: (S)PipPhos; **11**: N,N-dimethyl-(S,S)-taddol-phosphoramidite

Entry	$T/°C$	Aux. (mol%)	t/h	Conv[b] (%)	ee[c] (%)
1	45	**3** (2)	15	88	67 (+)
2	45	**4** (2)	15	99	41 (+)
3	45	**5** (2)	15	63	72 (+)
4	45	**6** (2)	15	19	85 (+)
5	45	**7** (2)	15	35	60 (+)
6	45	**8** (2)	15	23	70 (+)
7	45	**9** (2)	15	33	86 (+)
8	45	**10** (2)	15	40	90 (+)
9	45	**11** (2)	15	55	79 (+)
10	25	**2** (4)	24	56	99 (+)
11	25	**3** (4)	24	80	65 (+)
12	25	**4** (4)	24	45	99 (+)
13	25	**6** (4)	24	47	80 (+)

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), chiral phosphine (2 or 4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), THF (1 mL). [b] Conversion calculated using ^1H NMR spectroscopy. [c] ee determined by HPLC-TOF.

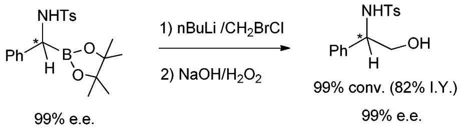
Table 4 Enantioselective organocatalytic pinacolboryl addition to tosylaldimines[a]



Entry	R	Chiral phosphine	Conv[b] (%)	ee[c] (%)
1	p-OMe–C_6H_4	**2**	83	75
2	p-OMe–C_6H_4	**4**	74	55
3	p-CF_3–C_6H_4	**2**	95	71
4	p-CF_3–C_6H_4	**4**	90	52
5	C_6H_{13}	**2**	97	24
6	C_6H_{13}	**4**	99	14

[a] Standard conditions: substrate (0.25 mmol), B_2pin_2 (1.2 eq.), chiral phosphine (4 mol%), Cs_2CO_3 (15 mol%), MeOH (2.5 mmol), THF (1 mL), 45 °C, 15 h. [b] Conversion calculated using ^1H NMR spectroscopy. [c] ee determined by HPLC–TOF.

performed in the presence of 2 mol% of (*R*)-Binap, and (*S*)-Quinap (Table 3, entries 1 and 2), but particularly successful was the use of chiral ferrocenyl type diphosphines and phosphoramidite ligands **10** and **11**(Table 3, entries 3–9). In order to find a compromise between the activity and the enantioselectivity of the organocatalytic system, we performed the reactions at room temperature with 4 mol% loading of chiral phosphines and 24 h of reaction time. Moderate conversions were observed but a significant increase in enantioselectivity up to 99% was achieved when Walphos (*R*)-(*R*)W001 (CF_3) (**2**) and (*S*)-Quinap (**4**) were involved (Table 3, entries 10–13).



Scheme 4

The scope of the enantioselective organocatalytic reaction was established with the related tosylaldimines **1b–d**, using **2** and **4** as chiral phosphines (Table 4). At 45 °C, the aliphatic tosylaldimine was transformed into the corresponding α-amino boronate ester with lower enantioselectivity.

It is well known that chiral α-amino boronate esters have a tremendous scope of applications in pharmacology,[9] and here we have described a new methodology for the direct asymmetric synthesis of this type of interesting organoboranes. But we have also envisaged a simple one-pot transformation from the tosylaldimines towards chiral 1,2-amino alcohols by using the enantioselective organocatalytic boryl addition to C=N followed by homologation/oxidation. In this reaction sequence, the treatment of the α-amino boronate ester intermediate (achieved in 99% ee, Table 3, entry 12) with CH_2BrCl/nBuLi and $NaOH/H_2O_2$[10] allowed the formation of the corresponding 1,2-amino alcohol with 99% ee indicating that the optical purity was completely preserved during the derivatisation process (Scheme 4). This new synthetic procedure opens a new strategic avenue towards the asymmetric synthesis of the very versatile 1,2-amino alcohols[11] and complements the current metal- and organocatalysed synthetic strategies.[12]

Based on this preliminary study, we claim that the *in situ* generated $MeO^- \rightarrow$ bis(pinacolato)diboron adduct combined with chiral phosphines, at 2–4 mol% loading, allows the asymmetric synthesis of α-amino boronate esters *via* enantioselective nucleophilic boron addition to tosylaldimines (ee up to 99%). The homologation/oxidation work up of the chiral α-amino boronate esters provides a direct access to chiral 1,2-amino alcohols.

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