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Novel transformation of α,β-unsaturated aldehydes and ketones into γ-amino alcohols or 1,3-oxazines *via* a 4 or 5 step, one-pot sequence†

Adam D. J. Calow,[a] Andrei S. Batsanov,[a] Elena Fernández,*[b] Cristina Solé[b] and Andrew Whiting*[a]

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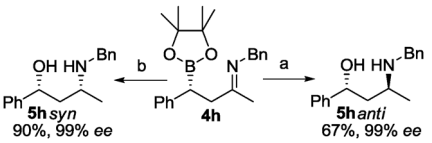
An efficient, 4-step, one-pot, highly stereoselective route to γ-amino alcohols has been developed *via* an *in situ* α,β-unsaturated imine formation, β-boration, reduction (C═N) and oxidation (C–B) sequence and especially for certain water-soluble γ-amino alcohols, a further step can be added to directly access the corresponding 1,3-oxazine derivatives.

β-boration of activated olefins has received considerable attention,[1,2] involving a Michael-like addition of a diboron reagent to a conjugated, electron deficient alkene (*e.g.* **1** or **2**), to give β-borylation (*e.g.* **4** from imine **2**). Asymmetric β-boration, coupled with known methods for C–B functionalisation, is an attractive concept for the control of stereochemistry. Herien, we report an efficient 4-step, one-pot route to γ-amino alcohols **5** *via* an *in situ* α,β-unsaturated imine formation, β-boration, reduction (C═N) and oxidation (C–B) sequence which can be extended to give the corresponding oxazines.

Asymmetric routes to γ-amino alcohols **5** are limited, despite their use in the pharma industry and as ligands,[3] due largely to the challenge of controlling up to 3 contiguous stereocenters. Despite this, useful progress has been made, but there remains scope for improved, efficient new methods.[4,5]

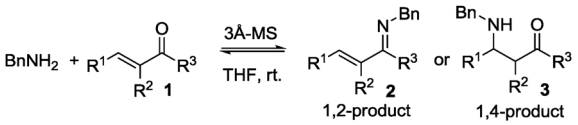
We demonstrated a highly enantio- and diastereo-selective route to γ-amino alcohols **5** *via* a three-step route involving α,β-unsaturated imines **2** (R^1 = Ar and R^3 = Me).[7,8] Asymmetric β-boration resulted in β-boryl imines **4**, which could undergo substrate-controlled asymmetric C═N reduction and C–B oxidation to give γ-amino alcohols **5** (Scheme 1). Although this was a powerful route to systems **5**, the application was severely limited by the range of α,β-unsaturated imines **2** that could be isolated. Normally, imines are prepared by 1,2-addition of an amine to the analogous carbonyl compound, however, competitive 1,4-addition and instability of the imines meant that this protocol was suitable solely for stable, chalcone derived-imines.



Scheme 1 Substrate controlled asymmetric reduction. (a) i, $NaBH_4$, MeOH; ii, NaOH, H_2O_2; (b) i, BH_3·THF; ii, NaOH, H_2O_2.

The ease of formation and stability of α,β-unsaturated imines is surprisingly underexplored compared to non-conjugated imines,[9] though the synthesis of dihydropyridines and pyridines from less-substituted α,β-unsaturated imines[11] has been reported. We investigated the formation of less-substituted α,β-unsaturated imines by ReactIR[12] to understand the relative rates and selectivity of α,β-unsaturated imine **2** formation *vs.* Michael addition (Table 1). Indeed, ReactIR proved to be an ideal tool for monitoring this reaction (Table 1) for both selectivity and rate. Most imine formations were complete within 3 h; the exception being methyl vinyl ketone (Entry 7, Table 1). Facile imine formation is exemplified (Fig. 1) by loss of the C═O stretch

Table 1 Monitoring imine formation by ReactIR



Entry	Substrate **1**	Addition product **2**/**3**[a]	Time[b] (min)
1	**1a**	**2a**[c]	12
2	**1b**	**2b**	15
3	**1c**	**2c**	50
4	**1d**	**2d**	90
5	**1e**	**2e**	100
6	**1f**	**2f**	360
7	**1g**	**3g**	30

[a] 1,2-, 1,4-addition. Conditions: THF (7 mL), 3 Å MS (2.5 g), **1** (2.8 mmol) and $BnNH_2$ (2.8 mmol). [b] Reaction completion. [c] **2a** – unstable.

[a] *Centre for Sustainable Chemical Processes, Dept. of Chemistry, Durham University, South Road, Durham DH1 3LE, UK. E-mail: andy.whiting@durham.ac.uk*
[b] *Dept. Química Física i Inorgànica, Universitat Rovira I Virgili, 43007 Tarragona, Spain*

† Electronic supplementary information (ESI) available: Experimental details, characterisation data, ReactIR, ^1H and ^{13}C NMR and crystallographic data in CIF format. CCDC 896882. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36129a

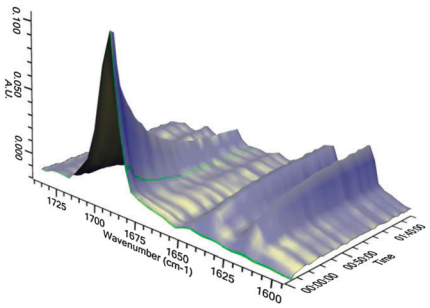


Fig. 1 ReactIR plots over time for the formation of **2d** *via* 1,2-addition of benzylamine to methacrolein **1d**, rt, THF, 3 Å MS.

(1698 cm^{-1}) and concomitant gain of the C=N (*asym* + *sym*) stretches (1640 & 1621 cm^{-1}).

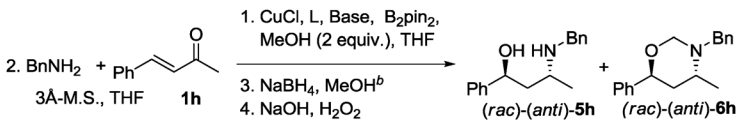
The *in situ*-generated α,β-unsaturated imines **2** formation was exploited by trapping with a borylnucleophile, *i.e.* developing a process not dissimilar to reductive amination where imine trapping is achieved using a hydride nucleophile.[13] In theory, it should be possible for *in situ*-formed imines to be utilised in a one-pot route to γ-amino alcohols **5** without isolation. Hence, initially chalcone **1h** (Table 2) was investigated using various Cu–ligand–base combinations and imine formation strategies (*i.e.* comparing the pre-formed imine with that formed *in situ*). Normal[6] catalyst loadings needed to be increased from 1 to 5% to improve conversion of **1h** to **5h** (Table 2, entries 1–3), and P*n*Bu_3 rather than PPh_3 also facilitated the formation of **5h** while minimising side products (Table 2, entries 4–6). Intriguingly, the formation of **5h** appeared to plateau to only 62–63% (see entries 3–6, Table 2), however, on further investigation, it was found that oxazine **6h** was also formed (*e.g.* entry 1, Table 2). This was unexpected since there was no obvious source of a formaldehyde equivalent in the reaction to explain the transformation of **4h** into **5h**.[12] MeOH solvent used for the C–B oxidation step was most likely to act as a precursor of formaldehyde (or equivalents thereof). This was circumvented by removing the MeOH (by evaporation) after the reduction step, which resulted in the formation of **5h** in 90% yield (entry 6, Table 2) and without oxazine **6h**. Deliberate formation of oxazine **6h** could also be achieved by increasing the MeOH and oxidant concentrations in the final step leading to the formation of **6h** in 51% yield (entry 9, Table 2).

Following the optimisation (Table 2), the conversion of further unsaturated aldehydes and ketones to the corresponding amino alcohols **5** was investigated (Table 3). This proved to be successful, resulting in yields varying from 20–90% of the amino alcohols **5** (Table 3). The structure of **5f** was confirmed by single crystal X-ray structure determination (Fig. 2). For most substrates, the more nucleophilic phosphine, P*n*Bu_3 (*i.e.* see entries 1–2, 5–10, Table 3), was required to facilitate efficient β-boration. However, purification of some γ-amino alcohols (*i.e.* **5c**, **d** and **j**) proved difficult due to high affinity to silica gel. In these cases, and as investigated on **1h** (entry 9, Table 2 and entry 7, Table 3), rather than isolation of the γ-amino alcohol, conversion to the oxazine **5** was achieved by addition of CH_2O to the crude amino alcohols, *i.e.* **5c**, **d** and **j**, resulting in 42–75% yields over 5 steps of the corresponding oxazines **6c**, **d** and **j** (Table 3, entries 2, 3 and 9).

ReactIR studies on the formation of the α,β-unsaturated imines derived from **1i** and **j** revealed that these substrates reacted significantly slower than **1a–g** with $BnNH_2$ and in fact were difficult to follow by ReactIR. Therefore, **1i** and **j** and $BnNH_2$ were added simultaneously to the borylation reaction in the presence of 3 Å molecular sieves (see ESI†) with the expectation that it might be possible to trap the more reactive unsaturated imine by borylation. Indeed, this strategy worked (see entries 8 and 9, Table 3) resulting in the formation of **5i** and **6j** in reasonable overall yields.

The asymmetric potential of this 4-step (or 5), one-pot method was also investigated using **1h** reacting with $BnNH_2$ with a Josiphos-type chiral diphosphine **7** (Scheme 2). Scheme 2b shows the formation of the β-boryl imine **4h** in up to 92% ee (+)-(*R*). Importantly, the asymmetric induction was almost identical to that obtained when the enantioselective β-boration took place from the isolated the α,β-unsaturated imine (Scheme 2),

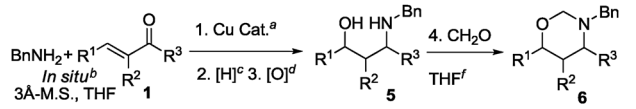
Table 2 Optimisation of the four-step, one-pot methodology on chalcone **1 h**

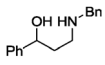
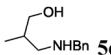
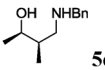
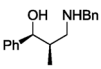
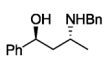
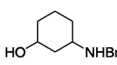
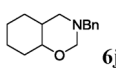


					Conversion[d] (%)		Isolated yield (%)		de[j] of the isolated product[d] (%)	
Entry	CuCl (%)	L (%)	Base (%)	Time[c] (h)	**5h**	**6h**[a]	**5h**	**6h**	**5h**[j]	**6h**
1	1	PPh_3 (2)	KO*t*-Bu (20)	24	37	30	17	32	*anti* >99%	*anti* >99%
2	3	PPh_3 (6)	NaO*t*-Bu (9)	24	42	29	40	—	*anti* >99%	*anti* >99%
3	5	PPh_3 (10)	KO*t*-Bu (18)	24	63	27	62	—	*anti* >99%	*anti* >99%
4	5	PPh_3 (10)	KO*t*-Bu (18)	48	62	36	56	—	*anti* >99%	*anti* >99%
5	5	P*n*Bu_3 (10)	KO*t*-Bu (18)	18[e]	63	34	63	—	*anti* >99%	*anti* >99%
6	5	P*n*Bu_3 (10)	NaO*t*-Bu (18)	18[f]	>95	0	90	—	*anti* >99%	*anti* >99%
7	10[i]	PPh_3 (20)	KO*t*-Bu (36)	24	40	27	25	—	*anti* >99%	*anti* >99%
8[g]	5	PPh_3 (10)	NaO*t*-Bu (15)	18[e]	52	34	—	30	*anti* >99%	*anti* >99%
9[h]	5	PPh_3 (10)	NaO*t*-Bu (15)	18[e]	44	54	—	51	*anti* >99%	*anti* >99%

[a] **6h** was confirmed by the reaction of **5h** with CH_2O (1.1 equiv.) in THF, rt, 4.5 h (74% yield). [b] $NaBH_4$ (4.2 mmol), MeOH (3 mL). [c] Time for reaction of **1h**, benzylamine and Cu–B cat. in one-pot. [d] Determined by ^1H NMR. [e] Imines were formed *in situ* (1 : 1 amine:α,β-unsaturated carbonyl, 3 Å MS, THF, 6 h) and transferred to Cu–B cat (18 h). [f] The same as entry 5 except MeOH removed prior to oxidation. [g] [O] NaOH, H_2O_2 (1 : 1, 20 equiv.), MeOH (10 ml), 4 h reflux. [h] [O] NaOH, H_2O_2 (1 : 1, 40 equiv.), MeOH (15 ml), 4 h reflux. [i] High catalyst loadings favour boration of the α,β-unsaturated carbonyl without formation of imine. [j] See previous work.[6a]

Table 3 Four-step, one-pot route to γ-amino-alcohols



Entry	Substrate	Conversion[e] (isolated yield) (%) 5	6	de[e] (%) 5	6
1[h]	 **1b**	 **5b** 63 (58)		—	—
2	 **1c**		 **6c** (50)	—	—
3[h]	 **1d**	 **5d** 82 (64)[g]		—	—
4[h]	**1d**		 **6d** (75)	—	—
5	 **1e**	 **5e** 79 (71)	 **6e** (28)	*rac-anti* >99	*rac-anti* >99
6	 **1f**	 **5f** 37 (20)		*rac-anti* >99	
7[i]	 **1h**	 **5h** >95 (90)	 **6h** (74)	*rac-anti* >99	*rac-anti* >99
8	 **1i**	 **5i** 78 (51)		40	
9	 **1j**		 **6j** (42)	>95	

[a] Standard borylation conditions: CuCl (5%), P*n*Bu$_3$ (10%), NaO*t*Bu (15%), B_2pin_2 (1.1 equiv.), MeOH (2 equiv.), THF. [b] *In situ* imine formation (0–7 h), see ESI. [c] $NaBH_4$ (excess), MeOH (2 h), removal of MeOH under reduced pressure. [d] NaOH, H_2O_2 oxidation (THF, reflux 1 hour). [e] Determined by ^{1}H NMR of isolated **5**/**6**, see ESI. [f] **5** stirred in THF and CH_2O (1.1 equiv.) overnight, **6** obtained by column chromatography. [g] 64%-inseparable impurity (see ESI). [h] Standard conditions, except PPh_3 (10%) used as ligand. [i] Standard conditions, except NaOtBu (18%) used as base.

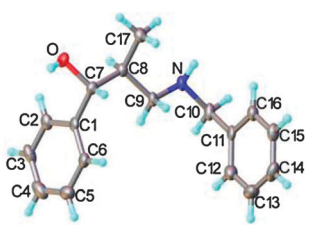
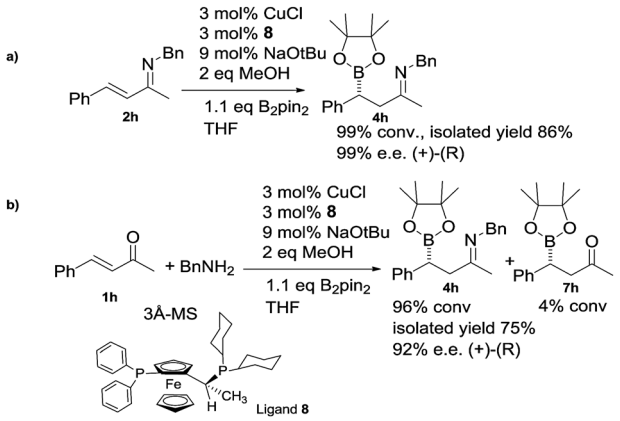


Fig. 2 Olex2[13] thermal ellipsoid plot (50% probability) of **5f**.

as well as the absolute stereochemistry. This is consistent with *in situ* imine formation followed by boration and not direct



Scheme 2 Asymmetric borylation by *in situ* imine formation followed by β-boration.

boration of α,β-unsaturated ketone **1h** followed by imine formation of the resulting β-boryl ketone **7h** (see ESI†).

In summary, a stereoselective 4-step, one-pot protocol for the synthesis of γ-amino alcohols in 20–90% yields has been developed. A 5-step version to 1,3-oxazines has also been demonstrated which exhibits impressive efficiency (42–75%) considering the number of steps. The asymmetric potential has been demonstrated and this methodology is being developed for the control of multiple stereogenic centres. In addition, although α,β-unsaturated imines are little used or studied compared to their carbonyl analogues, their formation can be followed by *in situ* IR, and subsequent trapping by borylation is an ideal way to demonstrate their formation. Further applications will be reported in due course.

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Notes and references

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