First enantioselective organocatalytic allylation of simple aldimines with allyltrichlorosilane†

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A new organocatalytic system, novel chiral bisformamide 3 and *in situ* generated L-proline-derived allylsilane reagent 14′, which converts different aldimines to homoallylic amines in good to high yields (up to 95%) and good enantioselectivities (up to 85% ee) has been described.

The development of enantioselective metal-free synthesis of homoallylic amines is of wide interest, since chiral homoallylic amines are useful intermediates for the synthesis of bioactive natural products and pharmaceutically important compounds.[1] Among various allylating agents, allylsilanes are preferable due to their low toxicity. Despite much effort directed at enantioselective organocatalytic aldehyde allylation with allyltrichlorosilane,[2] the development of chiral reagents and organocatalysts for the enantioselective allylation of aldimines has lagged behind.

Recently, Leighton and co-workers have reported on the use of a pseudoephedrine derived strained silacycle (allylsilane) as a chiral reagent for allylation of *N*-acylhydrazones.[3]

Kobayashi and co-workers have found that *N*-acylhydrazones in DMF as neutral coordinate-organocatalysts (NCO) without the use of any co-catalyst undergo smooth allylation with allyltrichlorosilane.[4–6] The same group has reported on chiral sulfoxides (used in 3 equiv.)[7] and BINAP dioxides (utilized in 2 equiv.)[8] as the first chiral neutral-coordinate organocatalysts for the enantioselective allylation of *N*-acylhydrazones.

While *N*-acylhydrazones were found to be reactive for allylation, it was observed that simple imines were resistant to allyltrichlorosilanes.[4,5] The first example of allylation of simple imines derived from aldehydes and 2-aminophenols with allyltrichlorosilane using DMF as NCO to afford the corresponding homoallylic amines was reported in 2003 by Kobayashi and co-workers.[9] However, no enantioselective allylation of these imines with allyltrichlorosilane has been attained to date.

Herein, we report the first example of an organocatalytic enantioselective allylation of simple 2-aminophenol-derived aldimines with allyltrichlorosilane utilizing novel chiral DMF-analogues and L-proline.

At the outset, we evaluated the potential of our novel C_2-chiral bisformamides **1–3** (Fig. 1) at 15 mol% as possible catalysts for the allylation of aldimine **4** (derived from electron-rich *para*-methoxybenzaldehyde) with allyltrichlorosilane in CH_2Cl_2. Similarly low yields (around 10%) and moderate to good enantioselectivities were observed (58% ee, 65% ee and 78% ee, respectively, Table 1, entries 1–3). Bisformamide **3** appeared to be the most promising with respect to enantioselectivity (78% ee) and was selected for further optimisation of the reaction conditions.

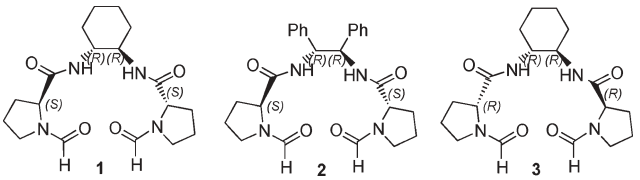
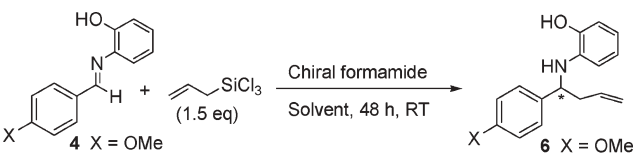


Fig. 1 Novel C_2-chiral bisformamide organocatalysts.

Next, in analogy to Kobayashi,[7,8] we have increased the amounts of chiral bisformamide **3** to 2 equivalents and carried out the allylation reaction of *para*-nitrobenzaldehyde-derived aldimine **5** in different solvents (CH_3CN, toluene, $CHCl_3$ and CH_2Cl_2, Table 1, enties 4–7). These screening studies identified CH_2Cl_2 as the optimal solvent for the reaction giving the product in 93% yield and 54% ee (entry 7). No allylation took place in CH_3CN and toluene (entries 4 and 5) and moderate yield (52%) as well as ee value (43% ee) was observed for the corresponding product in $CHCl_3$ (Table 1, entry 6).

In order to further improve the enantioselectivity and the yield of the homoallylic amine **7**, we screened several additives **8–14** in CH_2Cl_2 (Table 2). Use of Et_3N and/or *i*-Pr_2NEt (1 equiv.) in

Table 1 Screening of C_2-chiral bisformamides **1–3** for asymmetric allylation of simple 2-aminophenol-derived aldimines



4 X = OMe
5 X = NO_2
6 X = OMe
7 X = NO_2

Entry	X	Formamide (equiv.)	Solvent	Yield[a] (%)	ee[b] (%)
1	OMe	**1** (0.15)	CH_2Cl_2	<10	58 (*R*)
2	OMe	**2** (0.15)	CH_2Cl_2	<10	65 (*R*)
3	OMe	**3** (0.15)	CH_2Cl_2	⩾10	78 (*S*)
4	NO_2	**3** (2.0)	CH_3CN	Traces	n.d.
5	NO_2	**3** (2.0)	Toluene	Traces	n.d.
6	NO_2	**3** (2.0)	$CHCl_3$	52	43 (*S*)
7	NO_2	**3** (2.0)	CH_2Cl_2	93	54 (*S*)

[a] Determined by ^1H NMR spectroscopy. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AD) in comparison with authentic racemic material.

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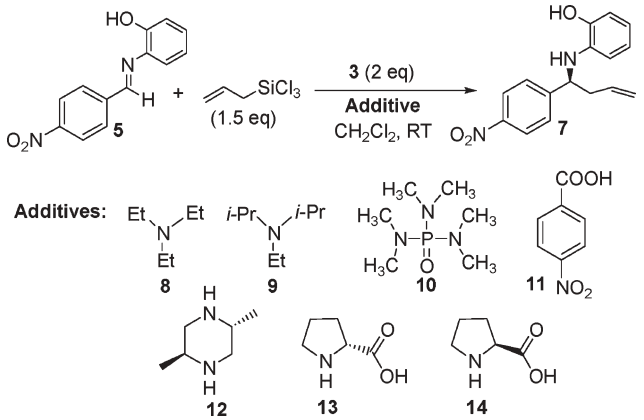
Table 2 Effect of additives **8–14**



Entry	*t*/h	Additive (equiv.)	Yield[a] (%)	ee[b] (%)
1	48	**8** (1.0)	83	61
2	48	**9** (1.0)	78	56
3	48	**10** (1.0)	98	38
4	48	**11** (1.0)	92	71
5	48	**12** (1.0)	94	72
6	48	**13** (1.0)	64	53
7	48	**14** (1.0)	65	76
8	4	**14** (2.0)	97	83

[a] Determined by ^{1}H NMR spectroscopy. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AD) in comparison with authentic racemic material.

combination with chiral bisformamide **3** provided the adduct **7** in 48 h with 83%, 61% ee and 78%, 56% ee, respectively (Table 2, entries 1 and 2). Addition of HMPA (1 equiv.) gave the product with 98% yield in only 38% ee (Table 2, entry 3). Interestingly, the use of *para*-nitrobenzoic acid (**11**) and *trans*-2,5-dimethylpiperazine (**12**) as additives provided similary good results in 48 h: 92%, 71% ee and 94%, 72% ee, respectively (Table 2, entries 4 and 5).

Next we tested proline (1 equiv.) as an additive for the bisformamide **3** catalyzed allylation reaction (entries 6, 7). Whereas similar yields were observed with D- and L-proline (64% and 65%, respectively), the combination of **3** with L-proline gave 76% ee (entry 7) and the D-proline/formamide **3** (entry 6) combination produced the product in only 53% ee.

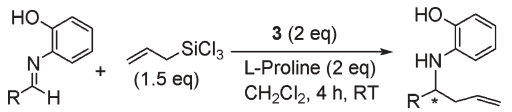
To our delight, the allylation yield and the enantioselectivity were improved by the use of 2 equiv. of L-proline (Table 2, entry 7 *vs.* entry 8). The presence of both bisformamide **3** and L-proline (2 equiv. each) notably increases the reaction rate as well as the enantioselectivity (4 h, 97%, 83% ee, entry 8, Table 2) with respect to independently acting bisformamide **3** (48 h, 93%, 54% ee, entry 7, Table 1) or L-proline (96 h, 41%, 0% ee). The enantioselectivity is much higher than the sum of its individual enantioselectivities, which indicates the possibility of synergistic effects.

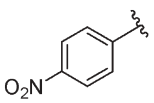
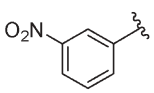
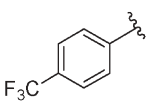
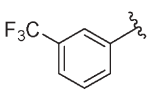
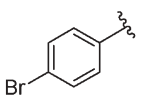
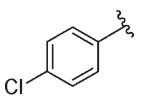
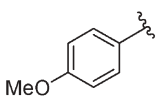
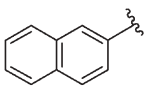
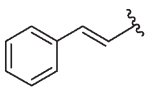
Intriguingly, L-proline, which is not soluble in CH_2Cl_2, desolves upon addition of allyltrichlorosilane to the reaction mixture. Considering this result one might anticipate the formation of two covalent bonds between the nucleophilic nitrogen (NH), as well as oxygen (OH) of the carboxylic group in L-proline and a silicon atom of allyltrichlorosilane, providing a chiral allylating reagent.

Indeed, the *in situ* formation of new L-proline-derived allylsilane reagent **14′** (Fig. 2) was confirmed using ESI- and EI-MS and ^{1}H NMR methods. The chemical shift values of all the methyne and methylene protons of the allylic group in **14′** have appeared at higher field than those of the corresponding allyltrichlorosilane.†

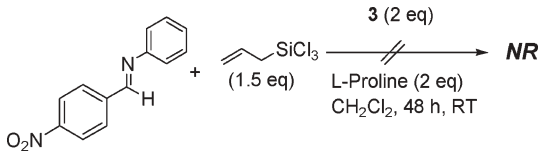
Next, we employed this new catalytic system for asymmetric allylation of different aldimines, and the results are summarized in Table 3. Good to high yields (ranging from 73% to 95%) and good enantioselectivities (47–85% ee) were achieved in all cases. Interestingly, while *meta*-substituted aldimines led to moderately enantioselective reactions (69% ee and 72% ee, respectively, entries 2 and 4, Table 3), the substrates with *para*-substituted aromatic rings provided adducts in good enantioselectivities (79–85% ee, entries 1, 3, 5 and 6).

Table 3 Asymmetric allylation of simple aldimines with allyltrichlorosilane under optimised conditions



Entry	R	Yield[a] (%)	ee (%)
1		94	83[b]
2		93	69[c]
3		91	81[c]
4		95	72[c]
5		84	79[c]
6		89	85[c]
7		94	68[b]
8		91	71[c]
9		88	51[b]
10		73	47[c]

[a] Yield of isolated product after column chromatography on SiO_2. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AD) in comparison with authentic racemic material. [c] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak OD) in comparison with authentic racemic material.



Scheme 1

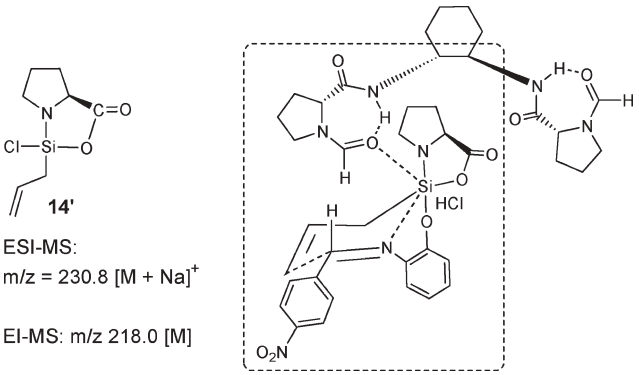


Fig. 2 ESI-MS and EI-MS experiments of the new L-proline-derived allylsilane reagent **14′** and proposed transition state structure for the formation of the *S* enantiomer.

The introduction of electron-donating group (*para*-OMe) on the aromatic ring significantly affected the enantioselectivity (68% ee *vs.* 85% ee, entry 7 *vs.* entry 6, Table 3).

Allylation of aldimines derived from 2-naphthalenealdehyde, cinnamaldehyde and 2-furaldehyde resulted in good to high yields (73–91%) and moderate to good enantioselectivities (47–71% ee, entries 8–10) under the present reaction conditions.

The imine derivative of *para*-nitrobenzaldehyde having a phenyl group instead of an *ortho*-hydroxyphenyl group were also subjected to reaction with allyltrichlorosilane in the presence of catalyst **3**/L-proline, however, no allylaltion product was observed (Scheme 1). Most probably, the *ortho*-hydroxyl group proximal to the imine nitrogen facilitates the reaction by covalent bond formation with the silicon atom of the allylating reagent.[9]

Based on these results and considering for simplicity only one formamide group of **3**, we propose a plausible transition-state model, which reasonably explains the absolute configuration of the allylation adduct **7** (Fig. 2). The second formamide moiety of C_2-chiral bisformamide **3** might similarly coordinate to the silicon atom of the second molecule of L-proline-derived allylsilane reagent **14′**, most probably enhancing its nucleophilicity.

This is the first example of enantioselective organocatalytic allylation of simple aldimines using allyltrichlorosilane. Further investigations to reduce the amout of chiral formamides are now in progress.

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Notes and references

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