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N-Allyl-*N*-*tert*-butyldimethylsilylamine for chiral ligand-controlled asymmetric conjugate addition to *tert*-butyl alkenoates†

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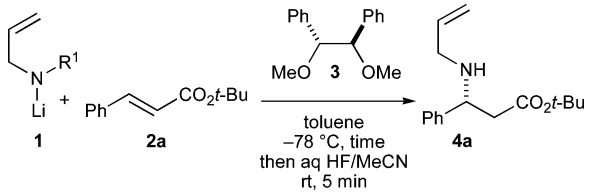
The chiral ligand controlled asymmetric conjugate addition reaction of lithium *N*-allyl-*N*-(*tert*-butyldimethylsilyl)amide to alkenoates proceeded smoothly to give, after protodesilylation, the corresponding 3-allylaminoalkanoates with high enantioselectivities in high yields. The allyl group on the nitrogen atom was easily removable to afford 3-aminoalkanoates.

Asymmetric conjugate addition of chiral lithium amides to alkenoates has been one of the most powerful methods for the synthesis of chiral 3-aminoalkanoates as has been extensively studied by Davies and his group.[1,2] A chiral ligand-controlled asymmetric reaction[3] of an achiral lithium amide has been recently reported[4] as a new entry to this interesting field. However, this method relies on the use of *N*-benzy-*N*-trimethylsilylamine as a nitrogen source that requires hydrogenolysis for removal of the benzyl group. We describe herein that allylamine is also a good source of a nitrogen nucleophile in the asymmetric addition to alkenoates, and the allyl group is easily removable by the isomerisation reaction with a rhodium catalyst.[5,6]

We began our studies with the reaction of allylamine (Scheme 1). The lithium amide **1a** (R^1 = H) was *in situ* prepared from allylamine with butyllithium in the presence of chiral ligand **3** in toluene and was then treated with *tert*-butyl cinnamate **2a**. Although the reaction proceeded within a half hour at −78 °C to give **4a** in 64% isolated yield, the enantioselectivity was unfortunately almost marginal (Table 1, entry 1).

The reaction of lithium *N*-allyl-*N*-trimethylsilylamide **1b** (R^1 = TMS, 3 equiv) was effected by **3** (3.6 equiv) at −78 °C to give, after purification by silica gel column chromatography, **4a** with 69% ee in 94% yield (entry 2). The absolute configuration and enantioselectivity of **4a** were determined by converting to **5** with the established absolute configuration as shown below. Dramatic improvement of enantioselectivity was observed by changing a TMS group to TES (triethylsilyl) (**1c**: R^1 = TES) giving **4a** with 83% ee in 91% yield (entry 3). A TES group was not removed on silica gel column chromatography, but easily protodesilylated with aqueous HF in acetonitrile at room temperature for 5 min to afford **4a**.[7] TBS (*tert*-butyldimethylsilyl) amide **1d** (R^1 = TBS)[8] was much more effective to give **4a** with 86% ee in 95% yield (entry 4). The enantioselectivity was improved to 89% ee by conducting the reaction at −95 °C (entry 5). TIPS (triisopropylsilyl) amide **1e** (R^1 = TIPS) was a poor nucleophile not to give a conjugate addition product probably because of a too much steric hindrance (entry 6).



Scheme 1 Asymmetric reactions of lithium allylamides **1** with *tert*-butyl cinnamate **2a** by the mediation of **3**.

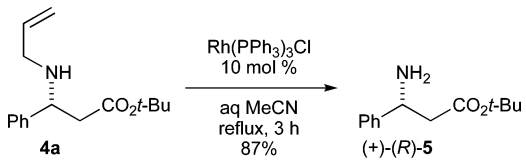
Table 1 Asymmetric addition of lithium allylamides **1** to cinnamate **2a** in toluene at −78 °C giving **4a**

Entry	1	R^1	time (h)	Yield (%)	Ee (%)
1	**a**	H	0.5	64	5
2	**b**	TMS	0.5	94	69
3	**c**	TES	1	91	83
4	**d**	TBS	1	95	86
5[a]	**d**	TBS	1.5	95	89
6	**e**	TIPS	5	0	

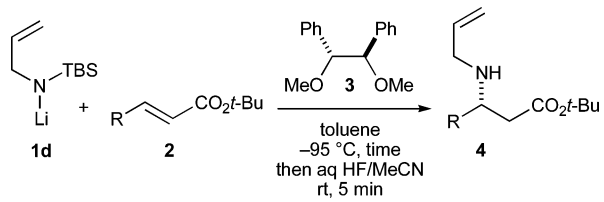
[a] Performed at −95 °C.

The allyl group of **4a** was easily removed with rhodium chloride[9] in refluxing aqueous acetonitrile for 3 h to give (+)-(*R*)-**5**[10] in 87% isolated yield without any racemisation (Scheme 2). The stereochemistry of the newly created stereogenic center was thus established to be (*R*).

The asymmetric addition reactions of **1d** with other acyclic and cyclic alkenoates **2** were also controlled by **3** at −78 °C or −95 °C in toluene to afford **4** with up to 94% ee (Scheme 3). Crotonate **2b** (R = Me) was converted to **4b** in 90% yield (Table 2, entry 1). The ee of **4b** was determined to be 90% by ^{1}H NMR using (*S*)-(−)-1,1′-bi-2,2′-naphthol as a chiral shift reagent.[11] The reaction of

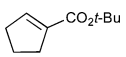


Scheme 2 Removal of the allyl group of **4a** to give **5** with the established absolute configuration.



Scheme 3 Asymmetric addition of **1d** to **2** by the mediation of a chiral ligand **3**.

Table 2 Asymmetric addition of *N*-TBS-allylamide **1d** to **2** in toluene at −95 °C giving **4**‡

Entry	2	R	time (h)	4	Yield (%)	Ee (%)
1	**b**	Me	1	**b**	90	90
2[a]	**c**	*i*-Pr	5	**c**	84	76
3[a]	**d**	(*E*)-MeCH=CH	18	**d**	88	75
4	**e**	1-Naph	3	**e**	89	94
5	**f**		1.5	*cis*-**f**	82	82
				trans-**f**	11	84

[a] Performed at −78 °C.

† Electronic supplementary information (ESI) available: general procedure for addition reaction, deallylation, silylation of allylamine and data for compounds. See http://www.rsc.org/suppdata/cc/b4/b405347h/

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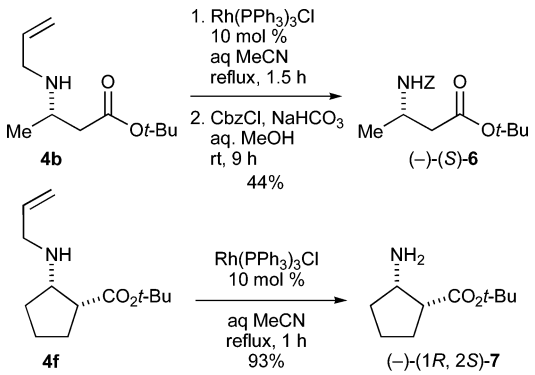
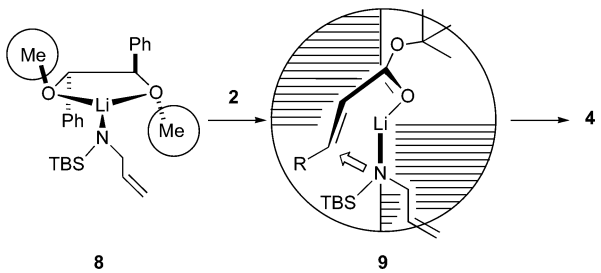
alkenoate **2c** having an isopropyl terminal group (R = *i*-Pr) gave **4c** with 76% ee in 84% yield (entry 2). Sorbate **2d** (R = (*E*)-MeCH=CH) was regioselectively converted to 1,4-addition product **4d** with 75% ee in 88% yield (entry 3). The reaction of **2e** (R = 1-naphthyl) gave **4e** with 94% ee in 89% yield (entry 4). Cyclopentenecarboxylate **2f** was also applicable in the reaction to give diastereoselectively *cis*-**4f** with 82% ee as a major product in 82% yield (entry 5). The minor *trans*-**4f** with 84% ee was also produced in 11% yield. It is important to note that chiral ligand **3** was recovered in high yield and was re-used in the asymmetric reaction without loss of selectivity.

Deallylation of **4b** and *cis*-**4f** was achieved by treatment with Wilkinson's catalyst in refluxing aqueous acetonitrile to give (−)-(*S*)-**6** in 44% overall yield after conversion to a Cbz derivative,[12] and (−)-(1*R*,2*S*)-**7**[13] in 93% yield without any racemisation. It is important to note that allylamine attacks to the bottom face of linear and cyclic alkenoates shown as **2** giving **4**.

The stereocontrolled formation of chiral **4** is predictable by using a model (Scheme 5). Coordination of the carbonyl oxygen atom of **2** to a lithium atom in a chelate **8** may be the first event for the reaction. Two etheral methyl groups are fixed in *trans* relationship to the adjacent two phenyl groups. It is reasonable to speculate that coordination of **2** takes place in the less hindered region avoiding steric repulsion by the methyl groups of **3** as shown in **9**.[14] The intra-complex attack of the nitrogen atom to the *si*-face (for example R = Me) at the 3-position of *s*-*cis*-**2** provides chiral **4** with the observed absolute configuration.



Scheme 4 Removal of the allyl groups of **4** giving **6** and **7** with the established absolute configurations.



Scheme 5 Plausible stereoselection for the production of **4** from **9**.

In summary, an external chiral ligand-controlled asymmetric conjugate addition of allylamine to alkenoates was developed. Since both of enantiomers **3** are available, either enantiomer of **4** is accessible. Synthetic utility of the products is the next target.

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Notes and references

‡ *Procedure* (Table 2, entry 1): *n*-BuLi (3.0 mmol) was added to **1d** (3.0 mmol) in toluene (8 mL) at −78 °C over 5 min. After 0.5 h, **3** (3.6 mmol) in toluene (6 mL) was added. The mixture was stirred for 0.5 h at −78 °C, then cooled to −95 °C. A toluene (2 mL) solution of **2b** (1.0 mmol) was added over 5 min. The mixture was stirred at −95 °C for 1.5 h and quenched with satd. NH_4Cl (3 mL). After addition of satd. $NaHCO_3$ (4.5 mL), the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The crude product in MeCN (30 mL) was treated with 46% HF (3 mL) at rt for 5 min. After addition of satd. $NaHCO_3$, the mixture was extracted with AcOEt. The organic layer was washed with brine and dried. Concentration and chromatography (AcOEt/hexane = 1/1) gave **3** (quant. recovery) and **4b** with 90% ee (determined by ^{1}H NMR using (*S*)-(−)-1,1′-bi-2,2′-naphthol as a chiral shift reagent).

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