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Asymmetric Construction of Quaternary Carbon Centers by Sequential Conjugate Addition of Lithium Amide and in Situ Alkylation: Utility in the Synthesis of (−)-Aspidospermidine

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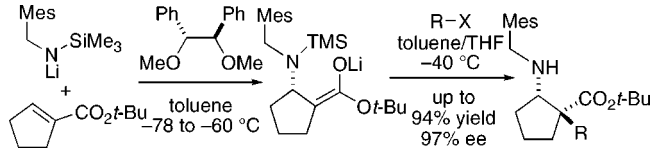
ABSTRACT



Chiral diether ligand-controlled asymmetric conjugate addition of a lithium amide to cyclopentenecarboxylate and subsequent in situ alkylation gave a chiral cyclopentane derivative bearing a quaternary carbon with high enantio- and diastereoselectivity. The cyclopentane derivative was converted successfully to (−)-aspidospermidine.

Synthetically useful asymmetric nitrogen−carbon bond formations that are otherwise difficult to accomplish have been achieved through conjugate addition reactions of both chiral[1] and achiral[2] lithium amides to enoates.[3] Since the resulting lithium enolate intermediate is a powerful nucleophile, subsequent in situ alkylation is quite promising. Thus, potentially, useful one-pot transformations to produce adjacent asymmetric carbon centers with concomitant installation of vicinal N−C and C−C bonds could be achieved.[4] Of particular interest is the asymmetric construction of quaternary carbons in tandem fashion. Given our success in the development of chiral diether-mediated asymmetric conjugate additions of lithium arylmethyl- and allyltrialkylsilylamides,[5] we envisioned a tandem asymmetric conjugate addition−alkylation strategy for the construction of a quaternary carbon center. Herein, we describe a highly efficient enantioselective construction of a quaternary carbon center with up to 97% ee and over 98% de and the use of the product in the asymmetric total synthesis of (−)-aspidospermidine.

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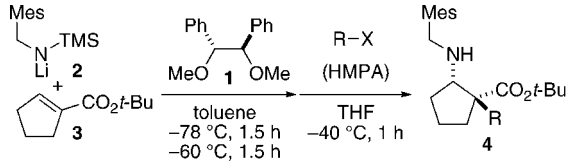
Table 1. Tandem Asymmetric Conjugate Addition−Alkylation[a]



entry	R−X	4	yield (%)	ee (%)	de (%)
1	$PhCH_2Br$	**4a**	90	97	>98
2	$H_2C{=}CHCH_2Br$	**4b**	93	95	>98
3	EtI[b]	**4c**	94	95	>98
4	MeI	**4d**	93	95	>98

[a] All reactions were performed using **2** (3 equiv), **1** (3.6 equiv), and **3** (1 equiv). In the alkylation step, R−X (2 equiv) was used in entries 1, 2, and 4. [b] For ethylation, EtI (10 equiv) and HMPA (6 equiv) were used.

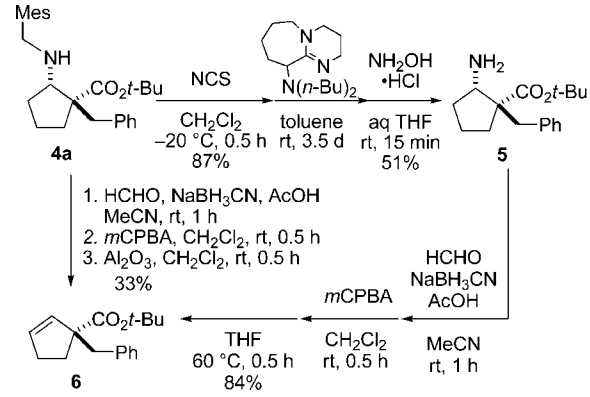
We began our studies with allylation of the lithium enolate intermediate generated by conjugate addition of lithium *N*-mesitylmethyl-*N*-TMS-amide **2** to *tert*-butyl cyclopentenecarboxylate **3** in the presence of C_2-symmetric chiral diether **1** in toluene at −78 °C (Table 1, entry 2).[5d] Treatment of a toluene solution of this lithium enolate with allyl bromide did not yield the expected allylation product **4b** (R = $CH_2CH{=}CH_2$), but instead yielded the conjugate addition product **4** (R = H) with 96% ee. Upon addition of THF to a toluene solution of the lithium enolate at −78 °C, the allylation process proceeded at −40 °C for 1 h, giving the desired product **4b** as nearly a single diastereomer in 92% yield. However, the enantioselectivity dropped to 90% ee. We overcame this problem by additional stirring at −60 °C for 1.5 h during the conjugate addition step (to complete the asymmetric conjugate addition, before the addition of THF, which accelerates the racemic conjugate addition reaction), giving the allylation product **4b** with 95% ee and over 98% de in 93% yield.

C-Benzylation and *C*-methylation also proceeded satisfactorily to give the corresponding quaternary carbon products **4a** (R = Bn) and **4d** (R = Me) with up to 97% ee as nearly single diastereomers (entries 1 and 4). *C*-Ethylation with ethyl iodide required the coaddition of HMPA to give the product **4c**[6] (R = Et) with 95% ee in 94% yield (entry 3).

Ready conversion of the secondary amine product to the primary amine was demonstrated by successively treating **4a** with NCS for *N*-chlorination (87%); *N*-dibutylamino-DBU for elimination to the imine, and; hydroxylamine for transoximation (51%, two steps). These successive reactions gave the β-amino acid derivative **5** (Scheme 1).[5d,7]

Elimination of the amino function of **5** to give olefin **6** was also performed by sequential *N*-dimethylation with formalin−sodium cyanoborohydride, *m*-CPBA oxidation to

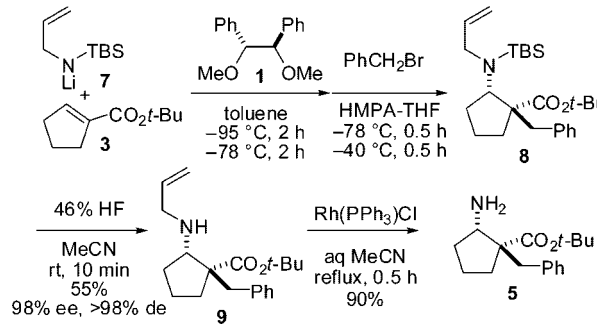
Scheme 1. Conversion of **4** to **5** and **6**



N-oxide, and thermal Cope elimination[8] in THF at 60 °C in 84% overall yield (Scheme 1). We also obtained olefin **6** from **4a** via *N*-methylation, *m*-CPBA oxidation, and Cope elimination[9] with dialuminium trioxide[10] in 33% overall yield.

Asymmetric conjugate addition of lithium allylamide **7**[5c] to **3** and in situ benzylation gave **8**, which was then treated without purification with aq HF for protodesilylation to provide **9** (Scheme 2). Olefin isomerization of **9** with Wilkinson's catalyst in aqueous acetonitrile at reflux and simultaneous hydrolysis of the imine gave primary amine **5** in 90% yield. In this benzylation, we obtained **9** with 98% ee in 55% yield, which is in stark contrast to 85% ee for the protonation product in the conjugate addition of **7**.[5c] Kinetic enantioenrichment in the benzylation step may be responsible for this high enantioselectivity. In fact, almost complete *C*-allylation and *C*-methylation gave the corresponding products with 85% ee in reasonably high yields of 88% and 94%, respectively.

Scheme 2. Asymmetric Conjugate Addition of Allylamine and Benzylation



The asymmetric total synthesis of aspidospermidine **18** has been considered to be a touchstone of the methodology for

(6) The stereochemistry of asymmetric conjugate addition has been reported in ref 5b. The relative configuration of **4c** was assigned by an NOE experiment. Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796–3798.

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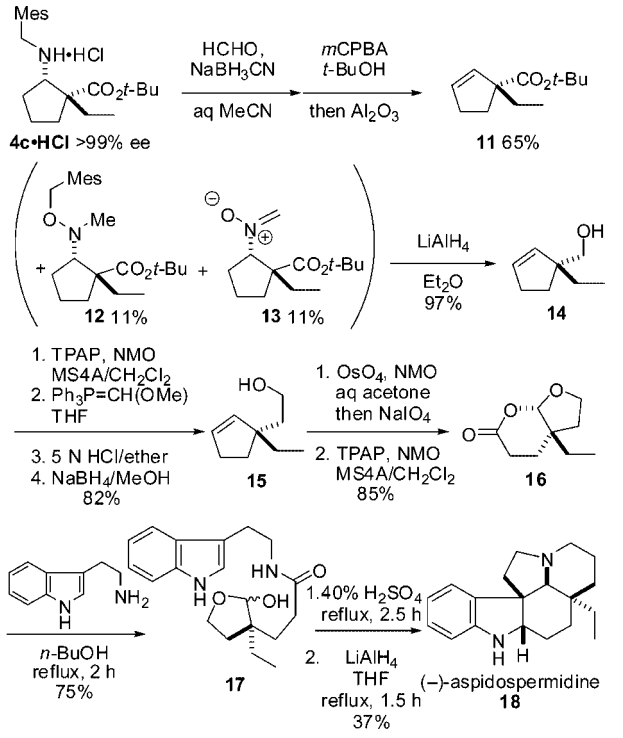
Scheme 3. Total Synthesis of (−)-Aspidospermidine **18**



the asymmetric construction of quaternary carbons.[11,12] The utility of the quaternary carbon product **4** was demonstrated by the asymmetric total synthesis of (−)-**18** (Scheme 3).[13]

The ee of the ethylation product **4c** (95% ee) was increased to >99% ee in 85% recovery by recrystallization of its hydrochloride from ethyl acetate. Successive methylation of the hydrochloride salt of **4c**, *N*-oxidation with *m*-CPBA, and Cope elimination with Al_2O_3 in *tert*-butyl alcohol[14] gave olefin **11** in 65% yield along with **12** (11%) and **13** (11%). Lithium aluminum hydride reduction of ester **11** to alcohol **14**, TPAP oxidation to the aldehyde, Wittig olefination for one-carbon elongation, hydrolysis to the aldehyde, and sodium borohydride reduction gave alcohol **15** in 79% yield (five steps from **11**). These steps should be carefully carried out because the products all have low boiling points and can easily be distilled off. Oxidative cleavage of olefin **15** with osmium tetroxide and sodium metaperiodate yielded a lactol, which was then oxidized to δ-lactone **16**, bearing three differently oxidized oxygen functionalities[15] in 85% yield. Amide formation with lactone **16** and tryptamine in *n*-butyl alcohol at reflux gave **17** in 75% yield. The remaining transformations were a modification of the Harley-Mason's protocol. Sulfuric acid treatment of **17** induced Pictet−Spengler cyclization. Simultaneous rearrangement occurred at reflux for 2.5 h. Lithium aluminum hydride reduction in THF at reflux for 1.5 h completed the synthesis of (−)-aspidospermidine **18** in 37% yield.[16]

In summary, we have developed an efficient method for constructing a chiral quaternary carbon by tandem asymmetric conjugate addition of a lithium amide to an enoate and its subsequent in situ alkylation. Total synthesis of (−)-aspidospermidine was successfully demonstrated as a touchstone of the strategic application of the asymmetric conjugate amination−alkylation protocol.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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