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Aminolithiation of carbon–carbon double bonds as a powerful tool in organic synthesis*

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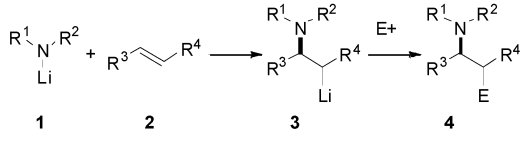
Abstract: A conjugate amination of α,β-unsaturated carbonyl compounds with lithium amides has become a powerful method of N–C bond-forming reactions. Chiral ligand-controlled asymmetric version of the conjugate amination of enoates was developed for practical bench chemistry, giving the enantioenriched amination product with over 99 % ee. In situ diastereoselective alkylation of resulting lithium enolates allowed us to form vicinal N–C and C–C bonds in a one-pot operation. This protocol enabled us to realize a short-step asymmetric synthesis of otamixaban key intermediate. Treatment of product 3-benzylamino- and 3-allylaminoesters with *tert*-butyllithium gave five- or seven-membered lactams through [1,2]- or [2,3]-rearrangement of intermediate β-lactams. Isolated C–C double bonds were also found to accept intramolecular aminolithiation affording the corresponding hydroamination products. Chiral lithiophilic ligand-catalyzed reaction gave enantioenriched hydroamination products with high ee. Stereoselective intramolecular aminolithiation of allylaminoalkenes was coupled with subsequent carbolithiation to give doubly cyclized product amines.

Keywords: hydroamination; aminolithiation; carbolithiation; enantioselectivity; asymmetric.

INTRODUCTION

A conjugate addition reaction of chiral α,β-unsaturated carbonyl compounds **2** ($R^4 = CO_2R$) with achiral lithium amides **1** has been proven to be a good way for the asymmetric synthesis of β-amino acid derivatives **4** via **3** (Scheme 1) [1]. Enantioface differentiating addition of chiral lithium amides to achiral enoates is the second generation of this type of asymmetric amination [2]. Our strategy in the asymmetric conjugate amination of prochiral enoates with achiral lithium amides is based on the use of a chiral lithiophilic diether **5** as a chiral activator of lithium amides (Scheme 2) [3]. We describe herein our aminolithiation story starting from the encounter of conjugate amination to the aminolithiation–carbolithiation tandem process.



Scheme 1 Aminolithiation of C–C double bond.

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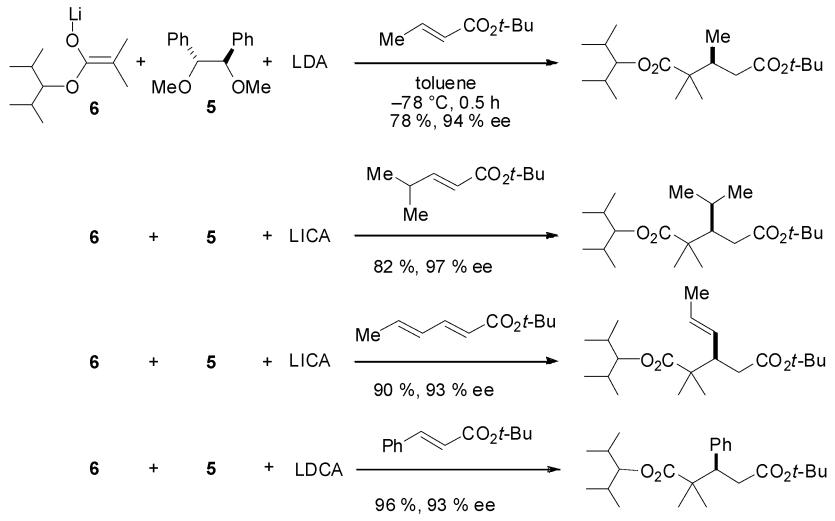
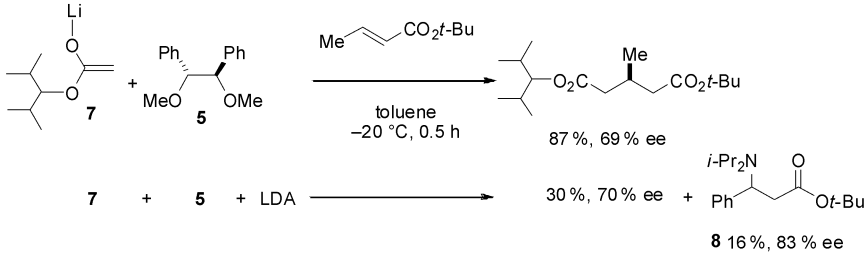


Scheme 2 Asymmetric Michael reaction of an enolate mediated by lithium amides and **5**.

ENCOUNTER WITH NUCLEOPHILIC CONJUGATE ADDITION OF LITHIUM AMIDES

We have been engaged in the external chiral ligand **5**-controlled asymmetric Michael reaction of a lithium ester enolate **6** with enoates by the mediation of lithium amides. The reaction proceeded very smoothly by the activation of disubstituted lithium enolate **6** with a lithium amide, such as lithium diisopropylamide (LDA), lithium cyclohexylisopropylamide (LICA), lithium dicyclohexylamide (LDCA), and **5** to give the corresponding Michael adducts with high ee in high yield as shown in Scheme 2 [4]. In the absence of a lithium amide, the reaction needs a higher temperature to complete giving the Michael adduct with rather lower ee.

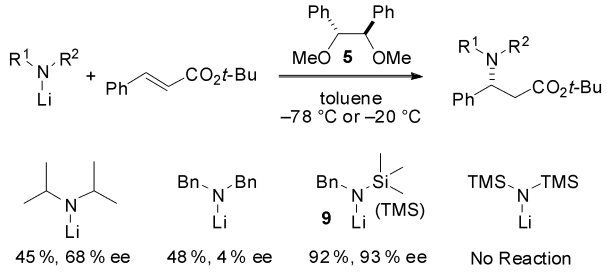
However, the reaction of unsubstituted enolate **7**, generated from *tert*-butyl acetate, with crotonate gave the Michael adduct in rather lower 30 % yield, in which the Michael adduct **8** of LDA was found to be the another adduct with relatively high 83 % ee in 16 % yield (Scheme 3). It is very reasonable to understand that LDA played its role as a nucleophile as well as a coordinating activator of a lithium enolate. We then turned our effort to an asymmetric conjugate amination of a lithium amide by the control of **5**.



Scheme 3 Accidental asymmetric Michael reaction of crotonate with LDA.

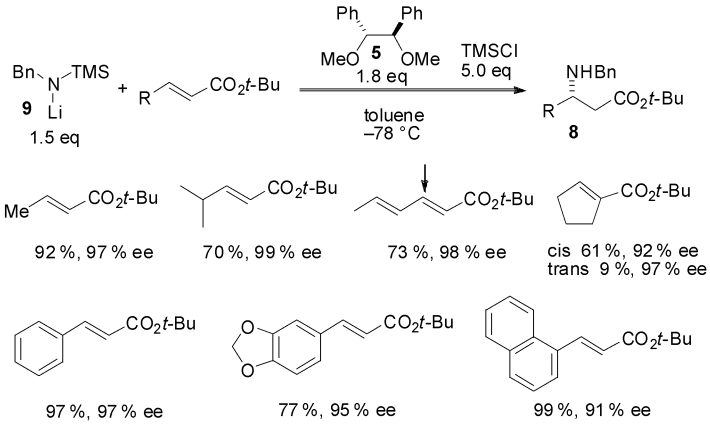
EFFICIENT ASYMMETRIC CONJUGATE AMINATION

We have screened some lithium amides to find one giving a higher ee and higher yield by using *tert*-butyl cinnamate as a Michael acceptor and **5** as a chiral ligand for lithium. As summarized in Scheme 4, benzyltrimethylsilylamide **9** gave the adduct with 93 % ee in 92 % yield. Other amides were not satisfactory.



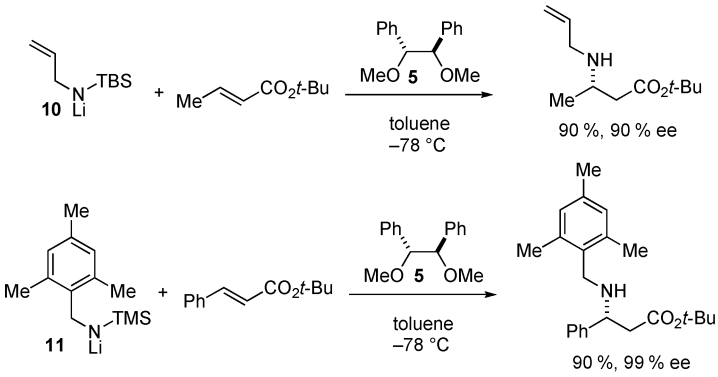
Scheme 4 Asymmetric Michael reaction of cinnamate with lithium amides.

A presence of trimethylsilyl (TMS)-chloride was beneficial to give the adduct with higher 97 % ee in 97 % yield (Scheme 5). The TMSCl trap of a lithium enolate intermediate that interferes with the lithium amide–**5** complexation is the origin of the higher efficiency [5].



Scheme 5 Asymmetric Michael reaction of enoates with **9**.

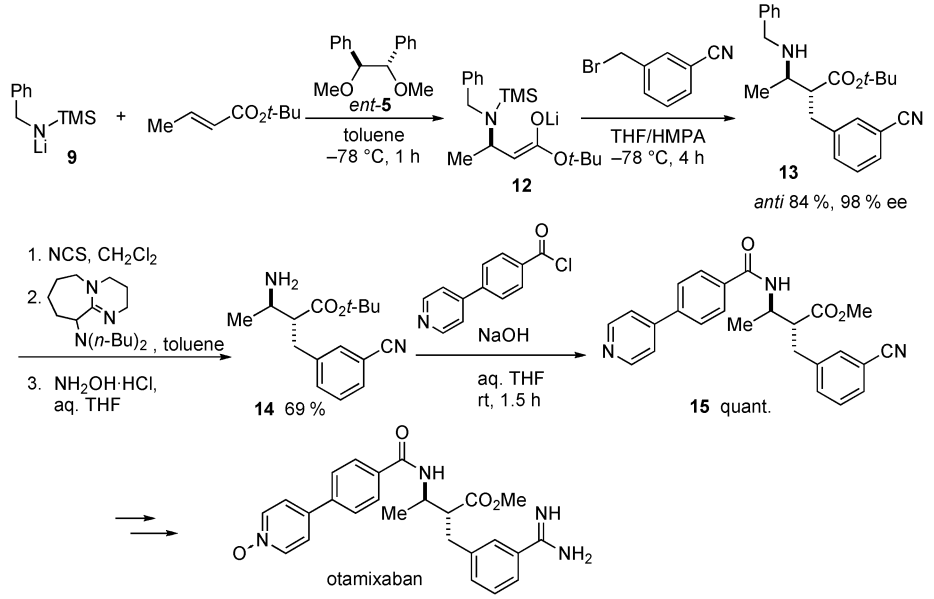
Allyl-*tert*-butyldimethylsilylamide **10** and mesitylmethyltrimethylsilylamide **11** were also good nucleophiles applicable in the highly efficient asymmetric conjugate amination (Scheme 6) [6,7].



Scheme 6 Asymmetric Michael reaction of enoates with **10** and **11**.

SHORT-STEP ASYMMETRIC SYNTHESIS OF OTAMIXABAN

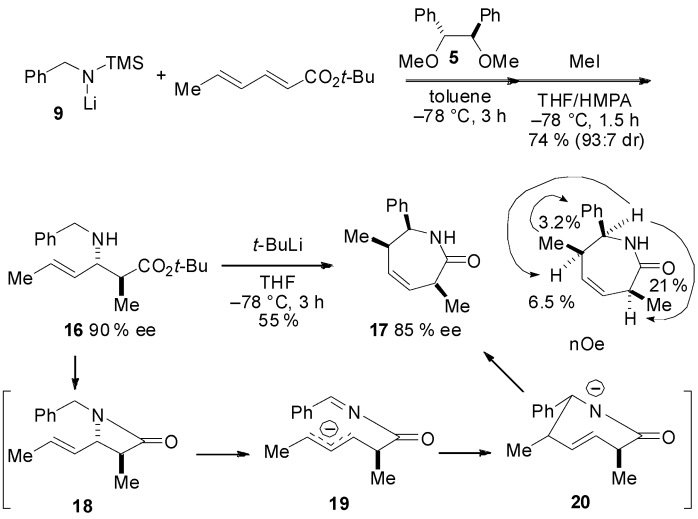
The advantage of our conjugate amination is the generation of the lithium enolate intermediate **12** that is applicable as a bond-forming reactive species (Scheme 7). Conjugate aminolithiation and subsequent alkylation tandem process of crotonate with benzyltrimethylsilylamide **9** allowed us to form vicinal N–C and C–C bonds in a one-pot operation, giving **13** with 98 % ee and 85:15 dr. Debenzylation of amine **13** was developed through oxidative imine formation and following transoximation to afford primary amine **14** [8]. Standard acylation of **14** gave **15**, the key synthetic intermediate for otamixaban in a short step [9,10].



Scheme 7 Short-step asymmetric synthesis of otamixaban.

ONE-POT STEREOSELECTIVE CONVERSION OF 3-AMINOCARBOXYLATES TO LACTAMS

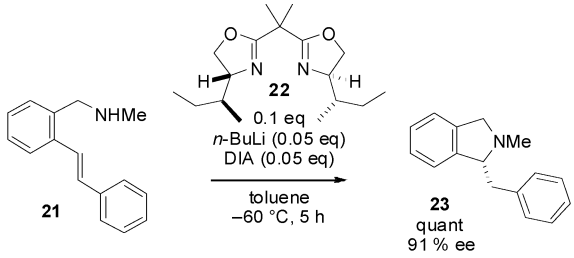
Highly *cis*-selective one-pot conversion of 3-allylamino- and 3-benzylamino-carboxylates **16** to seven-membered lactams **17** was developed by treating with *tert*-butyllithium (Scheme 8). Six reactions are involved in this transformation. The first step is a lithium amide formation that cyclizes to a β-lactam **18**. Deprotonation at the benzylic or allylic position of **18** directs the cleavage of N–C bond of the strained β-lactam ring to afford imino-anion **19** where the anion attacks an imino-carbon to complete lactam **20** formation. It is noteworthy that the formation of seven-membered lactam **20** is highly selective for *cis* while that of 5-membered lactam is *trans* selective. Two-step asymmetric and diastereoselective synthesis of enantiomerically enriched seven-membered lactam **17** is the highlight of this process [11].



Scheme 8 Two-step asymmetric and stereoselective synthesis of seven-membered lactam **17** bearing three stereogenic centers.

ASYMMETRIC HYDROAMINATION OF OLEFINS

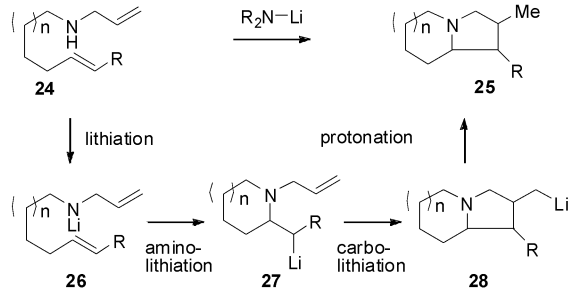
The technology of asymmetric conjugate aminolithiation of enoates is capable of extending to asymmetric intramolecular aminolithiation of rather simple olefins. An aminoolefin **21** is treated with butyllithium to generate a lithium amide, hopefully complexed with **22**. A crossover of a Li–N bond with a C–C double bond affords an aminolithiated compound available for protonation with **21** giving **23**. This cycle is changeable to a more sophisticated cycle by the protonation of the aminolithiated compound with other proto-delithiation agents like diisopropylamine (DIA). In the presence of 0.05 equiv of DIA, treatment of **21** with 0.05 equiv of butyllithium and 0.1 equiv of bisoxazoline (BOX) ligand **22** in toluene at –60 °C for 5 h gave the hydroamination product **23** with 91 % ee quantitatively (Scheme 9) [12].



Scheme 9 Catalytic asymmetric hydroamination of **21**.

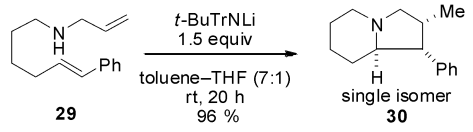
TANDEM AMINOLITHIATION AND CARBOLITHIATION OF ALLYLAMINOALKENES

Lithiation of allylaminoolefins **24** to lithium amides **26** provides a chance for aminolithiation over C–C double bond to give **27** whose protonation resulted in hydroamination (Scheme 10). Carbolithiation of **27** would give us a chance to yield **28** that upon protonation affords double cyclization products **25** [13].



Scheme 10 Aminolithiation and carbolithiation tandem process.

This scenario was realized by treating **29** with a bulky lithium amide to give **30** in 96 % yield (Scheme 11). Stereoselectivity was high as shown. The bulky amine seems to selectively protonate less bulky **28** instead of relatively crowded **27**.



Scheme 11 Double cyclization by aminolithiation and carbolithiation.

CONCLUSION

The chiral lithiophilic ligand-controlled asymmetric conjugate aminolithiation of enoates with a lithium amide provided two ways by which 3-amino esters and 3-amino-2-substituted esters are produced. In a one-pot, stereoselective formation of vicinal C–N and C–C bonds was possible. 3-Allylamino- and 3-benzylaminoesters were proven to be good precursors for the one-pot highly stereoselective conversion to five- and seven-membered lactams. The aminolithiation technology was extended to catalytic asymmetric hydroamination of aminoolefins. Furthermore, the aminolithiation–carbolithiation tandem

process was also developed. Application of these reactions to the synthesis of biologically important compounds is in progress in our laboratory.

ACKNOWLEDGMENTS

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