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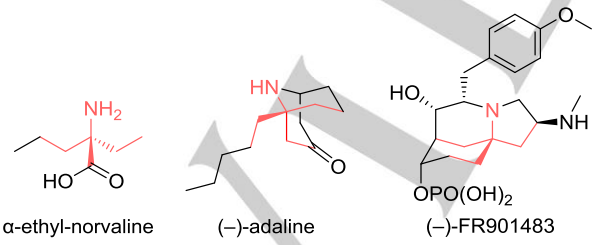
Asymmetric Synthesis of Less Accessible α-Tertiary Amines from Alkynyl *Z*-Ketimines

Taichi Kano*, Yusuke Aota, and Keiji Maruoka*

Abstract: A highly stereoselective synthesis of hitherto less accessible chiral α-tertiary amines having structurally similar, multiple linear carbon chains was achieved through chiral auxiliary mediated addition of organolithium reagents to the geometrically well-controlled alkynyl *Z*-ketimines. This stereoselective nucleophilic addition offers a general approach to the asymmetric synthesis of nitrogen-containing chiral materials.

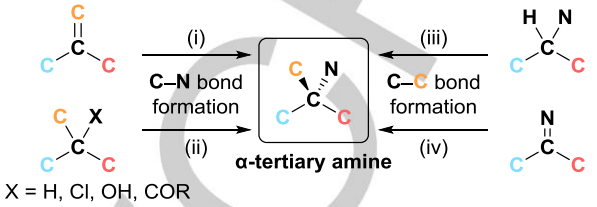
Chiral α-tertiary amines contain a tetrasubstituted carbon atom bearing one nitrogen atom and three different carbon substituents. They are fundamental and frequent motifs in naturally occurring and synthetic bioactive compounds.[1] Among them, nonproteinogenic α,α-dialkyl-α-amino acids, for instance, have attracted considerable interest in medicinal chemistry and peptide science due to their unique property.[2,3] The development of efficient methods for synthesis of chiral α-tertiary amines including such amino acids remains an important challenge in organic synthesis. In this context, we are interested in synthesis of hitherto less accessible chiral α-tertiary amines having structurally similar, multiple linear carbon chains (Figure 1). Conventionally, tetrasubstituted carbon centers of α-tertiary amines are constructed through various carbon–carbon bond or carbon–nitrogen bond forming reactions (Scheme 1).[4–16] Accessing chiral α-tertiary amines having multiple alkyl substituents in an optically pure form is not trivial; however, some methods utilizing 3,3-sigmatropic rearrangement[5], 1,2-rearrangement[6], asymmetric alkylation[7,8] or asymmetric 1,2-addition[9] have been developed for the asymmetric synthesis of these compounds.

Among such synthetic methods, the 1,2-addition of a carbon nucleophile to a ketimine is the most reliable and straightforward way to construct a tetrasubstituted carbon bearing a nitrogen atom.[9–16] A high level of enantiofacial discrimination of the



α-ethyl-norvaline (–)-adaline (–)-FR901483

Figure 1. Examples of bioactive compounds bearing an α-tertiary amine core.



Scheme 1. Current approaches for stereoselective synthesis of α-tertiary amines: (i) 3,3-sigmatropic rearrangement; (ii) electrophilic amination (X = H), metal-mediated C–N coupling (X = Cl), nucleophilic substitution with nitrogen nucleophiles (X = OH) or carbon to nitrogen 1,2-rearrangement (X = COR); (iii) deprotonation and asymmetric alkylation with carbon electrophiles; (iv) asymmetric addition of carbon nucleophiles to ketimines.

ketimine by utilizing a chiral catalyst or a chiral auxiliary is crucial for asymmetric synthesis of α-tertiary amines. The geometry of the *N*-substituent of the ketimine affect dramatically the enantioselectivity.[11,12,17] The *E*/*Z* ratio of the ketimine is dependent on the difference in size of the ketimine substituents. Due to rapid *E*/*Z* isomerization, the significant size difference between both substituents on the imine carbon is required to render one geometric isomer more favorable.[11] For instance, ketimines bearing both a small substituent (e.g., methyl) and a large substituent (e.g., isopropyl, *tert*-butyl and phenyl), which exist as single geometric isomers, tend to show high levels of stereoselectivity in asymmetric addition of carbon nucleophiles.[9–16] On the other hand, the ketimine with two similar alkyl groups exists as an inseparable mixture of nearly equal amounts of *E*- and *Z*-ketimines and inevitably yields the addition product in low stereoselectivity even using the reliable chiral auxiliary-based methods (Scheme 2a).[11] In other words, asymmetric synthesis of chiral α-tertiary amines having multiple similar alkyl groups (e.g., ethyl, propyl and butyl) is not possible through the most direct route based on the asymmetric nucleophilic addition to ketimines.

We proposed that we could generate preferentially one geometric isomer of ketimine having two different carbon chains and access chiral α-tertiary amines, previously unavailable from an *E*/*Z*-mixture of dialkyl-substituted ketimines. This could be achieved by replacing one alkyl substituent of the ketimine with a sterically less hindered alkynyl group and use of the Ellman's chiral auxiliary (Scheme 2b).[13,14] The steric repulsion between the alkyl substituent and the chiral auxiliary enforces the strong preference for the *Z*-ketimine leading to high stereoselectivity through a highly organized transition state. Hydrogenation of the resulting addition products provides chiral α-tertiary amine derivatives as synthetically challenging structural motifs.

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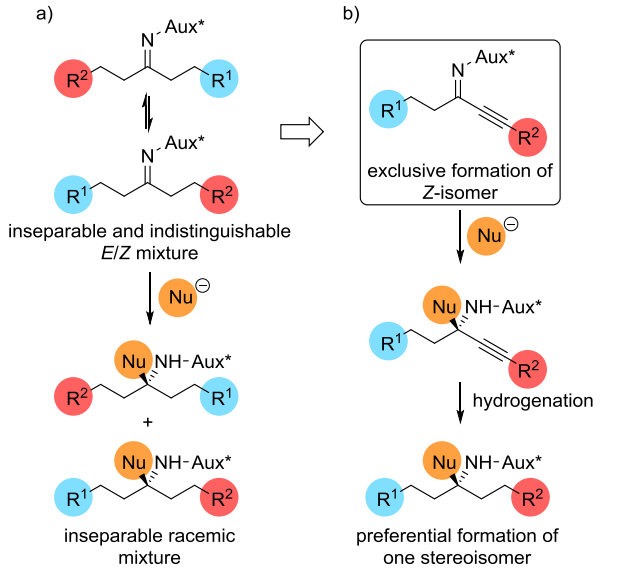
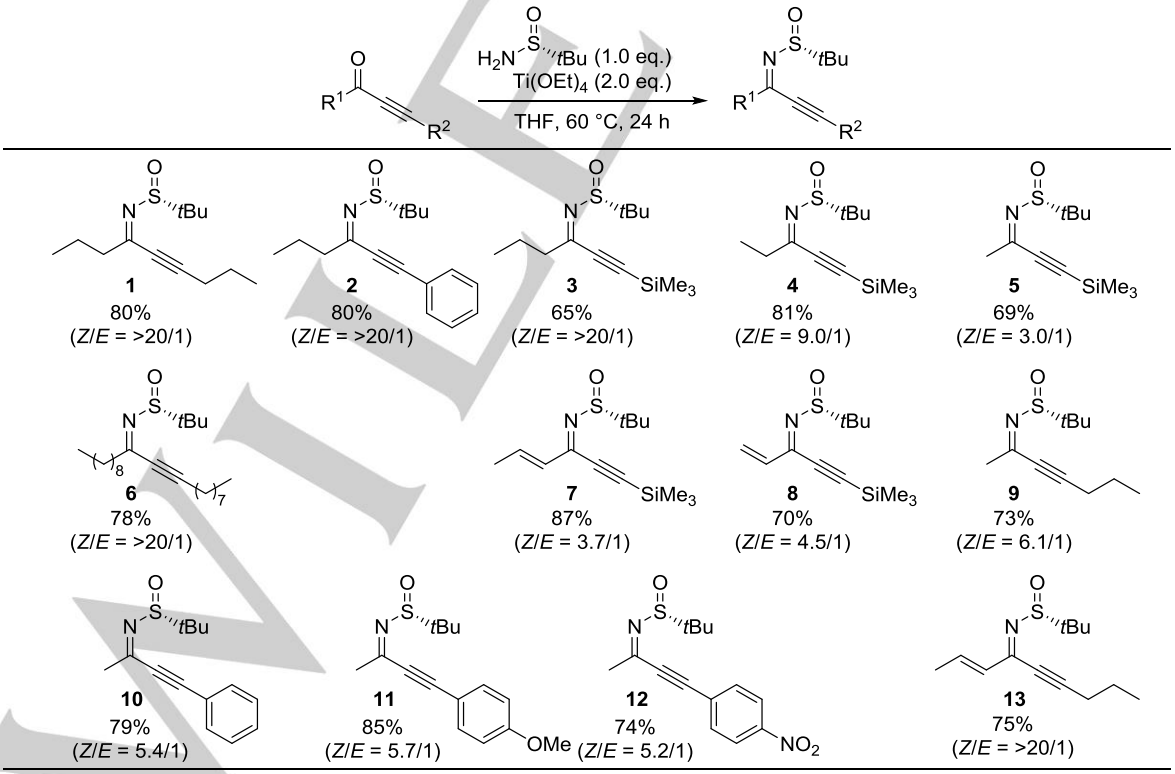


Scheme 2. a) Nucleophilic addition to a *E*/*Z* mixture of the dialkyl-substituted ketimine leading to the racemic α-tertiary amine. b) A new approach to the asymmetric synthesis of α-tertiary amines by stereoselective addition to *Z*-ketimines bearing an alkynyl substituent. Aux* = chiral auxiliary.

Ketimines having both alkyl and alkynyl substituents were prepared to probe whether the steric difference between linear alkyl and alkynyl groups is sufficient to preferentially afford one geometric isomer for asymmetric synthesis. Dehydrative condensation of various alkynyl ketones with (*R*)-*tert*-butanesulfinamide gave the corresponding alkynyl-substituted ketimines, and the effects of the other substituent on the *E*/*Z* ratio were investigated. The results are summarized in Table 1. In the case of alkynyl ketimines with a propyl substituent, *Z*-isomers were observed exclusively in the ^{1}H-NMR spectrum (Table 1, **1**, **2** and **3**).[15] Decreasing the size of the imine alkyl group to ethyl and methyl led to a gradual increase in the ratio of the *E*-isomer to the *Z*-isomer (**4** and **5**). Replacement of propyl or ethyl group with 1-propenyl or vinyl group, respectively, also resulted in increased amounts of the *E*-isomer (**7** and **8**). These results indicate that the alkyl group is sterically more hindered compared to the alkenyl group with the same length of carbon chain. Consequently the alkynyl ketimine having an alkyl group, which exists as the *Z*-isomer, was found to be more suitable for use in asymmetric synthesis. Additionally, the *E*/*Z* ratio of ketimines was affected significantly by steric factors of the ketimine substituents, because electronic perturbations of the phenylethynyl group had little effect on the *E*/*Z* ratio of ketimines (**10**, **11** and **12**).

We then examined the asymmetric synthesis of α-tertiary amines by diastereoselective addition of organometallic reagents to the geometrically controlled *Z*-ketimine. Treatment of *Z*-ketimine **1** with ethyllithium in toluene at –40 °C led to the formation of α-tertiary amine derivative **14** with high diastereoselectivity (Table 1, Entry 1). Use of either ethylmagnesium bromide or diethylzinc resulted in low yield even at higher temperature (Entries 2 and 3). With a Lewis acid such as trimethylaluminum, which is known to be effective in increasing yield and diastereoselectivity,[11] the improved result was obtained

Table 1. Dehydrative condensation of alkynyl ketones with (*R*)-*tert*-butanesulfinamide.[a]



[a] Reactions were performed on a 5.0 mmol scale in 10 mL of THF. Isolated yield. *Z*/*E* ratio determined by ^{1}H NMR spectroscopy in C_6D_6 at 25 °C.

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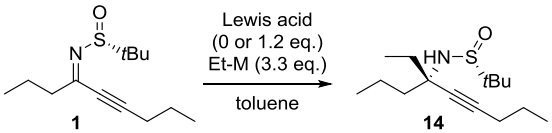
(Entry 4). The reaction of the aluminum ate complex generated from trimethylaluminum and ethyllithium did not proceed with or without using trimethylaluminum as Lewis acid (Entries 5 and 6). These results indicate that the aluminum Lewis acid forms a reactive complex with the ketimine to promote the reaction.

Table 2. Addition of organometallic reagents to Z-ketimine **1**.[a]



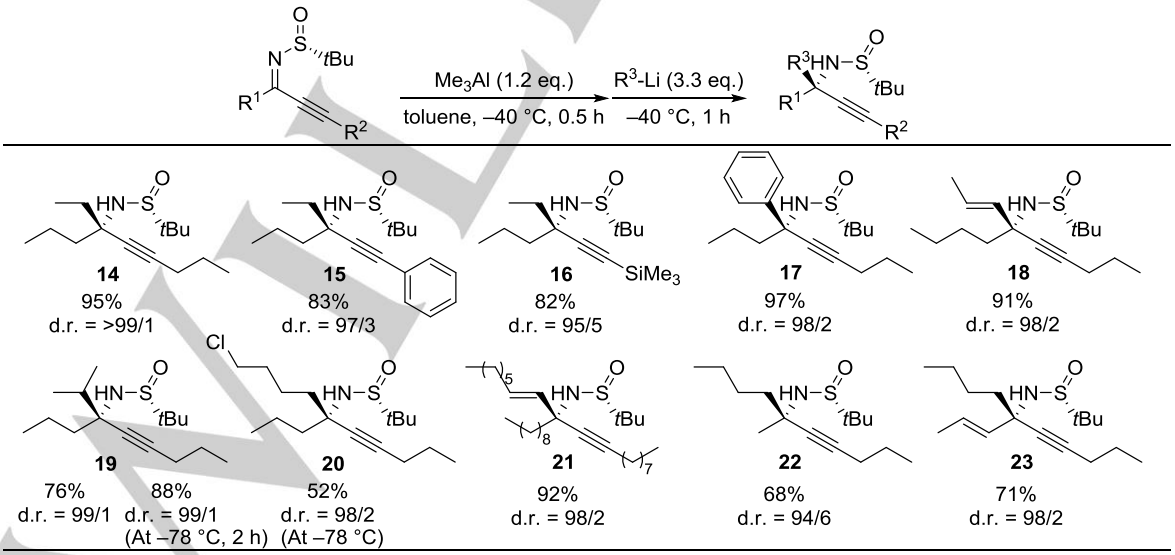
Entry	R-M	Lewis acid	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]
1	EtLi	-	–40	1	73	98/1
2	EtMgBr	-	0	1	18	n.d.
3	Et_2Zn	-	RT	3	<5	n.d.
4	EtLi	Me_3Al	–40	0.5	95	>99/1
5	$LiAlEtMe_3$	-	–40	3	0	n.d.
6	$LiAlEtMe_3$	Me_3Al	–40	3	0	n.d.

[a] Reactions were performed on a 0.2 mmol scale in 1.0 mL of toluene. [b] Isolated yield. [c] Diastereomeric ratio (d.r.) was determined by chiral HPLC after exchanging chiral auxiliary with benzyloxycarbonyl group. n.d. = not determined.

Under the optimized reaction conditions, the generality of the stereoselective addition of organolithium reagents to *Z*-ketimines was examined by varying the substrate combinations and the results were summarized in Table 3. In the case of ethyllithium, propyl, phenyl- and trimethylsilyl-substituted alkynyl ketimines gave the corresponding α-tertiary amine derivatives in good yields and high diastereoselectivities, while the steric hindrance on the alkynyl terminus slightly affected the diastereoselectivity (**14**, **15** and **16**). Similar results were observed when phenyllithium and 1-propenyllithium were used as nucleophiles (**17** and **18**). While use of isopropyllithium gave the addition product **19** in low yield due to undesired side reactions such as 1,2-hydride addition and deprotonation, lowering the reaction temperature led to the improved yield of **19**. The reaction of 4-chlorobutyllithium, which was generated in situ from 1-chloro-4-iodobutane and *t*-butyllithium,[18] provided **20** with high diastereoselectivity, albeit in moderate yield. The reaction of the ketimine **9** including a substantial amount of *E*-isomer with butyllithium gave the addition product **22** in higher diastereoselectivity (15.7:1) than the initial *Z*/*E* ratio of **9** (6.1:1) (see the Supporting Information for details). In the reaction of the alkenyl-substituted ketimine with butyllithium, the addition product **23**, which is the pseudo-enantiomer of **18**, was obtained in moderate yield due to a competing 1,4-addition. The observed absolute configuration of addition products, which was assigned by chemical correlation to known compounds, is in accordance with the transition state model proposed by Ellman for 1,2-addition of organolithiums to *tert*-butanesulfinyl ketimines.[11]

The utility of this method has been demonstrated in transformation of the obtained addition products to previously less accessible chiral amine derivatives (Scheme 3). Hydrogenation of **21** gave the chiral α-tertiary amine derivative **24** having similar length alkyl chains such as octyl, nonyl and decyl groups. The chiral α-tertiary amine derivative **26** bearing three slightly different alkenyl substituents was obtained by semi-hydrogenation of **25** with Lindlar's catalyst. The sulfinyl group of **20** was removed by treatment with HCl in methanol and the cyclization of the resulting amine under basic conditions gave the 2,2-disubstituted piperidine **27**. Replacement of the sulfinyl group of **18** with a Boc

Table 3. Addition of organolithium reagents to *Z*-ketimines.[a]



[a] Reactions were performed on a 0.2 mmol scale in 1.0 mL of toluene. Isolated yield. D.r. determined by chiral HPLC after exchanging chiral auxiliary with benzyloxycarbonyl group.

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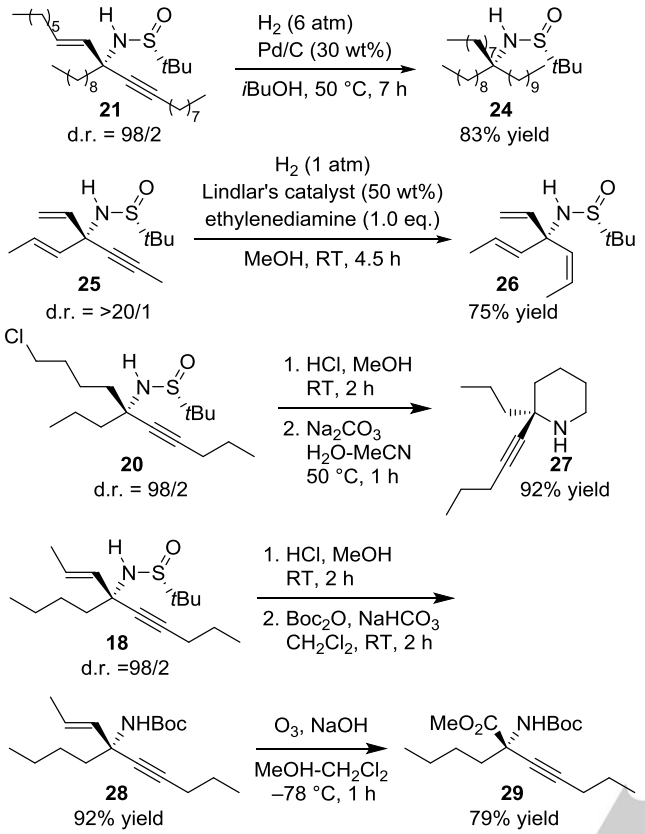

Scheme 3. Asymmetric synthesis of previously less accessible α-tertiary amines. D.r. of **25** was determined by ^{1}H-NMR.

group and the subsequent ozonolysis of the alkenyl group in methanol afforded the α,α-disubstituted amino acid derivative **29**.[2]

In summary, an asymmetric synthesis of α-tertiary amine derivatives from alkynyl-substituted *Z*-ketimines has been realized. In this process, a well-defined transition state can be achieved by introduction of *t*-butanesulfinyl group as a chiral auxiliary and an alkynyl substituent in the ketimine, leading to highly diastereoselective addition of organolithium reagents. This asymmetric addition offers a general approach to the asymmetric synthesis of α-tertiary amines having multiple linear carbon chains, and will probably find application in the synthesis of a range of nitrogen-containing chiral materials. The geometric control of ketimines in the present study may also provide a platform for development of a catalytic enantioselective nucleophilic addition to general ketimines.

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Keywords: diastereoselectivity • chiral auxiliaries • nucleophilic addition • imines • amines

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[17] The enantiofacial selectivity is highly dependent on the *E*/*Z* ratio of the ketimine in the transition state under the influence of a nucleophile and/or a catalyst, which correlates with the *E*/*Z* ratio of the ketimine alone.

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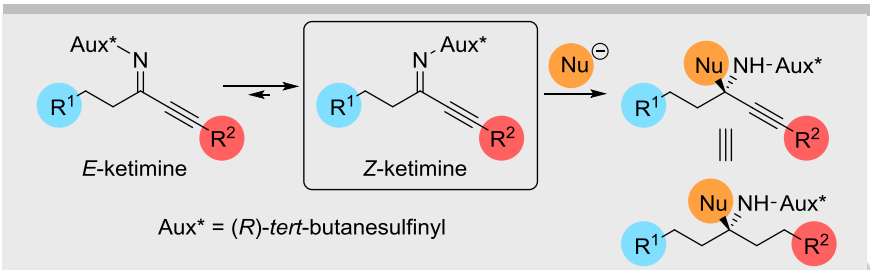

Beware beginnings: The geometrically well-controlled alkynyl *Z*-ketimines were prepared and successfully employed in the asymmetric synthesis of less accessible α-tertiary amines bearing multiple linear carbon chains through the chiral auxiliary mediated nucleophilic addition of organolithium reagents.

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