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Original article

Asymmetric hydroazidation of α-substituted vinyl ketones catalyzed by chiral primary amine

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Graphical Abstract

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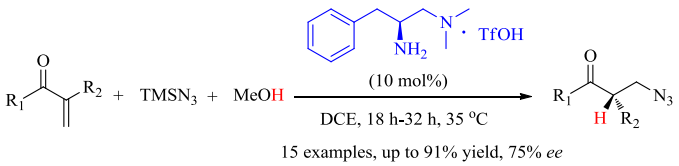

We report herein the first example of asymmetric hydroazidation of α-substituted vinyl ketones by using chiral primary amines as the catalysts. A simple chiral primary-tertiary diamine catalyst derived from L-phenylalanine was found to promote this aza-Michael addition reaction with enamine protonation as the key stereogenic step, thus enabling the effective synthesis of α-chiral β-azido ketones with good yields and moderate enantioselectivities.

ABSTRACT

We report herein the first example of asymmetric hydroazidation of α-substituted vinyl ketones by using chiral primary amines as the catalysts. A simple chiral primary-tertiary diamine catalyst derived from L-phenylalanine was found to readily promote this aza-Michael addition reaction with enamine protonation as the key stereogenic step, thus enabling the effective synthesis of α-chiral β-azido ketones with good yields and moderate enantioselectivities.

Keywords:
Chiral primary amine catalysis
Hydroazidation
Enamine protonation
α-Substituted vinyl ketones
Aza-Michael addition
Chiral β-azido ketones

1. Introduction

Organic azides are important precursors for the synthesis of *N*-containing structural motifs in organic synthesis [1] and their applications in click chemistry have also attracted intensive attentions in fields of pharmaceutical chemistry, supramolecular chemistry and material science [2]. As such, mild and efficient methods for their synthesis are of increasing importance and aza-Micahel addition of azide ion to unsaturated carbonyl compounds represents one of the most straightforward approaches for the synthesis of organic azides [3]. The resulted β-azido carbonyls could be readily converted into β-amino acids [4], an intriguing structural motif widely distributed in biologically and pharmacologically active compounds [5]. In this context, the asymmetric hydroazidation of unsaturated carbonyl compounds is highly desirable [6]. In 1999, Jacobsen and co-workers reported that chiral (salen)Al(III) complexes could effectively promote the enantioselective addition of hydrazoic acid to unsaturated imides [6b]. Subsequently, the first organocatalytic enantioselective hydroazidation of Michael acceptors was reported by Miller and co-workers by using a small peptide as the catalyst [6c-d]. Nitroalkenes have also been attempted as Michael acceptors in reaction with azide for the synthesis of optically enriched β-nitro azides, but unfortunately with limited success [6g-h]. Recently, Jang and co-workers reported a tandem reaction of enals with azide in the presence of chiral aminocatalyst and iron complex for the asymmetric synthesis of β-amino α-hydroxy aldehydes [7]. Most of these studies utilized β-substituted Michael acceptors, however, the reactions with β-unsubstituted vinyl carbonyls have not been achieved so far (Scheme 1). The most difficulty associated with this type of substrates comes from the challenging α-stereogenic protonation step.

Recently, we have developed chiral primary aminocatalysis for asymmetric conjugate addition to α-substituted acroleins and vinyl ketones with a wide range of nucleophiles [8]. These reactions feature enamine protonation as the key stereogenic step [9] and our detail mechanistic studies have disclosed a Curtin-Hammett stereocontrol for the reactions of α-substituted vinyl ketones [8f]. To further explore the potentials of this reaction, we have examined other types of nucleophiles such as azide in the reaction with α-substituted vinyl ketones. Following the established mechanistic scenario, the targeted reaction would provide a straightforward access of chiral β-azido ketones with promising enantioselectivity [8f]. In this communication, we wish to present the unprecedented stereoselective addition of azide to α-substituted vinyl ketones catalyzed by a simple chiral primary-tertiary diamine catalyst derived from L-phenylalanine.

2. Results and discussion

Our studies on this asymmetric Michael addition-protonation reaction with azide were carried out using $TMSN_3$ as the azide source. Using EtOH as the proton source, a preliminary result indicated that the vicinal primary-tertiary diamine catalyst **1** could promote the targeted reaction, with not unexpectedly low activity, but fortunately with a promising enantioselectivity (Table 1, entry 1). Further investigation led to the identification of **3a**/TfOH as the optimum catalyst system (Table 1, entries 2-9). In the presence of 10 mol% **3a**/TfOH, the reaction gave the desired product **5a** in 52% isolated yield and with 42% *ee* (Table 1, entry 3). The screening of reaction mediums demonstrated that the solvents had an obvious effect on both of the yield and stereocontrol. As can be seen from Table 1, the use of chlorinated solvent, especially 1,2-dichloroethane (DCE), could greatly improve the reaction outcome, affording the desired product in 63% isolated yield and 57% *ee* (Table 1, entry 10). Interestingly, when tetrahydrofuran was employed as solvent nearly no product could be detected (Table 1, entry 13).

Bearing in mind the dramatic effect of proton donors in enantioselective enamine protonation reactions [8], we next examined a range of proton donors, such as alcohols, water and phenols, in order to further improve the activity and stereoselectivity (Table 2). In general, the use of alcohol additives led to better results but have no significant effect on the stereocontrol and, the use of methyl alcohol afforded the product with the best yield outcome (Table 2, entry 1). Moreover, we disclosed that the drop-wise addition of $TNSN_3$ in one hour could greatly increase the enantioselectivity to 69% *ee* (Table 2, entry 10). Extensive efforts to improve the enantioselectivity were all in vain, reflecting the difficulties in controlling a stereogenic enamine protonation in this context. Nevertheless, the current results represent the best for this hydroazidation reaction with vinyl ketones. Finally, 10 mol% of **3a** as catalyst, 4.0 equipment of methyl alcohol as proton source and 1,2-dichloroethane as the solvent were chosen as the optimal conditions for our subsequent scope examination.

Under the optimal conditions, the substrate scope of the reaction was next explored. As shown in Table 3, α-substituted vinyl ketones are well tolerated in this reaction. Aromatic α-substituted vinyl ketones were identified as one class of preferred substrates, and *para*-substitution on the phenyl group bearing either electron-rich or electron-deficient substituents are equally applicable, giving the desired adducts with moderate to good enantioselectivity (Table 3, entries 2-7). Unfortunately, *meta*-substitution on the phenyl group, especially the incorporation of the elemental fluorine seems somehow detrimental to the reaction (Table 3, entries 8-11). We also found that a more bulky α-substituted group could lead to a sharp drop of the enantioselectivity (Table 3, entries 13-15).

To evaluate the practicality of this methodology, the Staudinger reduction procedure was performed to furnishe the α-chiral β-amino ketone **5a** in good isolated yield, and erosion of the enantioselectivity was observed, likely a result of the subsequent non-optimized basic reaction conditions (Scheme 2). Meanwhile, the click reaction between **5a** and **7** can also be readily achieved, affording the

benzotriazole addition product **8** in excellent yield.

3. Conclusion

In summary, we have developed the first example of asymmetric conjugate addition-protonation reactions of trimethylsilylazide to α-substituted vinyl ketones by chiral primary amine catalysis. The reaction proceeds under very mild reaction conditions and further synthetic modification of the products could provide chiral β-amino ketones or related compounds easily in one step.

4. Experimental

General procedure for chiral primary amine catalyzed asymmetric hydroazidation of α-substituted vinyl ketones: Catalyst **3a**/ TfOH (10 mol%), α-substituted vinyl ketone **4** (0.2 mmol) and methanol (0.4 mmol) in 0.5 mL 1,2-dichloroethane at 35 ^{o}C. To the mixture, trimethylsilylazide (0.1 mmol) was added in 0.5 mL DCE to this tube in 1 h and the progress of the reaction was monitored by TLC. After completion, the reaction mixture was directly separated by flash column chromatography on silica gel eluting with a mixture of petrol ether and EtOAc (PE/EA: 20/1). Collected fractions were concentrated under vacuum to afford the desired product. The characterization data of the products are summarized in the Supporting information.

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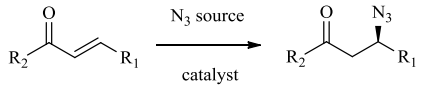

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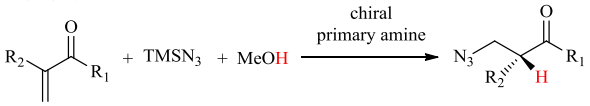
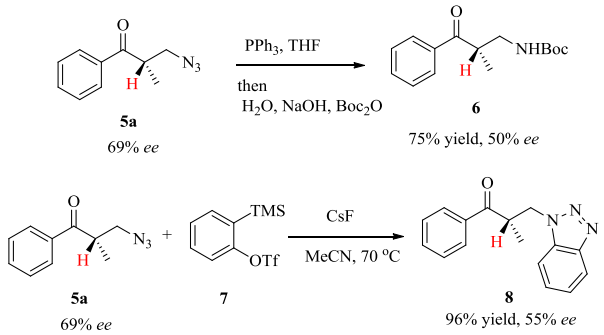


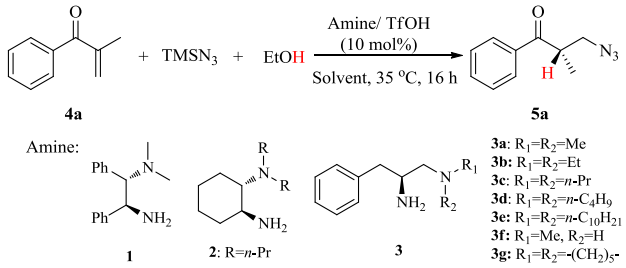
Scheme 1. Asymmetric Michael addition of trimethylsilylazide to enones.



Scheme 2. Transformations of the azido adducts.

Table 1

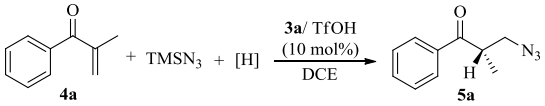
Screening of catalysts and solvents. [a]



Entry	Amine	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**1**	$CHCl_3$	8	44
2	**2**	$CHCl_3$	12	5
3	**3a**	$CHCl_3$	52	42
4	**3b**	$CHCl_3$	51	41
5	**3c**	$CHCl_3$	50	23
6	**3d**	$CHCl_3$	45	19
7	**3e**	$CHCl_3$	45	18
8	**3f**	$CHCl_3$	8	46
9	**3g**	$CHCl_3$	81	4
10	**3a**	DCE	63	57
11	**3a**	PhH	42	25
12	**3a**	CH_3CN	5	33
13	**3a**	THF	Trace	-

[a] General conditions: **4a** (0.20 mmol), trimethylsilylazide (0.10 mmol), EtOH (0.4 mmol), amine/TfOH (10 mol%) in solvent (0.10 mol/L) at 35 °C, 16 h.
[b] Isolated yields.
[c] Determined by chiral HPLC.

Table 2
Screening of proton sources. [a]



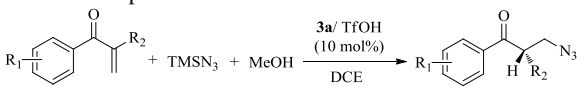
4a **5a**

Entry	Proton	Yield (%)[b]	*ee* (%)[c]
1	MeOH	77	58
2	EtOH	63	57
3	BnOH	57	57
4	H_2O	49	57
5	PhOH	28	56
6	*t*-BuOH	34	45
7	CF_3CH_2OH	60	46
8	PhCOOH	40	30
9	Ethylene glycol	34	19
10	MeOH[d]	72	69

[a] General conditions: **4a** (0.20 mmol), trimethylsilylazide (0.10 mmol), proton source (0.4 mmol), **3a**/TfOH (10 mol%) in DCE (0.10 mol/L), 5 °C, 16 h.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] Trimethylsilylazide was add in 1 h.

Table 3

Substrate scope. [a]



4 **5**

Entry	R_1	R_2	Product [b]	Time (h)	Yield (%)	*ee* (%)[c]
1	H	Me	**5a**	16	72	69
2	4-F	Me	**5b**	16	76	70
3	4-Cl	Me	**5c**	16	78	70
4	4-Br	Me	**5d**	16	91	75
5	4-OMe	Me	**5e**	20	78	69
6	4-CF_3	Me	**5f**	24	67	59
7	4-Et	Me	**5g**	16	90	45
8	3-F	Me	**5h**	20	72	44
9	3-Cl	Me	**5i**	20	74	55
10	3-Br	Me	**5j**	20	76	54
11	3-OMe	Me	**5k**	24	79	38
12	3-Br,4-F	Me	**5l**	24	69	56
13	H	Et	**5m**	20	68	43
14	H	n-Pr	**5n**	24	68	11
15	H	Bn	**5o**	32	56	16

[a] General conditions: **4** (0.20 mmol), trimethylsilylazide (0.10 mmol), MeOH (0.4 mmol), **3a**/TfOH (10 mol%) in DCE (0.10 mol/L) at 35 °C, at 1 h, trimethylsilylazide was add.

[b] Isolated yields.

[c] Determined by chiral HPLC.