

Enantioselective Formal Alkenylations of Imines Catalyzed by Axially Chiral Dicarboxylic Acid Using Vinylogous Aza-Enamines**

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Catalytic asymmetric synthesis of chiral allylic amines has been an extensively studied research field owing to their remarkable synthetic versatility. In this context, catalytic asymmetric alkenylation of imines, though considered to be quite a straightforward process, has only recently become an attractive option toward this end, following the prevalence of asymmetric allylic amination.^[1] The rapidly growing field of organocatalysis has played a pivotal role in this latest development as can be seen in the asymmetric Petasis reaction,^[2] which gives chiral allylic amines with an electron-rich alkene group being transferred from the corresponding alkenyl boron species.^[3–6] The organocatalytic aza-Morita–Baylis–Hillman reaction, wherein α,β -unsaturated carbonyl compounds formally act as an alkenyl anion at their α position via a catalytically generated ionic intermediate, constitutes another important strategy to afford chiral allylic amines with an electron-withdrawing alkene moiety.^[7]

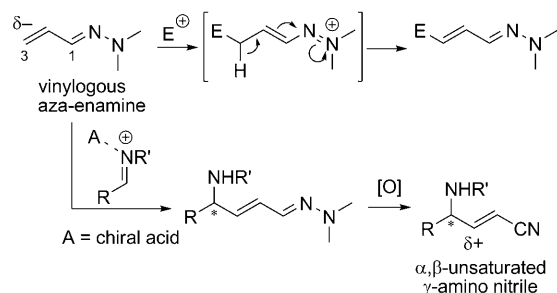
Vinylogous aza-enamines (hydrazones; Scheme 1),^[8] which can be easily prepared by the condensation of the corresponding α,β -unsaturated aldehydes and *N,N*-dialkylhydrazines, are known to be a class of umpolung species.^[9] These species exhibit nucleophilic character at the C1 and C3 positions (β position) as a result of the electron-donation from the *N,N*-dialkylamino group.^[10] Their reactions at C3

with highly electrophilic reagents have been sporadically reported in the literature,^[11,12] and its reaction mechanism is understood to proceed via the initial formation of the ionic intermediate and successive deprotonation to regenerate the alkene moiety. Although this fundamental understanding clearly implies the possibility of applying the catalytically activated prochiral substrates as electrophile in the reaction with vinylogous aza-enamines to formally realize asymmetric alkenylations, there has been no example reported to date realizing this appealing objective.^[13]

Herein we report the exploitation of this intriguing but yet unexplored property of vinylogous aza-enamines in axially chiral dicarboxylic acid catalyzed formal alkenylation of imines (vinylogous imino aza-enamine reaction), which is distinctive in that the reaction system generates highly enantioenriched chiral allylic amines while obviating the need for any kind of metallic sources in the catalyst and substrates. Furthermore, as an aza-enamines moiety can be easily converted into a nitrile group by treatment with a peracid, this is considered to be a facile method for the asymmetric alkenylation with acrylonitrile and its analogues at the intrinsically electron-deficient β -carbon atom realized by the reactivity umpolung, thus this process is complementary to aza-Morita–Baylis–Hillman reactions.

In general, the main obstacle on the use of aza-enamines in asymmetric catalysis lies in the difficulty to attain high enantioselectivities despite some landmark endeavors.^[14] In this context, we have recently reported that axially chiral dicarboxylic acid, originally developed in our research group,^[15] has a remarkable ability to achieve an excellent level of enantioselectivities in the asymmetric addition of formaldehyde- and arylaldehyde-derived aza-enamines to various *N*-Boc imines (imino aza-enamine reaction).^[14a,b,16] Based on this study, we set out to examine the axially chiral dicarboxylic acid catalyzed addition of the vinylogous aza-enamine **2a** (derived from acrolein) to benzaldehyde *N*-Boc imine (Table 1, entry 1). In this preliminary study, it immediately became obvious that the application of the reaction conditions optimized in our previous study was completely ineffective for this specific reaction system. The reaction was very sluggish, and the alkenylation product was obtained in less than 20 % yield as an *E/Z* mixture. Even worse, almost no asymmetric induction was observed for the major *E* isomer, thus requiring the development of a completely new reaction system.^[17]

Among the various parameters to be modified, replacement of the *N*-protecting group of the imine was found to have a significant effect. Namely, subjection of benzaldehyde *N*-benzoyl imine to the otherwise identical reaction conditions furnished the desired product as a 2.3/1 mixture of *E/*



Scheme 1. Reaction mode of vinylogous aza-enamines.

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Table 1: Optimization of the reaction conditions.^[a]

Reaction scheme showing the asymmetric allylation of an imine (Ph-CH=N-R) with an azide (2a) catalyzed by (R)-1 (5 mol%) in CH₂Cl₂ at 0 °C for 24 h, yielding a chiral allylamine product (Ph-CH=N-R-CH=CH-N₃).

Chemical structures of catalysts (R)-1a, (R)-1b, and (R)-1c are shown, which are based on a 2,6-dimethyl-4-(1-adamantyl)phenyl group. The substituents R' are defined as:

- 1a**: R' = *t*Bu
- 1b**: R' = Me
- 1c**: R' = Ad

Entry	R	Cat.	Solvent	Yield [%] ^[b]	<i>E/Z</i> ^[c]	<i>ee</i> [%] ^[d] (<i>E/Z</i>)
1	Boc	1a	CH ₂ Cl ₂	< 20	n.d.	1:–
2	Bz	1a	CH ₂ Cl ₂	62	2.3:1	74:53
3	Bz	1b	CH ₂ Cl ₂	65	2.0:1	79:57
4	Bz	1c	CH ₂ Cl ₂	77	2.3:1	79:57
5	Bz	1c	toluene	67	1.6:1	79:43
6	Bz	1c	(CH ₂ Cl) ₂	81	2.9:1	80:71
7 ^[e]	Bz	1c	(CH ₂ Cl) ₂	88	3.0:1	86:80
8 ^[f]	Bz	1c	(CH ₂ Cl) ₂	63	2.9:1	87:81
9 ^[g]	Bz	1c	(CH ₂ Cl) ₂	87 ^[h]	3.3:1	91:87

[a] Reactions were performed with the imine (0.10 mmol) and **2a** (0.12 mmol) in the presence of 5 mol% of (*R*)-**1** (0.005 mmol). [b] Combined yield of *E* and *Z* isomers determined by ¹H NMR spectroscopy of the crude mixture using an internal standard (nitromethane). [c] Determined by ¹H NMR spectroscopy of the crude mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Performed at –20 °C. [f] Performed at –35 °C. [g] Performed at –35 °C for 48 hours with 10 mol% of (*R*)-**1c** (0.010 mmol). [h] Yield of isolated product. Boc = *tert*-butoxycarbonyl, Bz = benzoyl, M.S. = molecular sieves, n.d. = not determined.

Z isomers in fairly good yield with a promising 74% *ee* for the *E* isomer (Table 1, entry 2). Notably, no product arising from the bond formation at the C1-position of the vinylogous aza-enamine was detected, nor was an isomerization of the *E* and *Z* isomers observed under the reaction conditions. To further increase the selectivity, we then turned our attention to the modification of the 3,3'-aryl groups of the catalyst. Replacement of the 4-substituent of the aryl group by a methyl or a 1-adamantyl (Ad) group led to substantial improvement of the enantioselectivity (Table 1, entries 3 and 4). Because the dicarboxylic acid (*R*)-**1c** bearing the 2,6-dimethyl-4-(1-adamantyl)-phenyl group was found to have a broader generality than (*R*)-**1b** in the successive study, (*R*)-**1c** was set as an optimal catalyst. Additional optimization with regard to solvents and temperatures led to the reaction conditions using 1,2-dichloroethane as the solvent at –35 °C (Table 1, entries 5–8). Under these conditions, a drastic increase of the enantioselectivity for the *Z* isomer was observed, thus dissipating the selectivity gap between *E* and *Z* isomers. Finally, we opted for an increase in catalyst loading to 10 mol%, in which the *E* and *Z* isomers could be isolated in 87% combined yield with 91% *ee* for the *E* isomer (87% *ee* for the *Z* isomer; Table 1, entry 9). Notably, the isolated *Z* isomer could be isomerized to the thermodynamically favored *E* isomer (*E/Z* ratio = 13:1) without deterioration of the enantioselectivity by treatment with acetic acid at room temperature.^[18]

With the optimized conditions in hand, we moved our attention to an investigation of applicable *N*-benzoyl imines as summarized in Table 2. Regardless of the substitution

Table 2: Formal alkenylations of imines catalyzed by axially chiral dicarboxylic acid using vinylogous aza-enamines.^[a]

Entry	R ¹	R ²	Yield [%] ^[b]	<i>E/Z</i> ^[c]	<i>ee</i> [%] ^[d] (<i>E/Z</i>)
1	Ph	H (2a)	87 (3a)	3.3:1	91:87
2	4-tolyl	H (2a)	82 (3b)	3.8:1	92:90
3	3-tolyl	H (2a)	81 (3c)	2.3:1	90:90
4	2-tolyl	H (2a)	71 (3d)	3.9:1	93:93
5	2-Np	H (2a)	79 (3e)	3.2:1	90:90
6	4-ClC ₆ H ₄	H (2a)	87 (3f)	4.1:1	93:88
7	4-MeOC ₆ H ₄	H (2a)	72 (3g)	3.0:1	90:87
8	Ph	Me (2b)	83 (3h)	1.2:1	90:63
9	Ph	<i>i</i> Pr (2c)	77 (3i)	1.5:1	89:71

[a] Reactions were performed with the imine (0.10 mmol) and **2** (0.12 mmol) in the presence of 10 mol% of (*R*)-**1c** (0.010 mmol). [b] Combined yield of *E* and *Z* isomers. [c] Determined by ¹H NMR spectroscopy of the crude mixture. [d] Determined by HPLC analysis using a chiral stationary phase. Np = naphthyl.

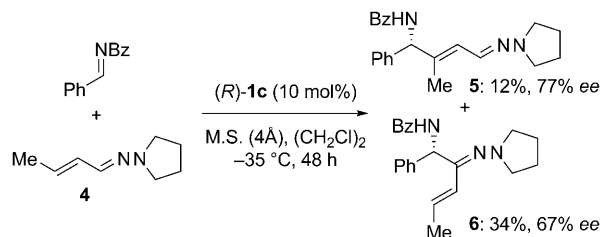
patterns of the aromatic ring, reactions proceeded without difficulty and gave the products **3** in high yields as a mixture of *E/Z* isomers in favor of the *E* isomer (Table 2, entries 2–4). In these cases, the enantioselectivities of the *E* and *Z* isomers were almost identical ranging from 90 to 93% *ee*. An *N*-benzoyl imine compound bearing a 2-naphthyl group could be employed as well, and gave the *E* isomer with 90% *ee* (Table 2, entry 5). Use of imines bearing electron-withdrawing and electron-donating functionalities was also tolerated (Table 2, entries 6 and 7).

As for the substrate scope with regard to vinylogous aza-enamines, attachment of a methyl group at the C2-position (**2b**) resulted in the formation of an almost equal amount of the *E* and *Z* isomers (Table 2, entry 8). Whereas the enantiomeric excess of the *E* isomer remained high (90%), that of the *Z* isomer was found to be modest. This tendency was further strengthened when the more bulky 2-isopropyl-substituted vinylogous aza-enamine **2c** was used as substrate, giving the *Z* isomer as a major product (*E/Z* = 1.5:1) with 71% *ee* (Table 2, entry 9). These results imply that *E* and *Z* regioisomers may possibly be generated via a different transition state, though further research is needed to elucidate this discrepancy.

On the other hand, introduction of a C3-substituent to vinylogous aza-enamines generally led to a decrease of the reactivity and the formation of two regioisomeric adducts, probably owing to the steric hindrance at the C3-position. For example, use of the crotonaldehyde-derived vinylogous aza-enamine **4** under the identical reaction conditions furnished the C3-adduct **5** in 12% yield with 77% *ee* as a single

E isomer, concomitant with a considerable amount of the C1-adduct **6** (34 %; Scheme 2).

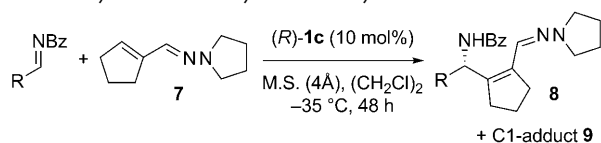
A unique and notable exception with regard to the reaction of the C3-substituted vinylogous aza-enamines, is



Scheme 2. Use of vinylogous aza-enamines substituted at the C3-position.

the use of the vinylogous aza-enamine **7** derived from cyclopentenecarbaldehyde (Table 3). In the reaction with benzaldehyde *N*-benzoyl imine, the C3-adduct **8a** was

Table 3: Use of cyclopentenecarbaldehyde-derived vinylogous aza-enamines in axially chiral dicarboxylic acid catalysis.^[a]



Entry	R	8/9 ^[b]	Yield [%] ^[b]	ee [%] ^[d]
1	Ph	5.3:1	80 (8a)	92
2	4-tolyl	8.3:1	79 (8b)	92
3	3-tolyl	8.8:1	82 (8c)	90
4	2-tolyl	0.7:1	39 (8d)	84
5	2-Np	3.1:1	73 (8e)	90
6	4-ClC ₆ H ₄	5.4:1	77 (8f)	92
7	4-MeOC ₆ H ₄	14:1	72 (8g)	85

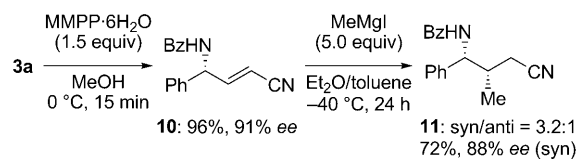
[a] Reactions were performed with the imine (0.10 mmol) and **7** (0.12 mmol) in the presence of 10 mol% of (*R*)-**1c** (0.010 mmol).

[b] Determined by ¹H NMR spectroscopy of the crude mixture. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase.

obtained as a major regioisomer (5.3:1) in 80 % yield of isolated product with 92 % *ee* (Table 3, entry 1). As this reaction would be a distinguished organocatalytic method for the asymmetric addition of the cycloalkenyl moiety to imines, we then examined the substrate scope with respect to imine compounds. In the reactions of tolualdehyde *N*-benzoyl imines, 3- and 4-tolualdehyde-derived imines were successfully converted into the desired products with good regio- and enantioselectivities (Table 3, entries 2 and 3), whereas attachment of a substituent at the 2-position was found to be detrimental for the regioselectivity (Table 3, entry 4). Use of 2-naphthaldehyde derived imine furnished the C3-adduct in 73 % yield with 90 % *ee* (Table 3, entry 5). The electronic

property of the substituent also affected the regioselectivity although the reaction proceeded in high yields and enantioselectivities (Table 3, entries 6 and 7).

Finally, synthetic application of thus obtained allylic amine **3a** was investigated as shown in Scheme 3. Trans-



Scheme 3. Preparation of chiral γ -amino nitriles.

formation of the aza-enamine moiety into the nitrile compound could be facilitated by a conventional oxidation procedure using MMPP (magnesium monoperoxyphthalate) and gave the α,β -unsaturated γ -amino nitrile **10** in 96 % yield without deterioration of the enantioselectivity.^[19] By taking advantage of the electron-withdrawing nature of the unmasked alkene moiety, this material was then treated with a Grignard reagent to give β -substituted γ -amino nitrile **11**. Consequently, addition of methyl magnesium iodide at low temperature in toluene led to the formation of the desired compound in 72 % yield with moderate diastereoselectivity in favor of the syn isomer.

In conclusion, we have succeeded in the use of vinylogous aza-enamines as a source of an alkenyl group in highly enantioselective formal alkenylations of imines catalyzed by axially chiral dicarboxylic acid. Owing to the ease of the oxidative transformation of an aza-enamine moiety into a nitrile compound, the synthetic method reported here offered facile access to enantiomerically enriched γ -amino α,β -unsaturated nitriles, which in turn could be easily modified to prepare the synthetically important chiral γ -amino acids. To the best of our knowledge, this study is the first example in which the synthetic potential of vinylogous aza-enamine could be actually demonstrated in asymmetric catalysis. Exploration of the further application of vinylogous aza-enamines in other asymmetric catalyses is currently underway in our laboratory.

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