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Diastereo- and Enantioselective Aza-MBH-Type Reaction of Nitroalkenes to *N*-Tosylimines Catalyzed by Bifunctional Organocatalysts

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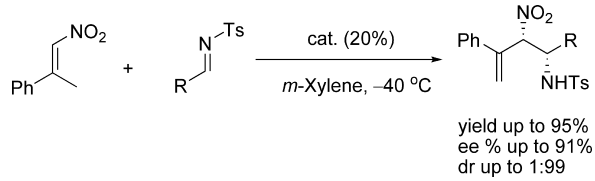
ABSTRACT



The first example of diastereo- and enantioselective aza-MBH-type reaction was accomplished by the asymmetric synthesis of β-nitro-γ-enamines via a (1*R*,2*R*)-diaminocyclohexane thiourea derivative mediated tandem Michael addition and aza-Henry reaction in good yields (up to 95%) and high enantioselectivities (up to 91% ee) and diastereoselectivities (up to 1:99 dr).

Reactions that involve the formation of C−C bonds are considered as the most important processes in organic synthesis. Tandem reactions that involve the production of multiple stereogenic centers in a single manipulation serve as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials with minimal production of waste.[1] Development of catalytic tandem reactions has proven to be a challenging task. The coupling of activated alkenes (vinyl anion equivalents) with various carbon electrophiles mediated by a tertiary amine or tertiary phosphine, commonly known as the Morita−Baylis−Hillman (MBH) reaction, has emerged as an important tandem C−C bond-forming reaction in organic synthesis.[2−4]

Recently Shi and co-workers described an enantioselective intermolecular cross-double addition between two Michael receptors promoted by chiral secondary amines.[5] However, a significant unmet challenge in this area still remains, such as diastereo- and enantioselective aza-MBH-type reactions using direct organocatalytic methods. A variety of activated alkenes have been employed as substrates in the MBH reaction for more than three decades,[2] but an olefin activated by a nitro group has been employed only recently.[5,6] As for the electrophiles, activated imines are the most sought-after

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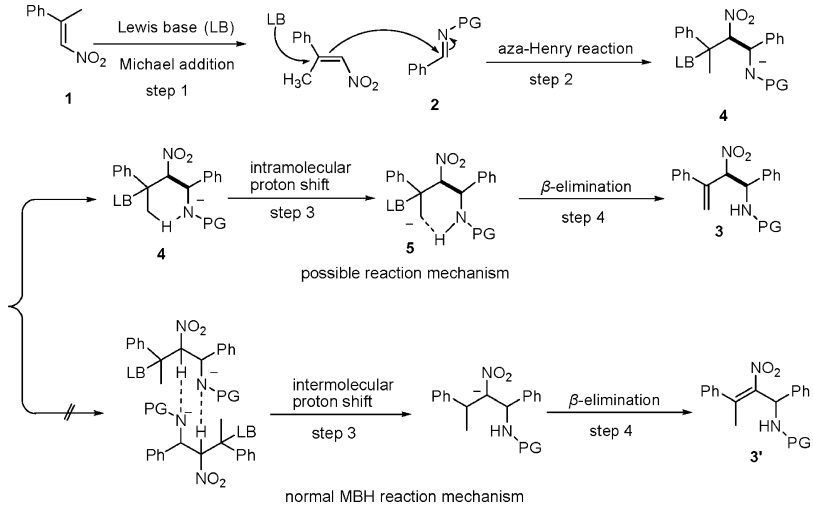
Scheme 1. Possible Reaction Mechanism



ones for the MBH reaction, besides aldehydes, by virtue of their electrophilicity and ability to provide aminoalkylated activated alkenes with new chiral centers.[7] However, to the best of our knowledge, the research on the coupling of activated imines and nitro activated olefins is very rare,[6e] and stereoselective synthesis in this coupling has not been reported.

We envisioned that the activated imines might react with nitroalkene **1** in the presence of an easily accessible chiral organic catalyst to afford aza-MBH-type reaction products. The resulting β-nitro-γ-enamines are important starting materials for diversity-oriented organic synthesis of biologically active compounds, which can be either oxidized to α-nitro-β-amino carbonyl compounds or reduced to 2, 3-diamino alkenes.[8,9]

The reaction involves a sequence of Michael addition, aza-Henry reaction, and β-elimination. A reversible conjugated addition of the nucleophilic catalyst to nitroalkene **1** generates an intermediate (step 1), which can intercept the imine **2** to afford the second intermediate **4** (step 2). A proton shift (step 3) followed by β-elimination gives the final product **3** with concurrent regeneration of the catalyst (step 4) (Scheme 1).

Several groups reported that thiourea derivatives with tertiary amino groups could act as bifunctional organocatalysts in enantioselective Michael addition and aza-Henry reaction.[10] In our designed tandem reaction, thiourea catalyst could first attack the nitroalkene by the tertiary amino group and also activate the imines via hydrogen-bonding. Our investigation began with the reaction of nitroalkene **1** with *N*-Boc imine **2A** catalyzed by quinine thiourea derivative (**8**, 20 mol %) in toluene at −20 °C (Table 1, entry 1), which afforded the desired product **3A** in 90% yield with high diastereoselectivity (dr 9:91) and low enantioselectivity (35% ee). Reaction at lower temperature provided an improved enantioselectivity (Table 1, entry 2). However, further lowering of the reaction temperature caused low reactivity (Table 1, entry 3). On the other hand, use of *N*-tosylimine **2B**, under the best reaction conditions for *N*-Boc imine **2A**, gave the product **3B** with a moderate enantioselectivity (Table 1, entry 4).

Encouraged by this result, we performed catalyst screenings with various chiral thioureas (Table 1, entries 5−9). It was found that all of the catalysts could catalyze the reaction to furnish the desired product. The reaction in the presence of (1*R*,2*R*)-diaminocyclohexane thiourea derivative **12** gave good diastereoselectivity and enantioselectivity, and (1*S*,2*S*)-diaminocyclohexane thiourea derivatives **13** gave the opposite and moderate diastereoselectivity and enantioselectivity. In addition, the results revealed that substituents in the aromatic ring of (1*R*,2*R*)-diaminocyclohexane thiourea derivatives had a significant effect on the diastereoselectivity and enantioselectivity but only marginally affected the reaction rate (Table 1, entries 6−8). In contrast, replacing the 3,5-bis(trifluorometh-

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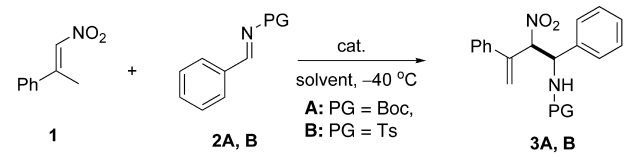
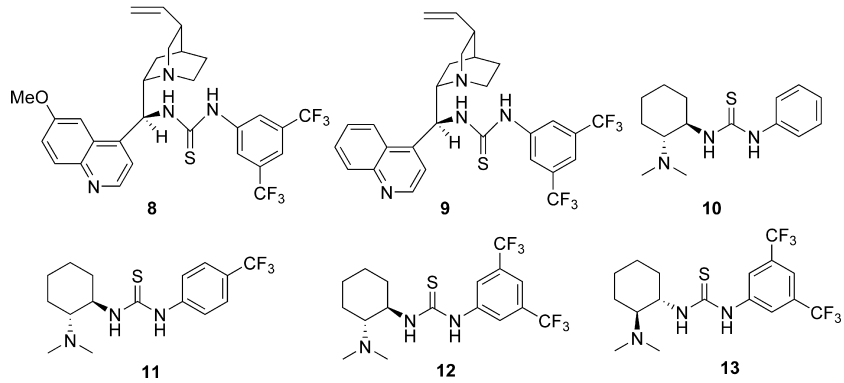
Table 1. Screening of the Reaction Conditions





entry	PG	catalyst	solvent	temp (°C)	time (h)[a]	yield (%)[b]	*anti*:*syn*[c]	ee % (*syn*)[d]
1	Boc	**8**	toluene	−20	5	90	9:91	35
2	Boc	**8**	toluene	−40	77	75	7:93	49
3	Boc	**8**	toluene	−50	72	trace	nd	nd
4	Ts	**8**	toluene	−40	28	73	17:83	65
5	Ts	**9**	toluene	−40	25	80	13:87	80
6	Ts	**10**	toluene	−40	24	77	35:65	61
7	Ts	**11**	toluene	−40	24	75	27:73	68
8	Ts	**12**	toluene	−40	22	82	11:89	86
9	Ts	**13**	toluene	−40	24	83	67:33	80[e]
10	Ts	**12**	DCM	−40	25	85	10:90	87
11	Ts	**12**	xylene	−40	48	90	4:96	91
12	Ts	**12**	*m*-xylene	−40	45	91	3:97	91
13	Ts	**12**	MeCN	−40	55	67	31:69	65
14	Ts	**12**	DMF	−40	21	78	43:57	10
15	Ts	**12**	MeOH	−40	30	75	37:63	50

[a] Reaction time was determined by TLC. [b] Yield of isolated product after chromatography. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Enantiomeric excess was determined by HPLC. [e] Enantiomeric excess of *anti* isomer.

yl)phenyl group with other aryl groups decreased the enantioselectivities as a result of weak hydrogen-bonding abilities.

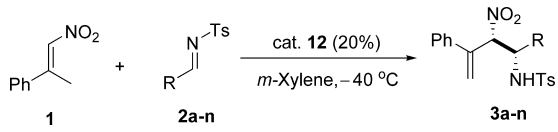
Other solvents were examined with **12** as a catalyst. As expected, polar solvents (MeCN, DMF, MeOH) decreased the activity of **12** and resulted in lower yields of **3B** (Table 1, entries 13−15). In contrast, **12** in nonpolar solvents (CH_2Cl_2, xylene) efficiently promoted the reaction in high yields of **3B** with good enantioselectivities (Table 1, entries 10−12).

Then we examined the scope of the reaction under the optimized conditions. Results obtained in the addition of nitroalkene **1** to a variety of *N*-tosyl imines **2a**−**n** are summarized in Table 2. All of the reactions were conducted in *m*-xylene at −40 °C in the presence of **12** as a catalyst. Good enantioselectivities (87−91% ee) were obtained for aryl imines with electron-rich groups (Table 2, entries 2, 5, 6, 11, and 13), whereas electron-deficient groups decreased the enantioselectivities (72−77% ee) (Table 2, entries 3, 4, 7−10, and 12). Reaction of *n*-propyl imine with **1** also yielded the desired product **3n** with good enantioselectivity (84% ee) (Table 2, entry 14). The absolute and relative configurations were unambiguously confirmed through X-ray crystal structure analysis of the compound **3g**[11] (see Supporting Information).

To study the reaction mechanism, a series of experiments were performed. No reaction was observed when nitroalkene **6** and imine **2B** were used as starting materials, which indicated β-methyl played an important role for this reaction. To further probe the proton shift process, deuterium-labeled nitroalkene **7** was subjected to the reaction conditions. Although the substrate was found to be less reactive as a result of steric effect, some products

(11) The structure of the compound **3g** was determined by X-ray analysis. CCDC-716780 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Reaction Substrate Scope

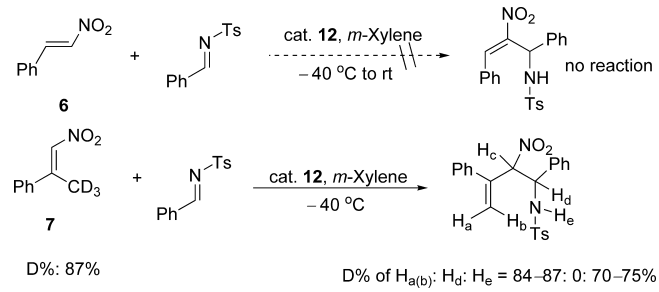


entry	3	R	time[a]	yield (%)[b]	*anti*: *syn*[c]	ee % (*syn*)[d]
1	**a**	Ph	45 h	91	3:97	91
2	**b**	2-MePh	65 h	90	7:93	89
3	**c**	2-BrPh	24 h	83	10:90	75
4	**d**	2-FPh	32 h	90	35:65	75
5	**e**	3-MePh	90 h	95	9:91	91
6	**f**	4-MePh	50 h	84	13:87	85
7	**g**	4-BrPh	30 h	82	8:92	77
8	**h**	4-ClPh	48 h	80	9:91	75
9	**i**	4-NO_2Ph	24 h	90	20: 80	72
10	**j**	4-CNPh	24 h	93	23:77	73
11	**k**	4-MeOPh	90 h	91	5:95	88
12	**l**	3-ClPh	52 h	95	9:91	77
13	**m**		72 h	92	<1:99	90
14	**n**	n-Pr	24 h	87	19:81	84

[a] Reaction time was determined by TLC. [b] Yield of isolated product after chromatography. [c] Diastereomeric ratio was determined by ^{1}H NMR. [d] Enantiomeric excess was determined by HPLC.

were isolated and the percentages of deuterium label on the terminal protons of the olefin and the proton within the amino group were 84−87% and 70−75%, respectively (Scheme 2). The results suggested that there was an intramolecular proton shift in the reaction. When nitroalkenes **6** were used, the reaction should be a normal MBH pathway (Scheme 1), but at low temperature intermolecular proton shift became more difficult and in the presence of β-methyl, it offered an intramolecular proton shift route that is easier than intermolecular.

Scheme 2. Study of the Reaction Mechanism



In summary, we have developed an enantioselective synthetic method via a (1*R*,2*R*)-diaminocyclohexane thiourea derivative mediated aza-MBH-type reaction/tandem Michael addition and aza-Henry reaction, in which easily prepared *N*-tosylimines and nitroalkene are employed as the starting materials. This strategy provides an easy access to structurally diverse β-nitro-γ-enamines. It is a noteworthy advantage of the organocatalyst that the new C−C bond formation proceeds efficiently with excellent diastereo- and enantioselectivity.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR and HRMS data for products **3** and X-ray crystal data in CIF format for **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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