Mild Michael Addition of Glycine Imines to Aromatic Nitroalkenes Catalyzed by DBU with LiOTf as an Additive

Wei Li,[a] Han Liu,[a] Da-Ming Du*[a,b]

[a] Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P. R. of China
Fax +86(10)68914985; E-mail: dudm@pku.edu.cn

[b] School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing 100081, P. R. of China

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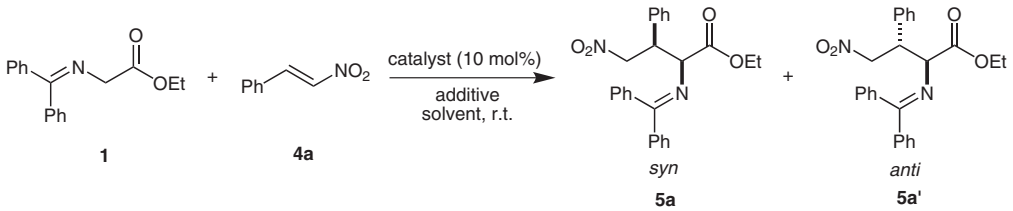
Abstract: A mild Michael addition of glycine imines to aromatic-nitroalkenes catalyzed by 10 mol% DBU with LiOTf as an additive was developed. In most cases, the products could be obtained in good yields (up to 96%) with moderate to good diastereoselectivities (up to 10:1). The selectivity for *syn* adduct can be reversed to *anti* when the R group of glycine imines was changed from methyl or ethyl to *tert*-butyl.

Key words: Michael addition, nitroalkene, catalysis, amino acids, DBU

The chemistry of peptide is one of the most important subjects on the boundary of synthetic chemistry, biochemistry, and pharmaceutical chemistry. The design and synthesis of novel unnatural amino acids, especially in enantiopure form, is one basis of peptide chemistry.[1] During the past century, a plethora of methodologies have been exploited for the synthesis of amino acids through different kinds of chemical bond formation, such as C–H bond formation, C–N bond formation, and C–C bond formation.[2] Compared with the former two methods, the formation of C–C bond at the α-position is more efficient in terms of reaction and product diversity.

The benzophenone-protected glycine derivatives (glycine imines) **1**–**3** are widely used as glycine anion equivalent in the synthesis of amino acids with one or two different kinds of substitutions on the α-position through C–C bond formation.[2e] From the first publication about these compounds in 1978,[3] many efficient transformations have been developed from these readily available starting materials. Generally, the introduction of α-substitutions can be facilitated in two ways, nucleophilic substitution of alkyl or phenyl halides, and Michael addition to unsaturated systems. In the Michael addition of glycine imines, acrylates and acrylamides,[4] unsaturated nitriles,[4e,h,i,l,m,5] linear and cyclic enones,[4e,i,4l–4o,5a,6] and vinyl phenyl sulfone,[4m,5a] have been applied as Michael acceptors. Good chemical and optical yields can be obtained by the catalysis of chiral phase-transfer catalysts derived from natural alkaloids or other chiral sources, chiral bisoxazoline complexes, and chiral guanidine compounds. On the contrary, Michael addition of benzophenone-derived glycine imines to nitroalkenes has been rarely developed,[7] though nitroalkenes are very important building blocks in organic synthesis.[8] In 1992, Rowley et al. reported the addition of glycine imine to nitrostyrene mediated by LDA and the application of the adduct in the synthesis of 4-substituted analogue of the glycine/NMDA antagonist HA-966.[9] In 1994, de Meijere et al. reported *n*-BuLi-mediated tandem Michael addition–intramolecular substitution of glycine imine with 3-bromo-1-nitroalkene for the preparation of cyclopropyl containing amino acids.[10] In 1998 and 2000, Cossío et al. reported the product of the Michael addition of **3** to nitroalkene **4c** under the catalysis of $LiClO_4$ and Et_3N in MeCN as an intermediate of 1,3-dipolar cycloaddition.[11] A recent example was published by Dougherty et al. in 2007.[12] In their synthesis of agonists for nicotinic acetylcholine receptor, nitroethene was use as Michael acceptor combined with LDA. Considering the air- and moisture-sensitivity of the base used and the low reaction temperature, milder conditions for this transformation are still in demand. As part of our project on the chemistry of nitroalkenes[13] for their high reactivity and potent diverse transformation of nitro group,[14] we would like to document the addition of glycine imines **1**–**3** to aromatic nitroalkenes **4** under the catalysis of DBU in the presence of LiOTf as an additive.



Scheme 1 Michael addition of glycine imine to nitrostyrene

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Table 1 Optimization of Reaction Conditions[a]

Entry	Catalyst	Additive[b]	Solvent	Yield (%)[c]	*syn*/*anti*[d]
1	TMG	–	THF	54	8.5:1
2	Et_3N	–	THF	23	1:1
3	DBU	–	THF	58	20:1
4	DBU	LiOTf	THF	82	8.9:1
5	DBU	LiOTf	CH_2Cl_2	80	1:2.2
6	DBU	LiOTf	$CHCl_3$	62	1:3.8
7	DBU	LiOTf	toluene	62	8.8:1
8[e]	DBU	LiOTf	THF	90	10.4:1

[a] The reaction was conducted in 0.25 mmol scale at r.t. for 24 h. Unless otherwise noted, the amount of nitrostyrene was equimolar with that of glycine imine.
[b] The amount of 10 mol% LiOTf was used.
[c] Determined by ^{1}H NMR using DMSO as internal standard.
[d] Determined by ^{1}H NMR of crude product.
[e] Molar ratio of nitrostyrene to glycine imine = 1.2:1.

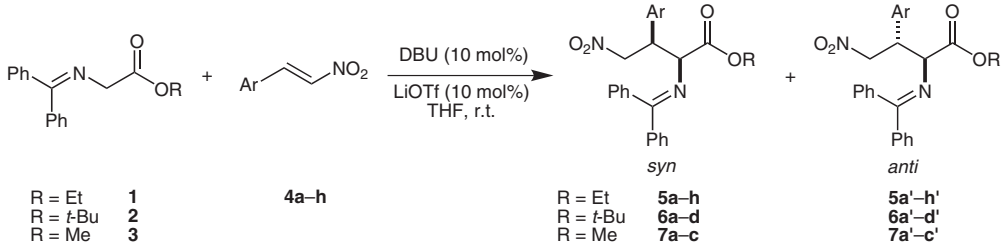
At the beginning of our work, we chose **1** and **4a** as model substrates (Scheme 1). Different organic bases were tested as catalysts in THF at room temperature. As shown in Table 1, Et_3N was not efficient in this transformation. Only 23% conversion of material was obtained (entry 2). When TMG and DBU with stronger basicity were used, the yields were improved significantly (entries 1 and 3), while higher *syn* selectivity was achieved in the later case. The relative configuration of the product was determined through comparison of the ^{1}H NMR with published spectral data. Considering lithium enolate was generated in former publications,[9–12] we added 10 mol% of LiOTf as an additive for further improvement. As we expected, the yield increased from 58% to 82%, though the diastereoselectivity decreased to 8.9:1 (entry 4). Higher yields may be ascribed to the stabilization of the anion by lithium cation through chelation. Other solvents such as CH_2Cl_2, $CHCl_3$, and toluene, did not give better results (entries 5–7). When the amount of nitrostyrene increased from 1.0 equivalent to 1.2 equivalents, slightly better yield and selectivity could be achieved (entry 8). If the reaction time was shortened to 6 hours, the desired product was obtained in lower yield for the incomplete conversion, with 7.6:1 diastereoselectivity. The lower selectivity compared to the value obtained after 24 hours reaction indicated that the diastereoselectivity was mainly kinetically controlled, while the slight epimerization of the stereocenter under the reaction conditions also provided some contributions.

Table 2 Michael Addition of glycine imines to nitroalkenes[a]

Entry	R	Ar	Product[15]	Yield (%)[b]	*syn*/*anti*[c]
1	Et	Ph	**5a**,**a′**	90	10.4:1
2	Et	4-MeC_6H_4	**5b**,**b′**	84	5.0:1
3	Et	4-$MeOC_6H_4$	**5c**,**c′**	89	6.0:1
4	Et	4-FC_6H_4	**5d**,**d′**	83	4.3:1
5	Et	4-ClC_6H_4	**5e**,**e′**	96	4.1:1
6	Et	4-BrC_6H_4	**5f**,**f′**	94	4.9:1
7	Et	3,4-$(MeO)_2C_6H_3$	**5g**,**g′**	86	3.1:1
8	Et	2-naphthyl	**5h**,**h′**	93	4.8:1
9	*t*-Bu	Ph	**6a**,**a′**	94	1:7.0
10	*t*-Bu	4-$MeOC_6H_4$	**6b**,**b′**	85	1:6.7
11	*t*-Bu	4-ClC_6H_4	**6c**,**c′**	84	1:2.1
12	*t*-Bu	2-naphthyl	**6d**,**d′**	88	3.1:1
13	Me	Ph	**7a**,**a′**	91	3.7:1
14	Me	4-$MeOC_6H_4$	**7b**,**b′**	99	4.6:1
15	Me	4-ClC_6H_4	**7c**,**c′**	89	2.3:1

[a] The reaction was conducted in 0.5 mmol scale in THF at r.t. for 24 h by the catalysis of 10 mol% DBU/LiOTf.
[b] Isolated total yield of *syn* and *anti* isomers.
[c] Determined by ^{1}H NMR of crude product.

With the optimized conditions in hand, more substrates were tested in this reaction (Scheme 2). As shown in Table 2, good yields were achieved in all cases, though the diastereoselectivities varied significantly with different substitutions on the aromatic system (entries 1–8). The lack of any reaction trend was difficult to interpret as there were many interactions between the two substrates, such as steric repulsion, electrostatic interaction, and π–π stacking. Interestingly, when the R group was changed from ethyl to *tert*-butyl, the *anti* isomer became the major product (entries 9–12). Such a phenomenon can be interpreted by the different steric repulsion of ethyl and *tert*-butyl group, as illustrated in Figure 1. In the case of sub-



Scheme 2 Michael addition of glycine imines to different aromatic nitroalkenes by the catalysis of DBU/LiOTf

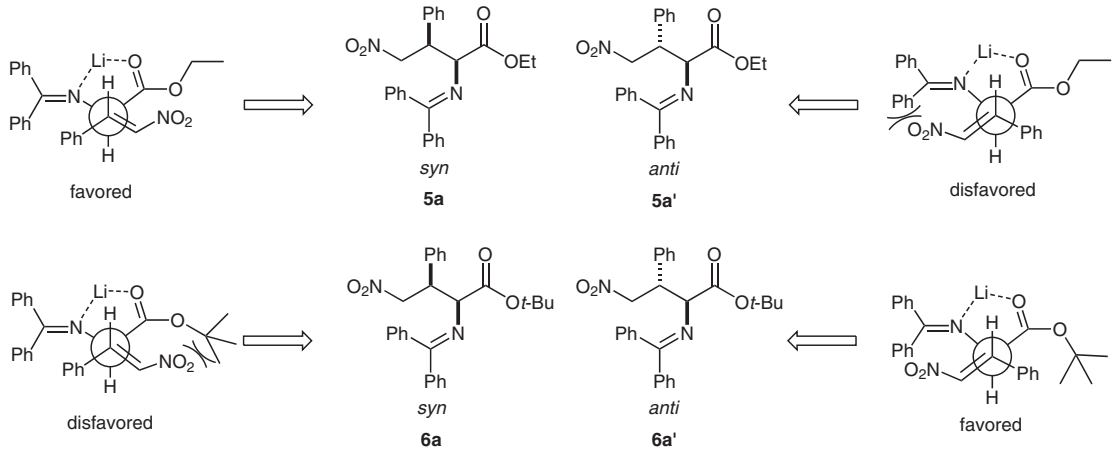


Figure 1 Proposed origin of inversed diastereoselectivity with **1** and **2**

strate **1** bearing ethyl group, the repulsion between nitro group and the imine fragment is stronger. The phenyl group tends to be vicinal to the imine fragment and the *syn* product **5a** is favored. In the case of **2** bearing the bulky *tert*-butyl group, the repulsion between nitro group and the ester fragment increases and overcomes the repulsion between nitro group and imine fragment, and the *anti* product **6a′** is favored instead. To get further evidence for our proposal, a glycine imine **3** in which R is a methyl group was also tested in this reaction (entries 13–15). As expected, the smaller methyl ester gave similar diastereoselectivities as compared to the ethyl ester, but was very different from the bulky *tert*-butyl ester. Such a result that two products with different relative configurations could be available under the same reaction conditions through a slight change of substrate structure could be useful in the application of this methodology.

In conclusion, we developed a mild Michael addition of glycine imines to aromatic nitroalkenes. In most cases, good yields and moderate to good diastereoselectivities can be achieved. Both the *syn* and *anti* adducts could be obtained under the same conditions through slight change of the substrate structure. This methodology could be applied in the synthesis of unnatural amino acids with functional group in the side chain. The asymmetric form of this reaction is under development in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for Michael Addition of Glycine Imines to Aromatic Nitroalkenes**

To a stirred solution of nitroalkene (1.2 mmol), LiOTf (16 mg, 0.1 mmol), and ethyl diphenylmethyleneiminoacetate (267 mg, 1 mmol) or *tert*-butyl diphenylmethyleneiminoacetate (295 mg, 1 mmol) in dry THF (1 mL) was added DBU (15 mg, 0.1 mmol) in dry THF (1 mL). The mixture was stirred at r.t. for 24 h. After being quenched by H_2O, the mixture was extracted by CH_2Cl_2. The organic phase was separated and dried with Na_2SO_4. The diastereoselectivity was determined by NMR analysis of curde product. The sample for analysis was purified on column chromatography (SiO_2, 200–300 mesh) using PE–EtOAc (20:1) as eluent and recrystallized from Et_2O and PE.

***syn*-Ethyl 2-Diphenylmethyleneimino-4-nitro-3-phenylbutanoate (5a)**

According to the general procedure, a white solid was obtained; mp 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H), 4.11–4.16 (m, 2 H), 4.27–4.38 (m, 2 H), 5.14–5.18 (m, 2 H), 6.60–6.62 (d, *J* = 6.9 Hz, 2 H), 7.14–7.48 (m, 1 1H), 7.64 (d, *J* = 6.9 Hz, 2 H). IR: 1735, 1551, 1446, 1368, 1316, 1290, 1190, 1024, 695 cm^{-1}. MS (70 eV, EI): *m/z* (%) = 416 (3) [M$^+$], 343 (10), 296 (23), 267 (21), 266 (100), 193 (47), 165 (50). Anal. Calcd (%) for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 71.74; H, 5.83; N, 6.55.2.

***syn*-Ethyl 2-Diphenylmethyleneimino-3-(4-methylphenyl)-4-nitrobutanoate (5b)**

According to the general procedure, a white solid was obtained; mp 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 6.9 Hz, 3 H), 2.29 (s, 3 H), 4.10–4.15 (m, 2 H), 4.27–4.32 (m, 2 H), 5.10–5.12 (m, 2 H), 6.65 (d, *J* = 6.0 Hz, 2 H), 7.04 (s, 4 H), 7.27–7.45 (m, 6 H), 7.65 (d, *J* = 7.5 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 21.0, 46.2, 61.5, 68.7, 76.3, 127.3, 128.0, 128.2, 128.3, 128.6, 128.9, 129.3, 130.9, 134.0, 135.4, 137.4, 138.7, 169.9, 172.6. IR: 1736, 1732, 1619, 1552, 1516, 1446, 1379, 1317, 1288, 1182, 1026, 695 cm^{-1}. MS (70 eV, EI): *m/z* (%) = 430 (4) [M$^+$], 413 (3), 357 (7), 310 (17), 267 (27), 266 (100), 238 (22), 193 (69), 165 (61). Anal. Calcd (%) for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.36; H, 6.22; N, 6.35.