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Aza-Henry Reaction

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Enantioselective Aza-Henry Reactions Assisted by Zn^{II} and *N*-Methylephedrine**

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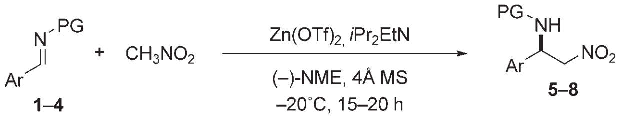
The addition reaction of nitro compounds to azomethine functions, known as the aza-Henry (or nitro-Mannich) reaction,[1] is a highly valuable C–C bond-forming process. The resulting 1,2-nitroamine adducts can be transformed into 1,2-diamines[2] by reduction[3] as well as α-amino acids by a Nef oxidation.[4] Whereas the production of both families of target molecules in nonracemic form bears considerable interest, the use of the aza-Henry approach in that endeavor remains largely unexplored because of the long-standing lack of (catalytic) asymmetric versions.[1,5] In this context, Shibasaki and co-workers[6] described the use of binaphthoxide (binol)-based heterobimetallic complexes of ytterbium and aluminum as catalysts of the reaction of nitro compounds with *N*-phosphinoyl imines derived from aromatic aldehydes, while Jørgensen and co-workers[7] used copper bis(oxazoline) complexes to catalyze the reaction of silyl nitronates with α-imino esters. These methods usually require a high catalyst loading (20 mol%), and the substrate scope is limited with regards to one or both of the reaction partners.[8] Three alternative organocatalytic aza-Henry reactions using unmodified nitro compounds have also appeared.[9] Johnston and co-workers[9a] reported a chiral bisamidine triflate salt that induced diastereoselective addition of nitroethane to several *N*-Boc-protected aryl imines (Boc = *tert*-butyloxycarbonyl), specifically those bearing electron-withdrawing groups, while Takemoto and co-workers described[9b] moderate enantioselectivities in reactions of nitromethane and aromatic *N*-phosphinoyl imines induced by bifunctional ureas. Most recently, Yoon and Jacobsen[9c] have documented a thiourea-based catalytic aza-Henry reaction of aromatic *N*-Boc imines leading to high enantioselectivities. Again, organocatalytic methods featured some important restrictions regarding the substrate scope and/or selectivity.

Some of us recently found[10] that cooperative activation[11] of nitro compounds and aldehydes towards the Henry reaction can be effected by combination of $Zn(OTf)_2$ (OTf = trifluoromethylsulfonate), (−)-*N*-methylephedrine (NME),[12] and a tertiary amine, all of which are available from commercial sources. This finding oriented new research towards establishing the validity of this activation model in related reactions. Our specific new finding is that the same system can effect highly enantioselective aza-Henry reactions (Scheme 1) of nitromethane and *N*-Boc aryl imines, thus providing a new entry to enantioenriched diamines and aryl glycines.



Scheme 1. The aza-Henry reaction between imines **1–4** and nitromethane. PG = protecting group, MS = molecular sieves.

Our initial aim was to identify the best-suited *N*-protecting group in the imine component in terms of both reaction conversion and enantioselection.[13] By using this activation system, *N*-sulphonyl and *N*-phosphinoyl imines **1** and **2**, respectively, led to the corresponding β-nitroamines **5** and **6** with poor enantioselectivity, if at all (Table 1). Gratifyingly,

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Table 1: Effect of the imine substituent (protecting group, PG) on the yield and enantioselectivity of the aza-Henry reaction.[a]

Imine	Ar	PG	Product	Yield [%]	*ee* [%][b]
1	Ph	$CH_3C_6H_4SO_2$	**5**	>99[c]	30
2	Ph	Ph_2PO	**6**	>99[c]	0
3	Ph	Cbz	**7**	82	82
4a	Ph	Boc	**8a**	80	94

[a] Reactions were conducted on a 1 mmol scale (**1**–**4**) in nitromethane (2 mL) using imine/$Zn(OTf)_2$/$i$$Pr_2EtN$/(−)-NME in a 1:1:1:1.5 molar ratio at −20 °C, except that for imine **2** which was conducted at room temperature. [b] Determined by HPLC. See Supporting Information for details. [c] Reaction conversion.

the *N*-Cbz-protected imine **3** (Cbz = carbobenzyloxy) afforded **7** with relatively much better *ee* values. The highest enantioselectivity (94 % ee) was obtained in the reaction with *N*-Boc-protected imine **4a**, which furnished the corresponding protected β-nitroamine **8a** in 80 % yield. A set of experiments in which the quantities of $Zn(OTf)_2$, $i$$Pr_2EtN$, and (−)-NME were varied for the reaction between nitromethane and imine **4a** proved informative (Table 2). Importantly, substoichiometric quantities of the three activating reagents sufficed for full conversion of the starting imine into adduct **8a**, with yields of about 80 % and generally high *ee* values. For example, a percentage mole (mol %) ratio of 30:30:45 and 20:20:30 for the three activating components gave selectivities of 94 % *ee* and 92 % *ee*, respectively (Table 2, entries 1 and 2). Loadings of $Zn(OTf)_2$ of 10 mol % or lower resulted in enantiomeric excesses below 90 % (Table 2, entry 3). Interestingly, while (−)-NME alone (entry 4) or a combination of $Zn(OTf)_2$ and (−)-NME in a ratio of 30:45 (Table 2, entry 5) led to racemic product, combinations of $Zn(OTf)_2$ and (−)-NME in a ratio of 30:75 or higher (entries 6 and 7) led to high enantioselectivities again. These results demonstrate that the presence of a base is key for success and suggest that the amino alcohol ligand, when used in excess, may play a dual role as base and as chiral inductor. Additionally, as supported by results from entries 8 and 9 (Table 2), the reaction selectivity is essentially independent of the nature of the amine base employed.

Table 2: The effect of the quantities of metal triflate, amine base, and amino alcohol ligand on the reaction between *N*-Boc imine **1a** and nitromethane.[a]

Entry	$Zn(OTf)_2$ [%][b]	Base	Base [%][b]	(−)-NME [%][b]	*ee* [%][c]
1	30	$i$$Pr_2EtN$	30	45	94
2	20	$i$$Pr_2EtN$	20	30	92
3	10	$i$$Pr_2EtN$	10	15	87
4	0	–	–	45	0
5	30	–	–	45	0[d]
6	30	–	–	75	97
7	30	–	–	90	95
8	30	Et_3N	30	45	92
9	30	Bu_3N	30	45	94

[a] Reactions conducted on a 1 mmol scale in nitromethane (2 mL) for 15–16 h at −20 °C. Virtually complete conversion was observed in all experiments, except for entry 5. [b] Percentage values refer to the mole percentage (% mol) of the catalyst constituents with respect to the *N*-Boc-protected imine. [c] Determined by HPLC. [d] Reaction conversion: 40 %.

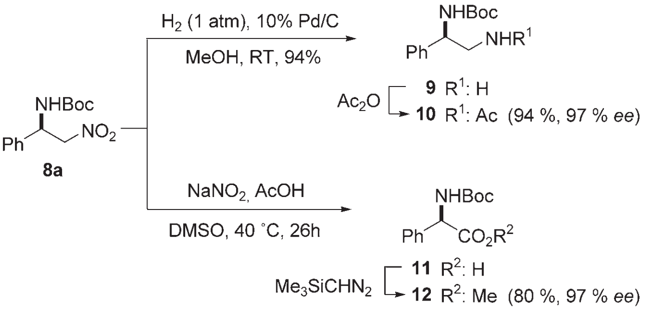
A preliminary evaluation of the reaction scope was carried out by using a series of *N*-Boc-protected aryl imines that vary in electronic character (Table 3). Imines **4**, which bear electron-rich, electron-neutral, or electron-poor aryl substituents, were well tolerated to give *N*-Boc β-nitroamines **8** in generally good yields and with high levels of stereocontrol.[14] The standard reaction conditions involved nitromethane as solvent, but other solvent systems, such as mixtures of nitromethane and dichloromethane or toluene (1:1 v/v), can also be used. It was also observed that the presence of traces of moisture or protic contaminants in the reaction mixture were detrimental to the enantioselectivity. In this regard, the addition of 4 Å molecular sieves was beneficial and gave the highest enantioselectivity in the present aza-Henry reaction. A practical aspect of the method is that a single recrystallization of the crude nitroamine from hexane and or mixtures of ethyl acetate and hexane can provide products of increased enantiomeric purity.

Table 3: Aza-Henry reaction of *N*-Boc imines **4** with nitromethane.[a]

Imine **4**	Ar	Yield [%][b]	Product **8** *ee* [%][c]
a	C_6H_5	81	97
b	$2\text{-}CH_3C_6H_4$	75	99
c	$4\text{-}CH_3C_6H_4$	90	92 (94)
		92	88[d]
		85	86[e]
d	$3\text{-}CH_3OC_6H_4$	80	90 (99)
		86	88[d]
e	$4\text{-}CH_3OC_6H_4$	73	91
f	$4\text{-}ClC_6H_4$	97	96[f] (98)
g	$4\text{-}F_3CC_6H_4$	98	92 (94)
h	$3\text{-}NO_2C_6H_4$	59	90 (92)
i	$4\text{-}NO_2C_6H_4$	65	87
j	$4\text{-}CH_3O_2CC_6H_4$	78	94
k	1-Naphthyl	95	94 (98)
l	2-Naphthyl	70	93
m	$3,5\text{-}Cl_2,4\text{-}MeOC_6H_2$	66	87[e] (95)

[a] Reactions conducted on a 1 mmol scale in dry nitromethane (2 mL) for 15–16 h at −20 °C using $Zn(OTf)_2$ (30 %), $i$$Pr_2EtN$ (30 %); (−)-NME (45 %), and 4 Å MS (100 mg mmol^{-1}), unless otherwise noted. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC after removal of traces of (−)-NME by column chromatography (see Supporting Information for details). The number in parentheses refers to the *ee* value for the product after a single crystallization from hexane/ethyl acetate. [d] $Zn(OTf)_2$ (20 %), $i$$Pr_2EtN$ (20 %), and (−)-NME (30 %). [e] $Zn(OTf)_2$ (30 %) and (−)-NME (75 %). [f] In the absence of 4 Å MS, 84 % *ee* was attained.

The elaboration of thus-obtained aza-Henry products into 1,2-diamines and amino acids, respectively, could be performed using known procedures. For example, reduction of the nitro group in **8a** led to the known monoprotected diamine **9**,[15] while Nef oxidation under the conditions described by Mioskowski and co-workers[16] followed by methylation afforded the *N*-Boc-protected (*R*)-phenylglycine methyl ester **12** without apparent loss of optical integrity (Scheme 2).[17] Further acetylation of **9** to the known compound **10** allowed the absolute configuration of the adducts to be confirmed.



Scheme 2. Assignment of the configuration of the adducts by transformation into 1,2-diamines. DMSO = dimethyl sulfoxide.

In conclusion, the pool of available methods for the asymmetric aza-Henry (nitro-Mannich) reaction has been enhanced by the approach described here which features a) tolerance to imines that bear aryl groups of diverse electronic nature and substitution patterns, b) exclusive use of commercially available reagents, in particular the relatively low-cost *N*-methylephedrine as the recyclable chiral inductor, and c) flexibility on the effective loading of the triggering system, which varies from stoichiometric to about 10 mol% with respect to the transformed imine substrate.

Experimental Section

In a typical procedure, diisopropylethylamine (1.05 mL, 6 mmol) was added dropwise to a solution of anhydrous zinc triflate (2.18 g, 6 mmol) in nitromethane (40 mL) under a nitrogen atmosphere and the resulting mixture was stirred at 25 °C for 1 h. The mixture became yellow. After addition of (−)-(1*R*,2*S*)-*N*-methylephedrine (1.6 g, 9 mmol) and 4 Å molecular sieves (2.0 g), the resulting mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was then kept for 10 min at −20 °C, imine **4a** (4.1 g, 20 mmol) was added, and the mixture was stirred for 21 h at −20 °C. The reaction was quenched with 0.1 M HCl (50 mL), and the mixture was extracted with dichloromethane (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (ethyl acetate/hexane) afforded **8a** (4.3 g, 80% yield). From the late fractions of the column, 0.432 g of (1*S*,2*R*)-*N*-methylephedrine was recovered. Recovery of the chiral ligand that remained in the acidic aqueous phase was carried out by dropwise addition of a solution of NaOH (20% w/v) until pH 10. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the organic layer was dried over $MgSO_4$, and the solvent was evaporated to afford an additional 1.12 g of (−)-NME (1.55 g (97%) combined yield of chemically and optically pure (−)-NME ligand).

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[14] Apparently, heteroaromatic *N*-Boc-protected imines are less-suitable substrates for the reaction. For instance, the aza-Henry adduct from the furfuraldehyde *N*-Boc imine derivative was obtained in 96% yield and with 66% *ee*.

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[17] Subjecting **8a** (97% *ee*) to the conditions reported in reference [4c] ($KMnO_4$, KOH, Na_2HPO_4) led to partially racemized **11a** (65% yield, 70% *ee*).