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Aza-Henry reaction of ketimines catalyzed by guanidine and phosphazene bases

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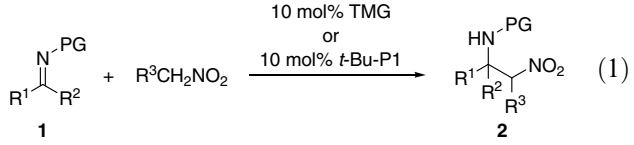
Abstract—A general catalytic addition of nitromethane to simple *N*-diphenylphosphinoyl ketimines is achieved using either 10 mol % 1,1,3,3-tetramethylguanidine (TMG) or 10 mol % phosphazene (*t*-Bu-P1) as organic base catalysts in good to high yields. On the other hand, *N*-sulfinylketimines also furnished the aza-Henry product in good yield with moderate diastereoselectivity (3:1). Thus, the methodology developed here is a good template for developing the first organocatalytic approach towards the aza-Henry reaction of ketimines.

The synthesis of β-nitroamines via the aza-Henry (or nitro-Mannich) reaction is an attractive tool to create carbon–carbon bonds.[1] Moreover, the product obtained can be easily converted into vicinal diamines and α-amino-acids, by reduction[2] and Nef reaction,[3] respectively, this highlights the several important synthetic applications of these compounds.[4]

Due to the importance of the 1,2-diamine structural motif in biologically active natural products and drug candidates, considerable effort has been devoted from academic and industrial researcher in this direction to the development of a general method to synthesize this class of compounds.[5] To date, most of the reactions are known for aromatic aldimines and the general catalytic method for ketimines has rarely been studied because of their low reactivity towards nucleophilic addition owing to steric hindrance as well as the electronic effect in the C–C bond forming step and their propensity to enolization.[6] These reactions are catalyzed or promoted by metal salts or strict conditions.[7,8] On the other hand, only few metal-free reactions of ketimines have been reported so far.[9,10] Recently, the diastereoselective aza-Henry reaction of sulfinyl ketimines has been reported using sub-stoichiometric amount of bases such as TBAF and NaOH.[11] After literature survey, we found that there is not even a single example of the aza-Henry reaction of ketimines catalyzed by an organic base to date. Therefore, the development of such a reaction in a simple, efficient, atom economical way and environmentally friendly approach is highly desirable. Herein we report significantly simplified methods for the catalytic aza-Henry reaction of ketimines using metal-free conditions (Eq. 1).



(1)

As an initial experiment, we chose tosyl (PG = Ts, R^1 = Ph, R^2 = Me) ketimine **1** as the model substrate due to its highly polarized character of C=N bond. The use of 10 mol % 1,1,3,3-tetramethylguanidine (TMG) base as catalyst and CH_3NO_2 as nucleophile as well as solvent partner at room temperature did not afford aza-Henry product **2**, but by-product **2′** was obtained quantitatively (Table 1, entry 1).[12] This result clearly indicates that the presence of the strong electron-withdrawing tosyl group led the product (**2**: PG = Ts) unstable under the present reaction conditions. We then searched for other protecting groups and the representative results are summarized in Table 1. The reactions of *N*-benzyl- and phenyl-protected ketimines as substrates were examined, but none of them furnished the desired products and complete recovery of the starting materials was observed, respectively (entries 2 and 3). The most probable reason for this

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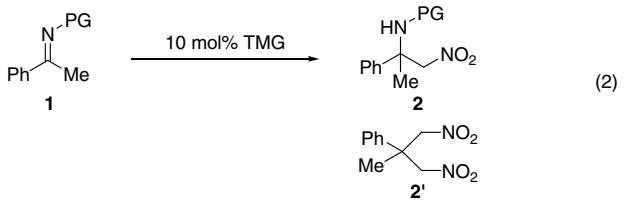
Table 1. Screening of protecting groups in aza-Henry reaction[a]

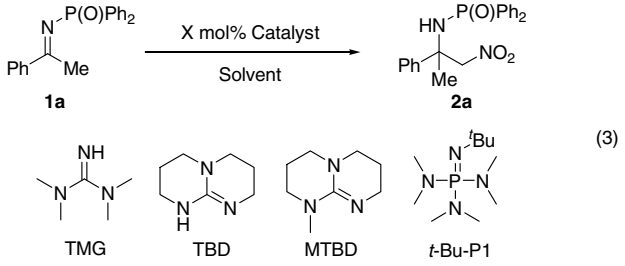


(2)

Entry	PG	Time (h)	Yield[b] (%)
1[c]	Ts	24	—
2[d]	CH_2Ph	24	—
3[d]	Ph	24	—
4	$P(O)Ph_2$	14	91

[a] Unless otherwise noted, all reactions were carried out with N-protected ketimines **1** (0.1 mmol) and nitromethane (2.0 mL) at room temperature.
[b] Isolated yield.
[c] The reaction was carried out at 0 °C to room temperature, the desired product was not obtained at all, but by-product **2′** was obtained quantitatively.
[d] Starting material was recovered.

Table 2. Screening of catalysts[a]



(3)

Entry	X mol % catalysts	Time (h)	Yield[b] (%)	SM (%)[c]
1	TMG (10 mol %)	14	50	43
2[d]	TMG (10 mol %)	14	85	10
3	TBD (20 mol %)	15	44	7
4[d]	MTBD (10 mol %)	15	43	5
5[e]	TMG (10 mol %)	14	91	—
6[e]	TBD (20 mol %)	15	88	—
7[e]	MTBD (10 mol %)	15	90	—
8[e]	*t*-Bu-P1 (10 mol %)	8	89	—

[a] Unless otherwise noted, all reactions were carried out with ketimine **1a** (0.1 mmol) and nitromethane (5 equiv) in the presence of indicated catalyst and THF (0.5 mL) at room temperature.
[b] Isolated yields.
[c] Recovery of starting materials.
[d] Nitromethane (10 equiv) was used.
[e] Nitromethane (2.0 mL) was used as solvent.

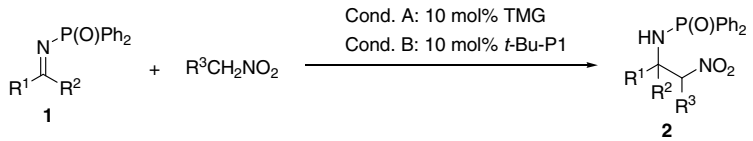
may be due to the low electrophilicity of ketimine under the present conditions. To our delight, when *N*-diphenylphosphinoyl ketimine[13,14] was used as substrate under the above conditions, the desired product was obtained in 91% yield (entry 4).

Next, we examined the catalytic activity of various other organic bases with *N*-diphenylphosphinoyl ketimine. The representative results are documented in Table 2 (Eq. 3). Among the conventional organic bases tested, the use of TMG ($pK_{BH+} = 23.3$ in CH_3CN)[15a,b] and nitromethane as solvent gave the best result (Table 2, entry 5); while reducing the amount of nitromethane dramatically decreased the yields of the product (entries 1–4). Other bases, such as 1,5,7-triazabicyclo(4.4.0)dec-5-ene (TBD, $pK_{BH+} = 26.03$ in CH_3CN) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, $pK_{BH+} = 25.49$ in CH_3CN), were also equally effective (entries 6 and 7). Then, we further investigated other strong organic bases. Phosphazene bases developed by Schwesinger et al.[15c,d] are well known to be an extremely strong, less nucleophilic, and metal-free bases. As expected, the use of 10 mol % phosphazene base (*t*-Bu-P1, $pK_{BH+} = 26.98$ in CH_3CN)[15e] efficiently produced the desired product at a shorter reaction time with comparable yield (entry 8). However, the common organic base, NEt_3 ($pK_{BH+} = 18.83$ in CH_3CN),[15a] did not promote the reaction at all. Other solvents, such as THF, CH_2Cl_2, CH_3CN, and diethyl ether, were also tested but none of them were effective since we observed remarkable reductions in the rates of reaction and yields, presumably due to the dilution effect.

With the optimal reaction conditions (i.e., 10 mol % TMG or 10 mol % *t*-Bu-P1) in hand,[16] a series of *N*-diphenylphosphinoyl ketimine (**1**) were reacted with nitromethane under conditions A and B to afford aza-Henry products (**2**) in good to high yields. The results are summarized in Table 3. In all the cases, the reactions proceeded smoothly to give the desired products. The substrates bearing electron-withdrawing and electron-donating groups at the *para*-position of the aromatic ring (R^1) as well as sterically demanding 1-naphthyl substituent were well tolerated under the reaction conditions and furnished the corresponding addition products (**2b–e**) in good to excellent yields (Table 3, entries 2–5). Although substrates (**1f–i**) seemed to exhibit diminished reactivity due to steric hindrance around the ketimine functionality compared to the other substrates (entries 1–5), their performance was still satisfactory and the addition proceeded smoothly with reasonable yields (entries 6–9). More interestingly, aliphatic type of substrate (**1j**: $R^1 = Ph(CH_2)_2$–, $R^2 = Me$) also underwent the reaction to furnish the desired product (**2j**) in good yield (entry 10). Finally, we examined the diastereoselective aza-Henry reaction using nitroethane under the optimized conditions, and the desired product was obtained as a diastereomeric mixture (ratio of 3:1) in more than 90% yield (entry 11).

In order to further explore the present reactions with better substrate scope, we envisioned that *N*-sulfinylketimine **3**[11,17] would be a model substrate to test the diastereofacial selective reaction. The fact that the *N*-sulfinyl group can act as a good chiral auxiliary and activate the C=N bond has attracted considerable interest in organic synthesis.[18] Initially, condition A was examined and the desired aza-Henry product was obtained as a diastereomeric mixture (1:1) in moderate yield even after the reaction time and the reaction temperature were increased (Eq. 5). Interestingly, when condition B was used, the product was obtained in excellent chemical yield and the selectivity was moderately increased (3:1).

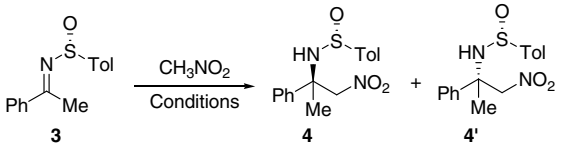
Table 3. Aza-Henry reaction of *N*-phosphinoyl ketimines catalyzed by TMG or phosphazene (*t*-Bu-P1)[a]



(4)

Entry	R^1	R^2	R^3	Time (h), yield[b] (%)		Product
				Condition A	Condition B	
1	**1a**: Ph	Me	H	14, 91	8, 89	**2a**
2	**1b**: *p*-Cl-C_6H_4–	Me	H	11, 95	11, 87	**2b**
3	**1c**: *p*-Me-C_6H_4–	Me	H	15, 80	15, 75	**2c**
4	**1d**: *p*-MeO-C_6H_4–	Me	H	15, 82	15, 80	**2d**
5	**1e**: 1-Naphthyl	Me	H	15, 93	15, 90	**2e**
6	**1f**: Ph	Et	H	15, 85	15, 82	**2f**
7	**1g**: Ph	*i*-Pr	H	24, 90	24, 84	**2g**
8	**1h**: Ph	*n*-Pr	H	24, 96	24, 85	**2h**
9	**1i**: Ph	*p*-Cl-C_6H_4–	H	21, 92	21, 90	**2i**
10	**1j**: Ph$(CH_2)_2$–	Me	H	30, 90	36, 91	**2j**
11	**1a**: Ph	Me	Me	36, 90 (dr: 77:23)[c]	36, 91 (dr: 76:24)[d]	**2k**

[a] Unless otherwise noted, all reactions were carried out with ketimines **1** (0.1 mmol) and nitromethane (2.0 mL) at room temperature under conditions A and B, respectively.
[b] Isolated yield.
[c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product mixture and the reaction was run at 0 °C.
[d] The reaction was run at room temperature with nitromethane (1.0 mL).



(5)

Condition A :10 mol% TMG, RT, 24 h,
yield: 50%, **4/4'** = 50:50
Condition B :10 mol% *t*-Bu-P1, 0 °C, 24 h,
yield: 95%, **4/4'** = 75:25

In conclusion, we have described for the first time the organic base-catalyzed aza-Henry reaction of ketimines. The wide substrate scope demonstrated under the present reaction conditions clearly indicates the potential utility of this reaction to further organic transformations. The template shown here provides the ground for the development of the reaction to be asymmetric version using chiral guanidines as an organic base catalyst.[19] To achieve this goal, improvements of the reaction efficiency are currently being pursued in our laboratory.

Acknowledgments

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12. Compound **2′** was fully characterized on the basis of spectroscopic data: Yellowish liquid; IR (ATR): 1373, 1447, 1544, 3094 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 1.66 (s, 3H), 4.90 (d, $J = 12.4$ Hz, 2H), 4.98 (d, $J = 12.4$ Hz, 2H), 7.20–7.39 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 21.8, 42.2, 81.9, 125.3, 128.5, 129.3, 137.9; HRMS (ESI): calcd for $C_{10}H_{12}N_2O_4Na$ $[M+Na]^+$ 247.0695, found 247.0689.
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16. *General procedure for the aza-Henry reaction of N-diphenylphosphinoyl ketimines* **1** *with nitromethane*: The preparation of **2a** is a representative reaction. To an argon flushed mixture of dry nitromethane (2.0 mL) and 10 mol % 1,1,3,3-tetramethylguanidine (TMG) [(0.01 mmol, 1.2 μL, *Condition A*)] or 10 mol % phosphazene base (*t*-Bu-P1 base) [(0.01 mmol, 2.6 μL, *Condition B*)] was added *N*-diphenylphosphinoyl ketimine **1a** (0.1 mmol, 31.9 mg), and the mixture was stirred at room temperature for 14 and 8 h, respectively. After completion of the reaction was confirmed by monitoring with TLC, the resulting solution was quenched with saturated aqueous NH_4Cl (a few drops), and extracted twice with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using hexane–AcOEt (4/1–3/2) as eluent to afford **2a** in 91% (34.5 mg) and 89% (34.0 mg) yields, respectively, as white solids. IR (ATR): 1120, 1186, 1437, 1542, 3181 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 3H), 4.42 (d, $J = 4.6$ Hz, 1H, NH), 4.96 (d, $J = 13.4$ Hz, 1H), 5.35 (d, $J = 13.4$ Hz, 1H), 7.18 (m, 1H), 7.27 (m, 2H), 7.36–7.43 (m, 8H), 7.74 (m, 2H), 7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.2 (d, $J = 4.1$ Hz), 59.8 (d, $J = 2.5$ Hz), 84.3, 124.5, 127.7, 128.5 (d, $J_{pc} = 13.2$ Hz), 128.7 (d, $J_{pc} = 12.4$ Hz), 128.8, 130.9 (d, $J_{pc} = 9.9$ Hz), 131.8_7 (d, $J_{pc} = 3.3$ Hz), 131.9_2 (d, $J_{pc} = 3.3$ Hz), 132.1 (d, $J_{pc} = 9.1$ Hz), 133.6 (d, $J_{pc} = 131.2$ Hz), 133.9 (d, $J_{pc} = 124.5$ Hz), 142.9 (d, $J_{pc} = 7.1$ Hz); HRMS (ESI): calcd for $C_{21}H_{21}N_2O_3PNa$ $[M+Na]^+$ 403.1182, found 403.1181.
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