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A Catalyst-Free, One-Pot Three-Component Aminomethylation of α-Substituted Nitroacetates: Theoretical and Experimental Studies into the Rate-Accelerating Effects of the Solvent Methanol

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During the past decades, several organic solvents have been found to serve as powerful catalyst-free reaction media for some transformations.[1] For example, *N*,*N*-dimethylformamide (DMF) enabled a highly efficient allylation of benzoylhydrazones by using allyltrichlorosilane[1a] and cyanosilylation of aldehydes and ketones.[1b] Alcoholic solvents could promote hetero-Diels–Alder reactions of unactivated ketones[1c] or imines.[1d] Ethylene glycol allowed a catalyst-free Strecker reaction of α-CF_2H or α-CF_3 ketimines with TMSCN (TMS = trimethylsilyl).[1e] Noticeably, some catalyst-free reactions enabled by a certain organic solvent can be more efficient than the corresponding process catalyzed by an acid or base catalyst.[1e] However, detailed mechanistic studies into the origin of the efficiency of catalyst-free reactions in a given medium (or solvent) are very limited.

We have found that alcoholic solvents such as MeOH and ethylene glycol are powerful catalyst-free reaction media for the cyanation of ketimines,[1e–f] and the major role of the alcohol was believed to be the activation of ketimines through H-bonding interactions. Herein, we wish to report a one-pot,[2] catalyst-free, three-component aminomethylation reaction of α-substituted nitroacetates, formalin, and amines in MeOH; this method allows the efficient and diverse synthesis of α,β-diamino acid derivatives. Most importantly, NMR spectroscopic analysis, together with theoretical studies, casted some light on the role of MeOH as a solvent to accelerate the reaction.

Owing to the ubiquitous nature of α,β-diamino acids as key structural fragments in bioactive compounds,[3] the incorporation of conformationally constrained C^{α}-tetrasubstituted α,β-diamino acids becomes a fruitful method in the design of peptides with enhanced properties.[4] In addition, cyclic ureas, imidazolines, and β-lactam antibiotics derived from α-alkyl-α,β-diamino acids showed versatile bioactivities.[5] While several methods for the synthesis of α-alkyl-α,β-diaminopropionic acids are available,[6] methods for α-aryl-α,β-diamino acids are scarce. In light of this, it is highly desirable to develop facile methods for the synthesis of both α-alkyl- and α-aryl-substituted α,β-diamino acid derivatives.

During our efforts in the synthesis of compounds that have a tetrasubstituted carbon center for biological evaluation,[7] we were interested in the functionalization of α-substituted nitroacetates,[8] owing to the rich chemistry associated with nitro groups. In this context, we have developed the first catalytic asymmetric hydroxymethylation and amination of α-substituted nitroacetates.[9] We noticed that no aminomethylation reaction[10] of α-substituted nitroacetates had been reported that would be a straightforward method for the synthesis of α,β-diamino acid precursors, even though the Mannich reaction of α-alkyl nitroacetates and *N*-protected aldimines has been intensively studied.[8a–h] Therefore, the reaction of nitroacetate **1a**, with 2.0 equivalents of formalin (**2**), and 2.0 equivalents of *p*-anisidine (**3a**) was carried out in CH_2Cl_2 at 40 °C. Base catalysts were first tested, and it was found that the desired aminomethylation product **4a** could be obtained in moderate yield, accompanied with the hydroxymethylation product **5** (Table 1, entries 1–3). The ratio of **4a** to **5** was determined by ^{1}H NMR spectroscopy of the crude mixture.

We had previously found that bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) were efficient catalysts for the hydroxymethylation reaction,[9a] therefore we next tried the catalyst-free version to suppress this side reaction, and found that only the desired Mannich reaction took place without any base, thereby affording the desired product **4a** in 91% yield after 5 h (Table 1, entry 4). We further checked the influence of the ratio of nitroacetate **1a**/formalin **2**/*p*-anisidine **3a** (Table 1, entries 4–6), and found that when only 1.2 equivalents of formalin **2** and 1.0 equivalent of *p*-anisidine **3a** were used, the reaction still worked well to

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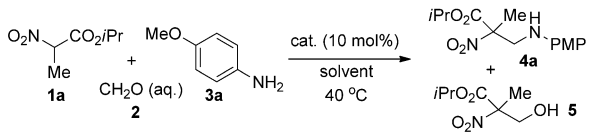
Table 1. Reaction development.[a]



Entry	**1a**/**2**/**3a**	Solvent	Catalyst	*t* [h]	**4a**/**5**	Yield [%][c]
1	1.0:2.0:2.0	CH_2Cl_2	K_3PO_4	0.5	5.5:1	38
2	1.0:2.0:2.0	CH_2Cl_2	DABCO	0.5	7.1:1	65
3	1.0:2.0:2.0	CH_2Cl_2	DBU	0.5	16.7:1	61
4	1.0:2.0:2.0	CH_2Cl_2	–[b]	5.0	–	91
5	1.0:2.0:1.0	CH_2Cl_2	–[b]	4.5	8.3:1	74
6	1.0:1.2:1.0	CH_2Cl_2	–[b]	11.0	–	85
7	1.0:1.2:1.0	$CHCl_3$	–[b]	5.5	–	72
8	1.0:1.2:1.0	toluene	–[b]	7.0	–	65
9	1.0:1.2:1.0	EtOAc	–[b]	4.0	–	76
10	1.0:1.2:1.0	THF	–[b]	4.0	–	89
11	1.0:1.2:1.0	Et_2O	–[b]	7.0	–	57
12	1.0:1.2:1.0	MeCN	–[b]	3.0	–	86
13	1.0:1.2:1.0	MeOH	–[b]	0.5	–	94
14	1.0:1.2:1.0	EtOH	–[b]	4.0	–	91
15	1.0:1.2:1.0	H_2O	–[b]	4.0	–	70

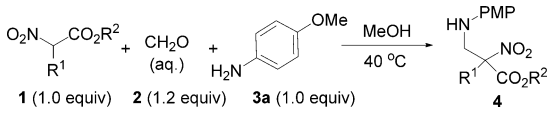
[a] Reaction was run on a 0.25 mmol scale; [b] No catalyst; [c] Yield of isolated product **4a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

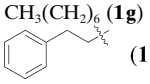
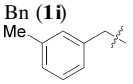
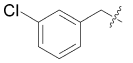
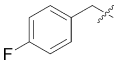
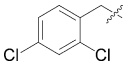
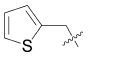
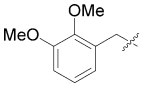
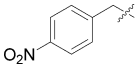
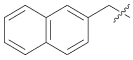
afford product **4a** in 85% yield (Table 1, entry 6). The evaluation of the solvent effects demonstrated that MeOH could significantly accelerate this catalyst-free reaction (Table 1, entries 7–15), and the reaction reached completion within 30 min to afford **4a** in 94% yield, and no hydroxymethylation reaction was detected. The reaction in water could also afford product **4a** in 70% yield (Table 1, entry 15), but the poor solubility of **1a** in water prevented its full conversion and required an extraction procedure for purification.

Accordingly, the optimal reaction conditions were in MeOH at 40 °C, with the ratio of nitroacetate **1a**/formalin **2**/*p*-anisidine **3a** being 1.0:1.2:1.0. The substrate scope of the α-substituted nitroacetates was then examined (Table 2). The ester group of the nitroacetates **1** had little effect on the reactivity. Isopropyl, ethyl, and *tert*-butyl esters **1a–c** all afforded the corresponding products **4a–c** in excellent yield (Table 2, entries 1–3). Gratifyingly, both α-aliphatic and α-aryl nitroacetates were viable substrates under these reaction conditions. Generally, both α-aliphatic nitroacetates **1a–g** and aryl-substituted α-aliphatic nitroacetates **1h–q** worked well to provide the desired products **4a–q** in good to excellent yields (Table 2, entries 1–17). The α-aryl-substituted nitroacetates **1r–v** afforded the corresponding adducts **4r–v** in lower yields (Table 2, entries 18–22), and especially, the nature and position of the substituent at the α-phenyl group greatly influenced the reaction outcome. No reaction took place in the case of *o*-chlorophenyl-substituted nitroacetate **1w** (Table 2, entry 23).

A wide range of structurally diverse amines were tolerated with this protocol, as shown in Table 3. Secondary amines such as piperidine, morpholine, and 3-piperazinobenzisothiazole gave the desired products **6a–c** in reasonable yields (Table 3, entries 1–3). The less reactive aliphatic

Table 2. The scope of the α-substituted nitroacetate **1**.[a]



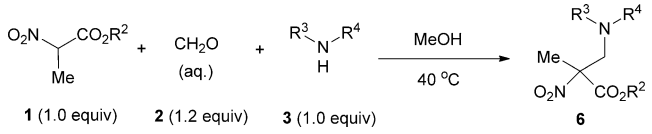
Entry	R^1	R^2	**4**	*t* [h]	Yield [%][b]
1	Me (**1a**)	*i*Pr	**4a**	0.5	94
2	Me (**1b**)	Et	**4b**	0.7	93
3	Me (**1c**)	*t*Bu	**4c**	1.0	73
4	Et (**1d**)	*i*Pr	**4d**	2.5	82
5	*n*Bu (**1e**)	*i*Pr	**4e**	2.5	77
6	*i*Bu (**1f**)	*i*Pr	**4f**	2.5	57
7	$CH_3(CH_2)_6$ (**1g**)	*i*Pr	**4g**	2.5	81
8	 (**1h**)	*i*Pr	**4h**	9.0	66
9	Bn (**1i**)	Et	**4i**	8.0	73
10	 (**1j**)	Et	**4j**	2.0	80
11	 (**1k**)	Et	**4k**	2.0	76
12	 (**1l**)	Et	**4l**	1.0	87
13	 (**1m**)	*i*Pr	**4m**	9.0	86
14	 (**1n**)	Et	**4n**	1.0	84
15	 (**1o**)	Et	**4o**	2.0	99
16	 (**1p**)	*i*Pr	**4p**	1.0	71
17	 (**1q**)	Et	**4q**	2.0	85
18	Ph (**1r**)	Et	**4r**	1.0	57
19	*p*-FC_6H_4 (**1s**)	*i*Pr	**4s**	8.0	56
20	*p*-ClC_6H_4 (**1t**)	Et	**4t**	4.0	53
21	*m*-BrC_6H_4 (**1u**)	*i*Pr	**4u**	4.0	61
22	*p*-$MeOC_6H_4$ (**1v**)	Et	**4v**	20.0	32
23	*o*-ClC_6H_4 (**1w**)	*i*Pr	**4w**	24	NR[c]

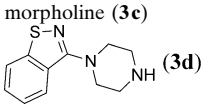
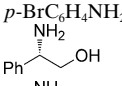
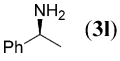
[a] Reaction was run on a 0.25 mmol scale; [b] Yield of isolated product; [c] No reaction.

benzyl amine **3e** provided product **6d** in 56% yield after 10 h (Table 3, entry 4). All of the aniline derivatives **3f–j** were excellent reaction partners, either with electron-donating or electron-withdrawing substituents, thus giving products **6e–i** in high to excellent yields (Table 3, entries 5–9). Chiral primary amines **3k**,**l** also afforded the corresponding products **6j–l** in good yields (Table 3, entries 10–12), albeit with poor diastereoselectivity (up to 1.0:1.5), even though several reaction parameters such as temperature and the structure of the chiral amines were optimized. When ammonium acetate was used as the amine source, a double Mannich reaction took place to afford amine **6m** in 70% yield and 1.7:1 d.r. (Scheme 1).

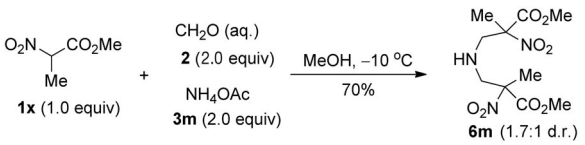
The practicability of this method was shown by the following preparative scale synthesis. For example, the reaction of nitroacetate **1a**, formalin **2**, and *p*-anisidine **3a** readily furnished the product **4a** in 92% yield, while the reaction

Table 3. The scope of amines.[a]



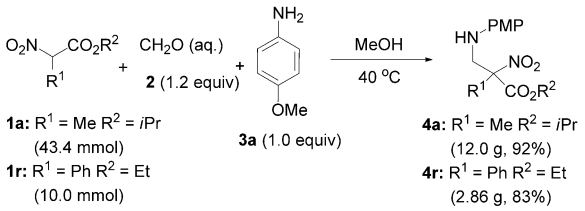
Entry	R^2	3	6	t [h]	Yield [%][b]
1	*i*Pr	piperidine (**3b**)	**6a**	0.5	30
2	*i*Pr	morpholine (**3c**)	**6b**	0.5	61
3	*i*Pr	 (**3d**)	**6c**	1.0	64
4	*i*Pr	$BnNH_2$ (**3e**)	**6d**	10	56
5	*i*Pr	*p*-$MeC_6H_4NH_2$ (**3f**)	**6e**	1.0	94
6	*i*Pr	*m*-$MeC_6H_4NH_2$ (**3g**)	**6f**	1.0	97
7	*i*Pr	*p*-$FC_6H_4NH_2$ (**3h**)	**6g**	1.0	90
8	*i*Pr	*m*-$ClC_6H_4NH_2$ (**3i**)	**6h**	23	80
9	*i*Pr	*p*-$BrC_6H_4NH_2$ (**3j**)	**6i**	17	80
10[c]	*i*Pr	 (**3k**)	**6j**	3.0	62 1.0:1.3 d.r.
11[c]	*i*Pr	 (**3l**)	**6k**	0.5	78 1.0:1.3 d.r.
12[c]	*t*Bu	(**3l**)	**6l**	4.0	54 1.0:1.5 d.r.

[a] Reaction run on a 0.25 mmol scale; [b] Yield of isolated product; [c] at −10 °C.



Scheme 1. Synthetic procedure for the synthesis of **6m**.

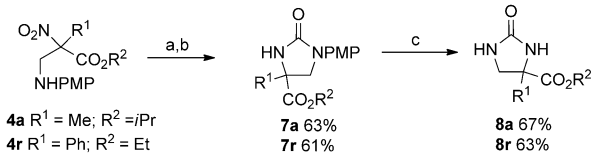
with nitroacetate **1r** furnished the product **4r** in 83% yield (Scheme 2).



Scheme 2. Gram-scale synthesis of **4a** and **4r**.

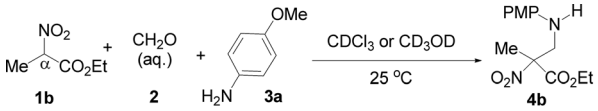
The versatility of the Mannich adduct **4** was demonstrated by the facile transformation into the corresponding α,β-amino acid-derived imidazolidinone **8** in good yield (Scheme 3).

To understand the rate-accelerating effect observed when using MeOH as the solvent, we conducted NMR spectroscopic studies to investigate the reaction mechanism, by using $CDCl_3$ or CD_3OD as the solvent. The catalyst-free reaction in $CDCl_3$ proceeded slowly, and the characteristic



Scheme 3. Synthetic procedure for the synthesis of **8a** and **8r**. Reaction conditions: a) Zn/HOAC, *i*PrOH; b) triphosgene (1.0 equiv)/Et_3N (1.0 equiv); c) CAN, CH_3CN/H_2O (3:1 or 1:1 v/v). CAN = ammonium cerium(IV) nitrate.

peaks of nitroacetate **1b** at 5.19 and 1.80 ppm remained during the reaction course (Figure 1A). In sharp contrast, the characteristic peak at 5.46 ppm gradually disappeared within 30 min and the doublet peak at 1.73 ppm, corresponding to the α-methyl group of **1b**, simultaneously emerged into a singlet peak at 1.84 ppm when run in CD_3OD (Figure 1,B). Similar results were obtained when



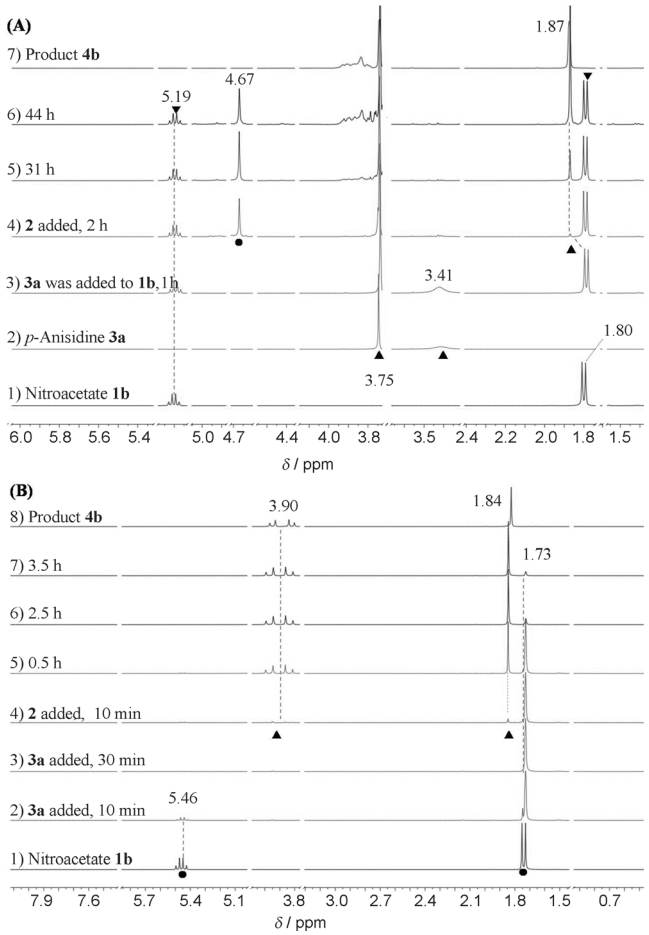


Figure 1. ^1H NMR spectroscopic analysis: (A) the reaction of **1b**, **2**, and **3a** in $CDCl_3$; (B) the reaction of **1b**, **2**, and **3a** in CD_3OD.

the nitroacetate **1b**, formalin, and PMP-NH_2 (PMP = *p*-methoxyphenyl) were added all at once. These changes could be explained by H/D exchange of the α proton of **1b** by ^{13}C NMR spectroscopy analysis, as the characteristic peak of the α carbon at 83.30 was split into a triplet peak at 82.48 ppm (see the Supporting Information). These results suggested that in MeOH, nitroacetate was activated by deprotonation for H/D exchange. Interestingly, when imine **9**, prepared from formalin and PMP-NH_2, was used to react with nitroacetate **1b** in CD_3OD, the peaks of nitroacetate **1b** at 5.46 and 1.70 ppm could be detected even after 40 h. These results suggested that **3a**, rather than the in situ formed imine **9**, was responsible for the activation of nitroacetate **1b**. In addition, ^1H NMR spectroscopic analysis of the formation of imine **9** in $CDCl_3$, CD_3OD, or CD_3CN demonstrated that imine formation was very fast, and was not the rate-determining step of this reaction. Accordingly, it was postulated that the rate-acceleration effect in MeOH was possibly due to the H-bonding interactions[11] between nitroacetate and MeOH, which facilitated the deprotonative activation[12] of nitroacetate by PMP-NH_2, a kind of dual activation. For further NMR data, please see the Supporting Information.

Because of the pervasive H-bond donors in MeOH and considering that the nitroacetate has four oxygen atoms as H-bond acceptors, we further performed theoretical calculations to study the proton-transfer processes with or without the assistance of MeOH, and the patterns of H-bonding interactions between MeOH and the nitroacetate. The optimized transition state (TS) structures are shown in Figure 2,

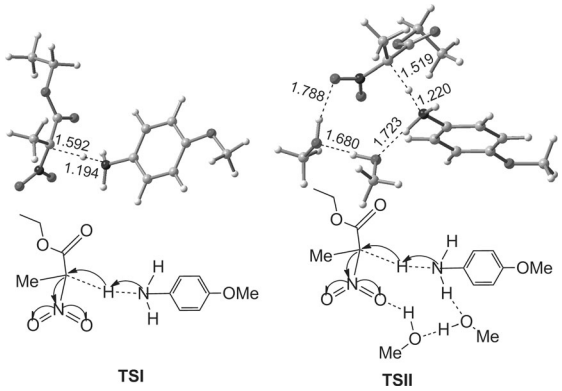


Figure 2. Optimized structures of the TS in the proton-transfer process from **1b** to PMP-NH_2. **TSI** and **TSII** are the TSs without and with MeOH, respectively. The bond distances of the optimized structures are in angstroms.

and the corresponding potential energy profiles are shown in Figure S7 (for computational methods and more details, see the Supporting Information). Theoretical studies revealed that no H-bonding interactions between $CHCl_3$ and nitroacetate were present, while MeOH can interact with **1b** and PMP-NH_2 to form hydrogen-bonded complexes. Our theoretical calculations showed that the activation barriers for the proton-transfer processes with and without the assistance of MeOH are 13.4 and 23.6 kcal mol^{-1}, respectively. The formation of hydrogen bonds can decrease the reaction barriers significantly. Interestingly, although hydrogen bonds might be expected between the MeOH and nitroacetates (with multiple H-bond acceptors), the optimized H-bonding interactions consisted of three O–H···O hydrogen bonds between two MeOH molecules and the reactants; this stabilizes the TS and lowers the energy barriers, as shown in Figure 2. The formation of H-bonding interactions between two MeOH molecules led to the enhanced H-bond activation, a form of Brønsted acid-assisted Brønsted acid catalysis that was proposed by Yamamoto, Rawal, and co-workers.[11e,f] Considering the solvent effects, we calculated the free-energy barrier and the total free-energy barrier in MeOH to be 15.4 and 18.9 kcal mol^{-1}, respectively; these values are significantly lower than those in $CHCl_3$ (22.8 and 24.5 kcal mol^{-1}, respectively), which provided a possible explanation for the rate-acceleration effect when using MeOH as the solvent.

In conclusion, to the best of our knowledge, we have developed the first example of a highly efficient aminomethylation of both α-alkyl- and α-aryl-substituted nitroacetates under catalyst-free conditions. The versatility of the products was demonstrated by their facile conversion into the corresponding α,β-amino acid-derived imidazolidinones. NMR spectroscopy studies and theoretical calculations revealed that the high efficiency of this catalyst-free transformation is owed to the dual activation of **1b** through the H-bonding interactions with MeOH and the deprotonative activation of **1b** by PMP-NH_2. The detailed reaction mechanism and the development of a catalytic asymmetric version[13] are now in progress in our laboratory.

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[1] a) S. Kobayashi, R. Hirabayashi, *J. Am. Chem. Soc.* **1999**, *121*, 6942–6943; b) G. K. S. Prakash, H. Vaghoo, C. Panja, V. Surampudi, R. Kultyshev, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3026–3030; c) Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663; d) Y. Yuan, X. Li, K. Ding, *Org. Lett.* **2002**, *4*, 3309–3311; e) Y.-L. Liu, X.-P. Zeng, J. Zhou, *Chem. Asian J.* **2012**, *7*, 1759–1763; f) Y.-L. Liu, F. Zhou, J.-J. Cao, C.-B. Ji, M. Ding, J. Zhou, *Org. Biomol. Chem.* **2010**, *8*, 3847–3850; g) R. Martínez, D. J. Ramón, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 8471–8474; h) J. Wu, X. Sun, W. Sun, *Org. Biomol. Chem.* **2006**, *4*, 4231–4235; i) A. Shirakawa, S. Shimizu, *Synlett* **2007**, 3160–3164; j) Y. Gu, J. Barrault, F. Jérôme, *Adv. Synth. Catal.* **2008**, *350*, 2007–2012; k) F. He, P. Li, Y. Gu, G. Li, *Green Chem.* **2009**, *11*, 1767–1773; l) C. Mukhopadhyay, P. Das, R. J. Butcher, *Org. Lett.* **2011**, *13*, 4664–4667.

[2] For reviews, see: a) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, Germany, **2005**; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; c) D. Enders, M. R. M. Hüttl, C. Grondal, G. Rabbe, *Nature* **2006**, *441*, 861–863. For recent reviews, see: d) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; e) A. de Meijere, P. V. Zezschwitz, S. Bräse, *Acc. Chem. Res.* **2005**, *38*, 413–422; f) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89; g) D. M. D′Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; h) X. L. Sun, Y. Tang, *Acc. Chem. Res.* **2008**, *41*, 937–948; i) M. M. Hussain, P. J. Walsh, *Acc. Chem. Res.* **2008**, *41*, 883–893; j) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439–4486; k) B. Ganem, *Acc. Chem. Res.* **2009**, *42*, 463–472.

[3] For reviews, see: a) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940–1948; b) A. Viso, R. F. de La Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167–3196.

[4] a) C. Palomo, J. M. Aizpurua, A. Benito, J. I. Miranda, R. M. Fratila, C. Matute, M. Domercq, F. Gago, S. Martin-Santamaria, A. Linden, *J. Am. Chem. Soc.* **2003**, *125*, 16243–16260; b) T. B. Durham, M. J. Miller, *J. Org. Chem.* **2003**, *68*, 35–42; c) C. Palomo, J. M. Aizpurua, E. Balentová, A. Jimenez, J. Oyarbide, R. M. Fratila, J. I. Miranda, *Org. Lett.* **2007**, *9*, 101–104.

[5] a) H.-J. Shue, X. Chen, N.-Y. Shih, D. J. Blythin, S. Paliwal, L. Lin, D. Gu, J. H. Schwerdt, S. Shah, G. A. Reichard, J. J. Piwinski, R. A. Duffy, J. E. Lachowicz, V. L. Coffin, F. Liu, A. A. Nomeir, C. A. Morgan, G. B. Varty, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3896–3899; b) V. Sharma, S. Peddibhotla, J. J. Tepe, *J. Am. Chem. Soc.* **2006**, *128*, 9137–9143; c) Y. Hsiao, L. S. Hegedus, *J. Org. Chem.* **1997**, *62*, 3586–3591; d) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437–4492; e) I. H. Gilbert, D. C. Rees, *Tetrahedron* **1995**, *51*, 6315–6336.

[6] a) E. Castellanos, G. Reyes-Rangel, E. Juaristi, *Helv. Chim. Acta* **2004**, *87*, 1016–1024; b) F. Zhang, Z.-J. Liu, J.-T. Liu, *Org. Biomol. Chem.* **2011**, *9*, 3625–3628; c) Y. Park, S. Kang, Y. J. Lee, T.-S. Kim, B.-S. Jeong, H. Park, S. Jew, *Org. Lett.* **2009**, *11*, 3738–3741; d) R. Badorrey, C. Cativiela, M. D. Diaz-de-Villegas, J. A. Gálvez, *Tetrahedron: Asymmetry* **1995**, *6*, 2787–2796; e) D. Blanco-Ania, P. H. H. Hermkens, L. A. J. M. Sliedregt, H. W. Scheeren, F. P. J. T. Rutjes, *Tetrahedron* **2009**, *65*, 5393–5401; f) C. K. De, N. Mittal, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 16802–16805; g) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088–14089; h) J. Hernández-Toribio, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150–16151; i) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, *13*, 1494–1497; j) S. Dong, X. Liu, Y. Zhang, L. Lin, X. Feng, *Org. Lett.* **2011**, *13*, 5060–5063.

[7] a) Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang, J. Zhou, *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178; b) J.-J. Cao, F. Zhou, J. Zhou, *Angew. Chem.* **2010**, *122*, 5096–5100; *Angew. Chem. Int. Ed.* **2010**, *49*, 4976–4980; c) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao, J. Zhou, *Chem. Sci.* **2011**, *2*, 2035–2039; d) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao, J. Zhou, *Chem. Commun.* **2009**, 6753–6755; e) M. Ding, F. Zhou, Z.-Q. Qian, J. Zhou, *Org. Biomol. Chem.* **2010**, *8*, 2912–2914; f) Y.-L. Liu, T.-D. Shi, F. Zhou, X.-L. Zhao, X. Wang, J. Zhou, *Org. Lett.* **2011**, *13*, 3826–3829; g) F. Zhou, M. Ding, Y.-L. Liu, C.-H. Wang, C.-B. Ji, Y.-Y. Zhang, J. Zhou, *Adv. Synth. Catal.* **2011**, *353*, 2945–2952; h) Y.-L. Liu, J. Zhou, *Acta Chim. Sin.* **2012**, *70*, 1451–1456; i) Y.-L. Liu, J. Zhou, *Chem. Commun.* **2012**, *48*, 1919–1921; j) Y.-L. Liu, J. Zhou, *Chem. Commun.* **2013**, *49*, DOI: 10.1039/c2cc36665g; k) J.-S. Yu, F. Zhou, Y.-L. Liu, J. Zhou, *Beilstein J. Org. Chem.* **2012**, *8*, 1360–1365; l) F. Zhou, X.-P. Zeng, X.-L. Zhao, J. Zhou, *Chem. Commun.* **2013**, *49*, 2022–2024; m) Z.-Y. Cao, F. Zhou, Y.-H. Yu, J. Zhou, *Org. Lett.* **2013**, *15*, 42–45.

[8] For Mannich reaction, see: a) B. Han, Q.-P. Liu, R. Li, X. Tian, X.-F. Xiong, J.-G. Deng, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 8094–8097; b) A. Singh, J. N. Johnston, *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867; c) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171; d) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879; e) K. R. Knudsen, K. A. Jørgensen, *Org. Biomol. Chem.* **2005**, *3*, 1362–1364; f) A. Puglisi, L. Raimondi, M. Benaglia, M. Bonsignore, S. Rossi, *Tetrahedron Lett.* **2009**, *50*, 4340–4342; g) D. Uraguchi, K. Koshimoto, C. Sanada, T. Ooi, *Tetrahedron: Asymmetry* **2010**, *21*, 1189–1190; h) J. C. Wilt, M. Pink, J. N. Johnston, *Chem. Commun.* **2008**, 4177–4179. For Michael addition, see: i) H.-H. Lu, X.-F. Wang, C.-J. Yao, J.-M. Zhang, H. Wu, W.-J. Xiao, *Chem. Commun.* **2009**, 4251–4253; j) J. R. Duvall, F. Wu, B. B. Snider, *J. Org. Chem.* **2006**, *71*, 8579–8590; k) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331–8338; l) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; m) H.-F. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu, G. Zhao, *Tetrahedron* **2011**, *67*, 312–317; n) R. Mancuso, A. Palmieri, R. Ballini, B. Gabriele, *Tetrahedron* **2012**, *68*, 5852–5856; o) E. Keller, N. Veldman, A. L. Spek, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 3403–3413; p) B. R. Linton, M. H. Reutershan, C. M. Aderman, E. A. Richardson, K. R. Brownell, C. W. Ashley, C. A. Evans, S. J. Miller, *Tetrahedron Lett.* **2007**, *48*, 1993–1997; q) L. Chen, G. Zhou, *Chin. J. Synth. Chem.* **2009**, *17*, 146–150; r) O. Baslé, S. Porcel, S. Ladeira, G. Bouhadir, D. Bourissou, *Chem. Commun.* **2012**, *48*, 4495–4497; s) X.-W. Wang, H.-F. Cui, H.-F. Wang, Y.-Q. Yang, G. Zhao, S.-Z. Zhu, *Tetrahedron* **2011**, *67*, 2468–2473; t) R.-J. Lu, W.-T. Wei, J.-J. Wang, S.-Z. Nie, X.-J. Zhang, M. Yan, *Tetrahedron* **2012**, *68*, 9397–9404; u) S. Shirakawa, S. J. Terao, R. He, K, Maruoka, *Chem. Commun.* **2011**, *47*, 10557–10559. For alkylation reaction, see: v) K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *Nat. Chem.* **2012**, *4*, 473–477; w) B. M. Trost, M. M. Hansmann, D. A. Thaisrivongs, *Angew. Chem.* **2012**, *124*, 5034–5037; *Angew. Chem. Int. Ed.* **2012**, *51*, 4950–4953. For aldol reactions, see: x) S. Shirakawa, K. Ota, S. J. Terao, K, Maruoka, *Org. Biomol. Chem.* **2012**, *10*, 5753–5755; For α-halogenation, see: y) N. G. Clark, B. Croshaw, B. E. Leggetter, *J. Med. Chem.* **1974**, *17*, 977–981; z) D. Cież, J. Kalinowska-Tłuścik, *Synlett* **2012**, 267–271.

[9] a) C.-B. Ji, Y.-L. Liu, Z.-Y. Cao, Y.-Y. Zhang, J. Zhou, *Tetrahedron Lett.* **2011**, *52*, 6118–6121; b) C.-B. Ji, Y.-L. Liu, X.-L. Zhao, Y.-L. Guo, H.-Y. Wang, J. Zhou, *Org. Biomol. Chem.* **2012**, *10*, 1158–1161.

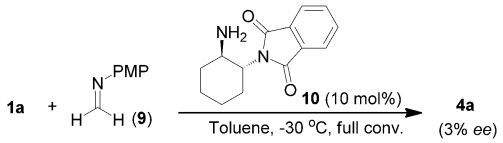
[10] a) X.-L. Liu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron Lett.* **2011**, *52*, 903–906; b) Y. Peng, R. Dou, G. Song, J. Jiang, *Synlett* **2005**, 2245–2247; c) Y. Chi, E. P. English, W. C. Pomerantz, W. S. Horne, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins, S. H. Gellman, *J. Am. Chem. Soc.* **2007**, *129*, 6050–6055; d) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805; e) S. Kobayashi, Y. Mori, J. S. Fossey, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626–2704; f) I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem.* **2004**, *116*, 6690–6693; *Angew. Chem. Int. Ed.* **2004**, *43*, 6528–6531; g) Y. Hamashima, N. Sasamoto, N. Umebayashi, M. Sodeoka, *Chem. Asian J.* **2008**, *3*, 1443–1455; h) I. Ibrahem, G.-L. Zhao, Armando Córdova, *Chem. Eur. J.* **2007**, *13*, 683–688; i) H. F. Anwar, L. Skattebøl, T. V. Hansen, *Tetrahedron* **2007**, *63*, 9997–10002; j) A. Clerici, R. Cannella, N. Pastori, W. Panzerib, O. Porta, *Tetrahedron* **2006**, *62*, 5986–5994; k) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2006**, *62*, 357–364.

[11] For examples of Brønsted acid catalysis, see: a) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; c) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516–532; d) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; e) A. K. Unni, N. Takenaka, H. Yamamoto, V. H. Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 1336–1337; f) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958–1977; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924–1942.

[12] For reviews on Brønsted base catalysis, see: a) E. M. O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron* **2011**, *67*, 1725–1762; b) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279; c) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; d) Y. G. Chen, P. McDaid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965–2983; e) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; f) S.-K. Tian, Y.

Chen, J. Huang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621 – 631.

[13] Despite extensive screening of a variety of easily available chiral Brønsted bases for the reaction of nitroacetate **1a** and preformed imine **9** under the indicated reaction conditions, **4a** was obtained in only 3% *ee*.



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