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1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted efficient and versatile aza-Michael addition

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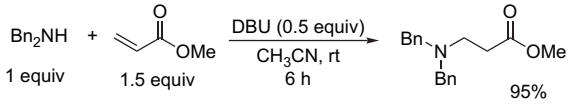
Abstract—A convenient and versatile method was developed for aza-Michael addition using a substoichiometric amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Various nitrogen nucleophiles were efficiently introduced to α,β-unsaturated carbonyl compounds employing 0.5 equiv of DBU. Furthermore, other heteroatomic nucleophiles could also be introduced successfully under the same reaction conditions.

1. Introduction

β-Aminocarbonyl compounds have been used as building blocks for many nitrogen-containing biologically important compounds[1] such as β-aminoalcohols, 1,2-diamines, and β-lactams.[2] Therefore, a number of efficient methods for the preparation of this unit have been developed. For a long time Mannich reaction[3] has been mainly utilized for the construction of β-aminocarbonyl compounds, however, it often requires harsh reaction conditions, allowing for a relatively narrow scope of substrates since it has to go through an iminium intermediate. Recently, aza-Michael reaction has attracted much attention as a promising alternative due to its mildness and operational simplicity.[4] It also has a prominent advantage over the Mannich reaction covering a wide range of nitrogen nucleophiles including amides, carbamates, and sulfonamides, which can hardly be utilized using conventional Mannich condensations. Most aza-Michael reaction protocols often employ Lewis acidic catalysts such as transition metals or Brønsted acids, i.e., $PdCl_2(MeCN)_2$,[5a] $InCl_3$,[5b] $CeCl_3\cdot 7H_2O$,[5c] $Yb(OTf)_3$,[5d] SmI_2,[5e] $Cu(OTf)_2$,[5f] $Bi(NO_3)$,[5g] $Bi(OTf)_2$,[5h] $LiClO_4$,[5i] $FeCl_3\cdot 6H_2O$,[5j] TMSCl,[5k] boric acid,[5l] acidic solids,[5m] and so on. However, above methods are often associated with some drawbacks, for example, high price and toxicity of catalysts, harsh reaction conditions, limited scope of substrates, and unexpected side reactions such as polymerization of Michael acceptors. Accordingly, several other reagents have been developed as a mild promoter of the aza-Michael reaction, i.e., fluoride,[6a] ionic liquid,[6b–d] β-cyclodextrin,[6e] and sodium dodecylsulfate (SDS).[6f]

DBU's excellent catalytic activity in Baylis–Hillman reaction was reported in 1999 by Aggarwal and Mereu, and DBU was found to be far superior to other tertiary amines.[7] This unusual reactivity was suggested to be originated from the stabilization of β-ammonium enolate, an intermediate from the reaction of DBU and a Michael acceptor. In relation to this work, progress based upon the nucleophilic nature of DBU has been made during the past decades.[8]

Inspired by the recent advances based upon DBU, we examined DBU as a promoter for aza-Michael reaction and were pleased to find that with a substoichiometric amount of DBU (0.5 equiv to amine), methyl acrylate and dibenzylamine were condensed smoothly at room temperature, affording methyl β-(dibenzylamino)acrylate in 95% yield (Scheme 1). This preliminary study prompted us to carry out in-depth investigation on this novel protocol.



Scheme 1. DBU-promoted aza-Michael reaction.

2. Result and discussion

First, we screened several tertiary amines, which all have the potential to promote this condensation (Table 1). The result was in agreement with Aggarwal and Mereu;[7] DBU was significantly more effective in the conjugate addition between dibenzylamine and methyl acrylate than DABCO (entry 2), DMAP (entry 3), and slightly more effective than TMG (entry 4). Furthermore, in a control reaction without DBU, only 3.8% of the desired product was obtained under

Keywords: Aza-Michael; DBU; Catalytic; Nitrogen nucleophiles; Conjugate addition.
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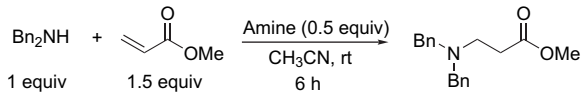
Table 1. Results of screening of various amine promoters in the conjugate addition between dibenzylamine and methyl acrylate



Entry	Amine	Yield[a] (%)
1	DBU	95
2	DABCO	21
3	DMAP	9
4	TMG	89
5	None	3.8

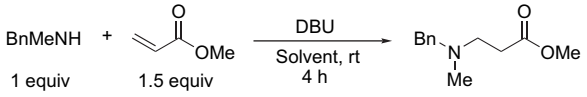
[a] Yields of isolated products.

otherwise the same reaction conditions (entry 5). This observation clearly indicates that DBU is uniquely effective for aza-Michael addition.[9]

To optimize the reaction conditions in detail, solvent effect was studied in the conjugate addition between *N*,*N*′-benzylmethylamine and methyl acrylate using 0.5 equiv of DBU (Table 2, entries 1–4). Interestingly, the reaction media showed no significant influence on the progress of the reaction, and the reaction proceeded smoothly even under solvent-free conditions (entry 4). Among the solvents examined, acetonitrile, in which the best yield of the products was obtained, was chosen as an appropriate medium for our studies.

To see if the action of DBU is truly catalytic, we gradually reduced the amount of DBU from 0.5 to 0.01 equiv in the reaction between *N*,*N*′-benzylmethylamine and methyl acrylate as a model reaction (Table 2). From this study, it is evident that a low loading of DBU is still effective, although the reactivity was decreased consequently (entries 5–8). Even 0.01 equiv of DBU afforded the desired adduct in 52% yield after 4 h, which did not change even after 12 h (entry 8). However, in the case of the aza-Michael addition between less reactive nucleophiles and sterically more hindered Michael acceptors, highly prolonged reaction time was required to yield a satisfactory result with a small amount of DBU. As a result, we adopted 0.5 equiv as an optimal loading amount of DBU for the following investigations.

Table 2. Results of decreasing the amount of DBU and varying solvents in the condensation between *N*,*N*′-benzylmethylamine and methyl acrylate

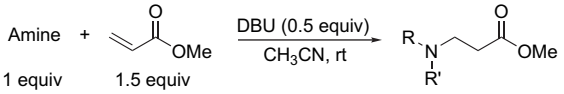


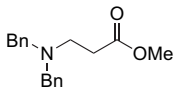
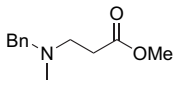
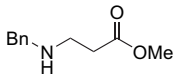
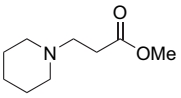
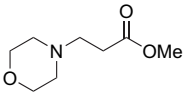
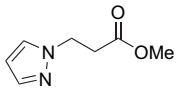
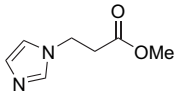
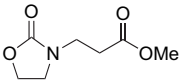
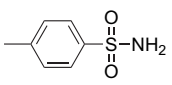
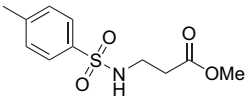
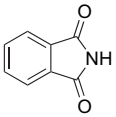
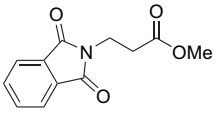
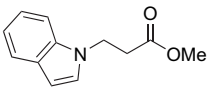
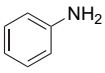
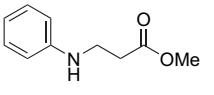
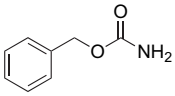
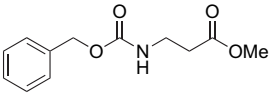
Entry	DBU (equiv)	Solvent	Yield[a,b] (%)
1	0.5	CH_3CN	95
2	0.5	DMF	85
3	0.5	Toluene	83
4	0.5	None	89
5	0.3	CH_3CN	85 (7 h)
6	0.1	CH_3CN	76 (8.5 h)
7	0.05	CH_3CN	63 (10 h)
8	0.01	CH_3CN	52 (12 h)

[a] Yields of isolated products.
[b] Values in parentheses indicate the time required for complete consumption of the starting material.

Study on the substrate scope of the DBU-promoted aza-Michael reactions was carried out with a wide range of nitrogen nucleophiles with 1.5 equiv of methyl acrylate, and the results are collected in Table 3. Acyclic secondary amines were introduced at the β-position of Michael acceptor in

Table 3. Results of conjugate addition of various nitrogen nucleophiles to methyl acrylate with DBU in acetonitrile

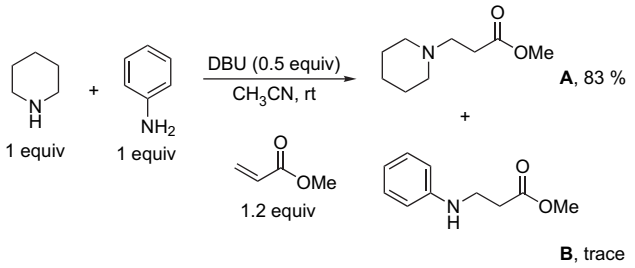


Entry	Nucleophile	Product	Time (h)	Yield[a] (%)
1	Bn_2NH		6	95
2	BnMeNH		4	94
3[b]	$BnNH_2$		3	75
4	Piperidine		4	88
5	Morpholine		4	90
6			14	95
7			14	95
8			14	98
9			14	97
10			20	92
11[c]			14	99
12			48	24
13			14	0

[a] Yields of isolated products.
[b] Di-substituted product was isolated in 18% yield using 1.2 equiv of methyl acrylate.
[c] This reaction was performed at 50 °C.

excellent yields irrespective of steric bulkiness (entries 1 and 2). Unfortunately, reaction with primary amine suffered from over-alkylation producing a low yield of the mono-alkylated product. However, the ratio between mono- and di-substituted products was considerably improved when a reduced amount of methyl acrylate (1.2 equiv) was employed (entry 3). Cyclic amines such as piperidine (entry 4), morpholine (entry 5), pyrazole (entry 6), and imidazole (entry 7) also underwent the conjugate addition successfully. Surprisingly, relatively weak nucleophiles such as carbamate (entry 8), sulfonamide (entry 9), and phthalimide (entry 10) also gave the aza-Michael adducts in excellent yields, though prolonged reaction time was required for complete conversions. At this stage, we were curious of the reaction with indole since it often leads to rather complicated results.[10] Two types of reactions are possible: Michael reaction at the NH and Friedel–Crafts alkylation at the C_3 position of the indole ring. In addition, unwanted side reactions can be observed, e.g., dimerization and polymerization. To our delight, using this protocol N-alkylation of indole proceeded regioselectively giving excellent yield of the product, when the reaction was heated slightly (entry 11). Unfortunately, the addition of aniline was rather sluggish furnishing only 24% yield even after 2 days (entry 12). A simple carbamate such as $CbzNH_2$ was totally unreactive under the reaction conditions (entry 13).

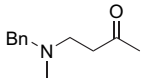
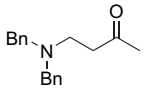
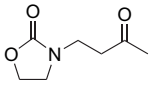
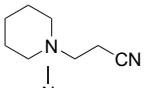
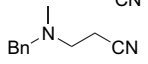
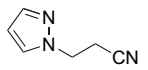
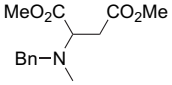
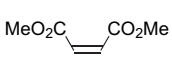
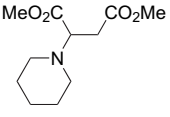
Based upon the low reactivity of aromatic amines, we assumed that selective addition of aliphatic over aromatic amines would be feasible under this reaction system. Accordingly, a control reaction was carried out to evaluate the selectivity; an equimolar mixture of piperidine and aniline was allowed to react with 1.2 equiv of methyl acrylate in the presence of 0.5 equiv of DBU in acetonitrile (Scheme 2). After 3.5 h, piperidine adduct (product **A**) was obtained almost exclusively, in 83% yield, leaving a trace of the aniline adduct (product **B**).



Scheme 2. Selective 1,4-addition of piperidine to methyl acrylate over aniline.

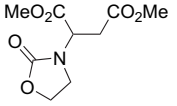
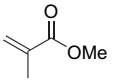
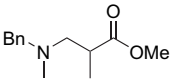
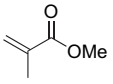
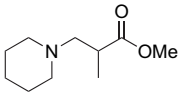
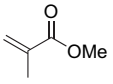
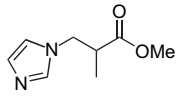
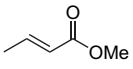
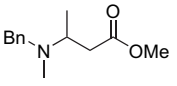
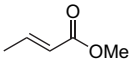
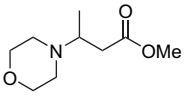
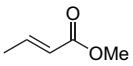
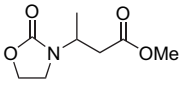
To evaluate the scope of this method, conjugate additions between a variety of Michael acceptors and nitrogen nucleophiles were screened extensively (Table 4). Unsubstituted α,β-unsaturated compounds such as methyl vinyl ketone and acrylonitrile gave moderate to good yields of the corresponding Michael adducts with several nitrogen nucleophiles (entries 1–6). In the case of acrylonitrile, excess amount (2 equiv) was required for the completion of the reaction presumably due to the volatility of the reagent (entries 4–6). To test the steric effect, substituted α,β-unsaturated carbonyls such as dimethyl maleate, methyl methacrylate, and methyl crotonate were tested as Michael acceptors (entries 7–15). Reactions of *N*,*N*′-benzylmethylamine, piperidine, and 2-oxazolidinone with dimethyl maleate underwent readily at room temperature (entries 7, 8, and 9,

Table 4. Results of conjugate addition of nitrogen nucleophiles to α,β-unsaturated compounds in the presence of 0.5 equiv of DBU in acetonitrile

Entry	Nucleophile	Acceptor	Product	Time (h)	Temperature	Yield[a] (%)
1	BnMeNH			3	rt	71
2	Bn_2NH			6	rt	79
3				14	rt	85
4[b]				24	rt	98
5[b]	BnMeNH			24	rt	97
6[b]				24	rt	99
7	BnMeNH			14	rt	93
8				14	rt	95

(*continued*)

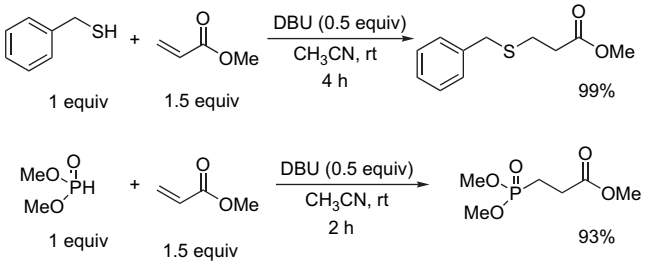
Table 4. (*continued*)

Entry	Nucleophile	Acceptor	Product	Time (h)	Temperature	Yield[a] (%)
9				14	rt	93
10	BnMeNH			8	50 °C	73
11				8	50 °C	81
12				14	50 °C	94
13	BnMeNH			14	50 °C	77
14				10	50 °C	82
15				18	50 °C	89

[a] Yields of isolated products.
[b] 2 equiv of acrylonitrile were added.

respectively), however, reactions with either α- or β-methyl substituted acrylates proceeded significantly more slowly. When the reaction temperature was elevated to 50 °C, reactions proceeded smoothly and good to excellent yields of products were obtained in the reactions of methyl methacrylate with *N*,*N*′-benzylmethylamine, piperidine, and imidazole (entries 10, 11, and 12, respectively) and in the reactions of methyl crotonate with *N*,*N*′-benzylmethylamine, morpholine, and 2-oxazolidinone (entries 13, 14, and 15, respectively).

Encouraged by the versatility and effectiveness of this method, we attempted hetero-Michael addition reactions with other heteroatomic nucleophiles. As representative nucleophiles, a thiol and a phosphite were examined, and the results were also good in both cases. At room temperature, benzyl mercaptan and dimethyl phosphite were introduced at the β-position of methyl acrylate with ease to afford the corresponding adducts in 99 and 93% yields, respectively, as shown in Scheme 3.



Scheme 3. Results of hetero-Michael addition using a thiol or a phosphite as nucleophiles.

As for the role of DBU for the activation in the Michael addition of the amines to α,β-unsaturated systems, we speculate that simple basic catalysis cannot fully explain the mechanism. More work should be done to clarify the exact mechanism of the DBU-promoted reaction.

3. Conclusion

We developed a novel method for a mild and efficient aza-Michael addition promoted by DBU. Primary and acyclic and cyclic secondary amines efficiently provided Michael adducts with unsubstituted and α- or β-methyl-substituted acrylates and their analogs. In the case of a primary amine, side product formation could be minimized by controlling the amount of a Michael acceptor. Less reactive amines such as 1,2-diazole, imidazole, 2-oxazolidinone, sulfonamide, phthalimide, and indole can also be applied successfully without additional modification of the experimental procedure. Reaction of aniline, however, was very sluggish. Reactions of substituted Michael acceptors such as maleate ester and α- and β-methyl acrylates also proceeded smoothly with all secondary amines examined, sometimes assisted by moderate heating. This method is versatile, high yielding, and operationally very simple; it does not require intricate precautions such as exclusion of air and moisture.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere in dried solvents. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz)

spectra were recorded in $CDCl_3$ on Bruker AM-300 instruments. Chemical shifts were reported in parts per million (δ units) downfield of Me_4Si (TMS) as the internal standards, or residual $CHCl_3$. High-resolution mass spectra (HRMS) were obtained from JEOL JMS 600 mass spectrometer. Acetonitrile (CH_3CN) was purchased from Aldrich as a reagent grade in a Sure/Seal™ bottle, and used directly without further purification. DBU and other commercially available materials were purchased from supplier (Aldrich, Acros, and TCI) and used without further purification. All reactions as well as column chromatography were monitored routinely by thin layer chromatography, which is performed with aluminum backed silica gel plates coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck). Column chromatography was performed with indicated eluting conditions on silica gel (Merck 7734 or 9385 Kieselgel 60). All known Michael adducts were analyzed by NMR analysis, and their data were in agreement with the literature values.

4.2. General procedure for the aza-Michael reaction (Table 1, entry 1)

To a magnetically stirred solution of dibenzylamine (1.0 mmol) and methyl acrylate (1.5 mmol) in CH_3CN (0.5 ml) was added DBU (0.5 mmol) at room temperature. After 6 h, the mixture was concentrated through vacuum evaporation. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=6:1), and the pure aza-Michael adduct was isolated in 95% yield.

4.2.1. Methyl 3-(*N*-benzylamino)propionate (Table 3, entry 1). See Ref. 11a.

4.2.2. Methyl 3-(*N*,*N*-dibenzylamino)propionate (Table 3, entry 2). See Ref. 5c.

4.2.3. Methyl 3-(*N*-benzyl-*N*-methylamino)propionate (Table 3, entry 3). See Ref. 11b.

4.2.4. Methyl 3-piperidinylpropionate (Table 3, entry 4). See Ref. 11a.

4.2.5. Methyl 3-morpholinylpropionate (Table 3, entry 5). See Ref. 5m.

4.2.6. Methyl 3-pyrazolylpropionate (Table 3, entry 6). See Ref. 11c.

4.2.7. Methyl 3-imidazolylpropionate (Table 3, entry 7). See Ref. 11d.

4.2.8. Methyl 3-(2-oxazolidinyl)propionate (Table 3, entry 8). See Ref. 6a.

4.2.9. Methyl 3-(4-toluenesulfonylamino)propionate (Table 3, entry 9). See Ref. 11e.

4.2.10. *N*,*N*-Phthaloyl-β-alanine methyl ester (Table 3, entry 10). See Ref. 11f.

4.2.11. Methyl 3-(1-indolyl)propionate (Table 3, entry 11). See Ref. 11g.

4.2.12. Methyl 3-(*N*-phenylamino)propionate (Table 3, entry 12). See Ref. 11h.

4.2.13. 4-(*N*-Benzyl-*N*-methylamino)butan-2-one (Table 4, entry 1). See Ref. 5c.

4.2.14. 4-(*N*-Dibenzylamino)butan-2-one (Table 4, entry 2). See Ref. 5c.

4.2.15. 4-(2-Oxazolidinyl)butan-2-one (Table 4, entry 3). See Ref. 6a.

4.2.16. 3-Piperidinylpropionitrile (Table 4, entry 4). See Ref. 12a.

4.2.17. 3-(*N*-Benzyl-*N*-methylamino)propionitrile (Table 4, entry 5). See Ref. 12b.

4.2.18. 3-Pyrazolylpropionitrile (Table 4, entry 6). See Ref. 12c.

4.2.19. 2-(*N*-Benzyl-*N*-methylamino)succinic acid dimethyl ester (Table 4, entry 7). Colorless oil (eluted with *n*-hexane/EtOAc=10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.27 (m, 5H), 3.90 (dd, J=7.9, 7.3 Hz, 1H), 3.77 (s, 3H), 3.75–3.67 (m, 2H), 3.68 (s, 3H), 2.88 (dd, J=15.8, 7.9 Hz, 1H) 2.68 (dd, J=15.8, 7.3 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.7, 139.0, 128.7, 128.3, 127.1, 62.3, 59.1, 51.8, 51.5, 37.9, 34.8; HRMS (EI) Calcd for $C_{14}H_{19}NO_4$ $[M]^+$: 265.1314, found: 265.1313.

4.2.20. 2-Piperidinylsuccinic acid dimethyl ester (Table 4, entry 8). See Ref. 12d.

4.2.21. 2-(2-Oxazolidinyl)succinic acid dimethyl ester (Table 4, entry 9). Colorless oil (eluted with EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 1H), 4.37 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.64 (t, J=7.6 Hz, 2H), 2.97 (dd, J=16.5, 7.8 Hz, 1H) 2.75 (dd, J=16.5, 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.2, 158.2, 62.5, 52.9, 52.9, 52.3, 42.9, 34.4; HRMS (CI) Calcd for $C_9H_{14}NO_6$ $[M+H]^+$: 232.0821, found: 232.0821.

4.2.22. Methyl 3-(*N*-benzyl-*N*-methylamino)-2-methylpropionate (Table 4, entry 10). See Ref. 12e.

4.2.23. Methyl 3-piperidinyl-2-methylpropionate (Table 4, entry 11). See Ref. 12a.

4.2.24. Methyl 3-imidazolyl-2-methylpropionate (Table 4, entry 12). Colorless oil (eluted with EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 4.25 (dd, J=14.0, 7.7 Hz, 1H), 4.00 (dd, J=14.0, 6.2 Hz, 1H), 3.68 (s, 3H), 2.88 (m, 1H), 1.19 (d, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 137.6, 129.6, 119.1, 52.1, 49.2, 41.4, 14.9; HRMS (CI) Calcd for $C_8H_{13}N_2O_2$ $[M+H]^+$: 169.0977, found: 169.0978.

4.2.25. Methyl 3-(*N*-benzyl-*N*-methylamino)-3-methylpropionate (Table 4, entry 13). See Ref. 12f.

4.2.26. Methyl 3-methyl-3-morpholinylpropionate (Table 4, entry 14). See Ref. 5m.

4.2.27. Methyl 3-methyl-3-(2-oxazolidinyl)propionate (Table 4, entry 15). See Ref. 12g.

4.2.28. Methyl 3-benzylsulfanyl-propionate (Scheme 3). See Ref. 13a.

4.2.29. Methyl 3-dimethoxyphosphorylpropionate (Scheme 3). See Ref. 13b.

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References and notes

1. (a) Misra, M.; Luthra, R.; Singh, K. L.; Sushil, K. *Comprehensive Natural Products Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Cohn, O., Eds.; Pergamon: Oxford, 1999; Vol. 4, p 25; (b) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, NY, 1997; (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; (d) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117.
2. (a) Kleinmann, E. F. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, NY, 1991; Vol. 2, p 893; (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, NY, 1993; (c) Devine, P. N.; Heid, R. M.; Tschaen, D. M. *Tetrahedron* **1997**, *53*, 6739.
3. (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
4. (a) Jung, M. E. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, NY, 1991; Vol. 4, pp 30–41; (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, NY, 1992; p 114; (c) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274.
5. (a) Kobayashi, S.; Karumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319; (b) Loh, T. P.; Wei, L. L. *Synlett* **1998**, 975; (c) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052; (d) Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233; (e) Reboule, I.; Gil, R.; Collin, J. *Tetrahedron Lett.* **2005**, *46*, 7761; (f) Wabnitz, T. C.; Spencer, J. B. *Tetrahedron Lett.* **2002**, *43*, 3891; (g) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (h) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 720; (i) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383; (j) Xu, L.-W.; Li, L.; Xia, C.-G. *Helv. Chim. Acta* **2004**, *87*, 1522; (k) Xu, L.-W.; Xia, C. G. *Tetrahedron Lett.* **2004**, *45*, 4507; (l) Chaudhuri, M. K.; Hussain, S.; Kantam, M. L.; Neelima, B. *Tetrahedron Lett.* **2005**, *46*, 8329; (m) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045.
6. (a) Yang, L.; Xu, L.-W.; Xia, C. G. *Tetrahedron Lett.* **2005**, *46*, 3279; (b) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2003**, *32*, 988; (c) Kantam, M. L.; Neeraja, V.; Kavita, B.; Neelima, B.; Chaudhuri, M. K.; Hussain, S. *Adv. Synth. Catal.* **2005**, *347*, 763; (d) Xu, L.-W.; Li, J.-W.; Zhou, S.-L.; Xia, C.-G. *New J. Chem.* **2004**, *28*, 183; (e) Surendra, K.; Srilakshmi Krishnaveni, N.; Sridhar, R.; Rama Rao, K. *Tetrahedron Lett.* **2006**, *47*, 2125; (f) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *Adv. Synth. Catal.* **2005**, *347*, 655.
7. Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.
8. (a) Reed, R.; Réau, R.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 399; (b) Shieh, W.-C.; Dell, S.; Repič, O. *Org. Lett.* **2001**, *3*, 4279; (c) Ghosh, N. *Synlett* **2004**, 574 and references cited therein.
9. Known pK_{aDMSO} values of protonated Lewis bases; DABCO: 8.93, proton sponge: 7.50, TMG: 13.6, DBU: 12.0 (estimated value), for details, see: (a) Bordwell, F. G. Bordwell pK_a Table (Acidity in DMSO). http://chem.wisc.edu/areas/reich/pkatable (accessed July 2006); (b) Ripin, D. H.; Evans, D. A. David Evans Research Group. http://daecr1.harvard.edu/pKa/pka.html (accessed July 2006).
10. (a) Houlihan, W. J. *Indoles*; Wiley: New York, NY, 1972; Vol. 1, p 71; (b) Iqbal, Z.; Jackson, A. H.; Rao, K. R. N. *Tetrahedron Lett.* **1988**, *29*, 2577.
11. (a) Matloubi Moghaddam, F.; Mohammadi, M.; Hosseinni, A. *Synth. Commun.* **2000**, *30*, 643; (b) Leonard, N. J.; Durand, D. A. *J. Org. Chem.* **1968**, *33*, 1322; (c) Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Sakurai, M.; Matsumoto, Y.; Tawara, S.; Chiba, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1409; (d) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565; (e) Pak, C. S.; Kim, T. H.; Ha, S. J. *J. Org. Chem.* **1998**, *63*, 10006; (f) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145; (g) Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron* **1996**, *52*, 8601; (h) Barluenga, J.; Villamana, J.; Yus, M. *Synthesis* **1981**, 375.
12. (a) Zhang, H.; Zhang, Y.; Liu, L.; Xu, H.; Wang, Y. *Synthesis* **2005**, 2129; (b) Zhang, C.; Maeda, Y.; Shirai, N.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 25; (c) Elguero, J.; García, J. I.; Toiron, C.; Vedsø, P. *Magn. Reson. Chem.* **1993**, *31*, 107; (d) Sheldrake, H. M.; Wallace, T. W.; Wilson, C. P. *Org. Lett.* **2005**, *7*, 4233; (e) Moffette, R. B.; Strube, R. E.; Skaletzky, L. *J. Med. Chem.* **1971**, *14*, 1088; (f) Etxebarria, J.; Vicario, J. L.; Badia, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790; (g) Menand, M.; Dalla, V. *Synlett* **2005**, 95.
13. (a) Kim, J. K.; Souma, Y.; Beutow, N.; Ibbeson, C.; Caserio, M. C. *J. Org. Chem.* **1989**, *54*, 1714; (b) Olagnon-Bourgeot, S.; Chastrette, F.; Wilhelm, D. *Magn. Reson. Chem.* **1995**, *33*, 971.