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# Diamine-Catalyzed Conjugate Addition to Acrylate Derivatives

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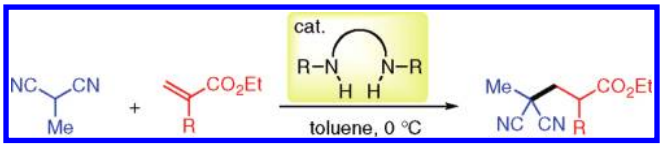
## ABSTRACT




**Diamines were found to promote catalytic conjugate addition of α-cyano active methine nucleophiles to various acrylate derivatives.**

Conjugate addition of carbon nucleophiles to electron-deficient C=C bonds is one of the most essential carbon–carbon bond forming reactions in organic synthesis.[1] Recently, catalytic use of artifically functionalized organic amines such as cinchona alkaloid and α-amino acid derivatives has been extensively studied for asymmetric conjugate addition reactions.[2] Although α,β-unsaturated aldehydes and ketones[3] as well as vinyl sulfones[4] and nitroalkenes[2e,5] are commonly employed as an electrophile in the organic amine-catalyzed conjugate addition, utilization of α,β-unsaturated acid derivatives, especially, simple acrylates, is much more unprecedented.[6–8] This is attributed mainly to the less electrophilic nature of acrylates and the fact that they could not form an iminium ion bearing a lower LUMO energy by the reaction with amino catalysts. Therefore, an alternative approach that possesses a distinct activating function toward both acrylates and nucleophiles

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(2) For reviews, see: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (e) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (f) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (g) List, B. *Chem. Commun.* **2006**, 819.

(3) For selected recent reports, see: (a) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450. (b) Jiang, Z.; Yang, Y.; Pan, Y.; Zhao, Y.; Liu, H.; Tan, C.-H. *Chem.—Eur. J.* **2009**, *15*, 4925. (c) Mei, K.; Jin, M.; Zhang, S.; Li, P.; Liu, W.; Chen, X.; Xue, F.; Duan, W.; Wang, W. *Org. Lett.* **2009**, *11*, 2864. (d) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302. (e) Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. *Org. Biomol. Chem.* **2008**, *6*, 349. (f) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (g) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (h) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 12051.

(4) For selected recent reports, see: (a) Moteki, S. A.; Xu, S.; Arimitsu, S.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 17074. (b) Li, H.; Deng, L. *Tetrahedron* **2009**, *65*, 3139. (c) Zhu, Q.; Cheng, L.; Lu, Y. *Chem. Commun.* **2008**, 6315.

(5) For selected recent reports, see: (a) Baslé, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246. (b) Xiao, J.; Xu, F.-X.; Lu, Y.-P.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 1220. (c) Rodriguez-Llansola, F.; Miravet, J. F.; Escuder, B. *Chem.—Eur. J.* **2010**, *16*, 8480. (d) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 10958. (e) Zhou, W.-M.; Liu, H.; Du, D.-M. *Org. Lett.* **2008**, *10*, 2817. (f) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (g) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (h) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (i) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

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(7) For reports on conjugate addition to acrylimides, see: (a) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (b) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (c) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. (d) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032.

(8) For reports on conjugate addition to 2-chloroacrylonitrile, see: (a) Li, X.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2010**, *16*, 14290. (b) Wang., B.; Wu, F.; Wang, Y.; Liu, X.; Deng., L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928.

(9) For selected reports on phase transfer catalyzed conjugate addition employing acrylate electrophiles, see: (a) Kano, T.; Kumano, T.; Maruoka, K. *Org. Lett.* **2009**, *11*, 2023. (b) Arai, S.; Takahashi, F.; Tsuji, R.; Nishida, A. *Heterocycles* **2006**, *67*, 495. (c) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734. (d) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (e) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.

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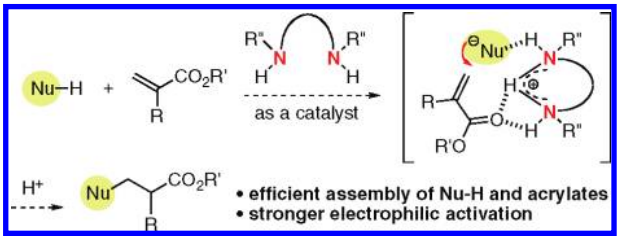
would be needed for the conjugate addition to acrylate derivatives.[9] Herein, we report the catalytic reactivity of diamines to promote the conjugate addition of α-cyano active methine nucleophiles to various acrylate derivatives.

To achieve the conjugate addition of carbon nucleophiles to acrylates, we planned to use diamines as a catalyst where the amines could be oriented in such a way as to cooperatively bind a single proton from the prenucleophile. It was speculated that the acid−base complex generated from the prenucleophile (Nu−H) and the diamine base could activate acrylates electrophilically via multihydrogen bonding[10] that would result in efficient assembly of the prenucleophile and the acrylate followed by smooth conjugate addition and consecutive protonation (Scheme 1).

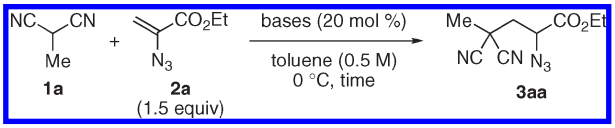
**Scheme 1.** A Working Hypothesis




Based on this hypothesis, we embarked on the investigation of conjugate addition reactions of 2-methylmalononitrile (**1a**) and ethyl 2-azidoacrylate (**2a**)[11,12] with various organic diamines to target α-azido ester derivatives, which could be utilized as a potential precursor for α-amino acids[13] (Table 1). As expected, 1,2-diaminocyclohexanes **A**−**C** exhibited remarkable catalytic reactivity to the conjugate addition at 0 °C, affording ethyl 2-azido-4,4-dicyanopentanoate (**3aa**) in good yields (Table 1, entries 1−3). Other types of diamines were next examined (entries 4−10). Among ethylenediamine derivatives (entries 4−8), the reaction with *N*,*N*′-dimethylethylenediamine (DMEDA) **E** was the most efficient (87% yield, entry 5), whereas that with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) **H** bearing two tertiary amine motifs was sluggish (entry 8).

It was noteworthy that utilization of propane-1,3-diamine **I** led to a remarkable promotion in the reaction effeciency, resulting in the formation of **3aa** in 98% yield within 4 h (entry 9), while butane-1,4-diamine **J** led to a reduction in the yield (entry 10). In the presence of triethylenetetramine **K**, the reaction was finished within 0.5 h, whereas the yield of **3aa** was moderate (entry 11). *trans*-1,2-Diaminocyclohexane-derived primary amine thiourea **L** (called as bifunctional thiourea) did not promote the reaction, providing **3aa** only in 28% yield even after 10 days (entry 12). The reactions with a series of alkyl monoamines as well as aryl amines such as aniline, 1,2-diaminobenzene, and 1,8-diaminonaphthalene resulted in no reaction.

**Table 1.** Diamine-Catalyzed Conjugate Addition of 2-Methylmalononitrile (**1a**) and Ethyl 2-Azidoacrylate (**2a**)[a]




| entry | amine bases | | time | yield of **3aa**[b] |
|---|---|---|---|---|
| 1 | *dl*-*meso* mixture | **A** | 13 h | 80% |
| 2 | *dl* (*trans*) | **B** | 13 h | 78% |
| 3 | *meso* (*cis*) | **C** | 9 h | 83% |
| 4 | $H_2N$ $NH_2$ | **D** | 24 h | 38% (19%)[c] |
| 5 | Me N H N H Me | **E** | 25 h | 87% |
| 6 | *i*-Pr N H N H *i*-Pr | **F** | 36 h | 75% |
| 7 | Me N H N Me Me | **G** | 36 h | 77% |
| 8 | Me Me N Me N Me Me | **H** | 24 h | 10% (15%)[c] |
| 9 | $H_2N$ $NH_2$ | **I** | 4 h | 98% |
| 10 | $H_2N$ $NH_2$ | **J** | 4 h | 65% |
| 11 | $NH_2$ $H_2N$ N $NH_2$ | **K** | 0.5 | 68% |
| 12[d] | $H_2N$ N H S N-Ph H | **L** | 10 days | 28% (26%)[c] |

[a] Reactions were carried out on the scale of 0.5 mmol of **1a** and 1.5 equiv of **2a** in toluene (1 mL) at 0 °C under a $N_2$ atmosphere. [b] Isolated yields. [c] Recovery yields of **1a**. [d] A racemic form was utilized.

By utilizing organic diamines as a base, we surveyed a variety of prenucleophiles for the conjugate addition to ethyl 2-azidoacrylate (**2a**), and Table 2 lists the best diamine catalyst for each nucleophile.[14] As a substituent at C2 of malononitirile, benzyl, phenyl, and allyl moieties could be introduced (entries 1−3). In the case of 2-propargylmalononitrile (**1e**), the desired conjugate addition was followed by intramolecular azide−alkyne cycloaddition to form bicyclic 1,2,3-triazole **4ea** in moderate yield in a one-pot fashion (entry 4). The reaction of malononitrile bearing an ethyoxycarbonyl functionality **1f** proceeded smoothly to

(10) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

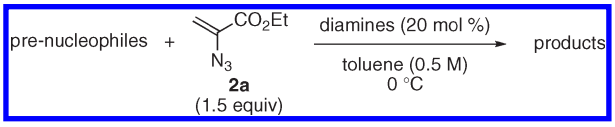
(11) For our reports on synthesis of azaheterocycles from vinyl azides, see: (a) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (b) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (c) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313.

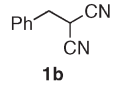
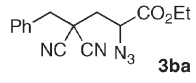
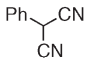
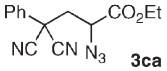
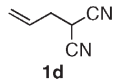
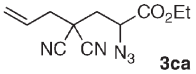
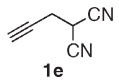
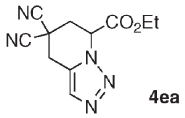
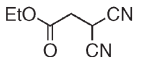
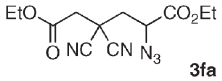
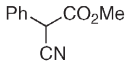
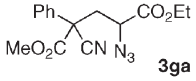
(12) For a report on conjugate addition of alcoholates and thiolates to ethyl 2-azidoacrylate (**2a**) under strong basic conditions, see: Kakimoto, M.; Kai, M.; Kondo, K.; Hiyama, T. *Chem. Lett.* **1982**, 527.

(13) (a) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(14) Optimization of the reaction conditions by varying diamine catalysts has been done for each nucleophile in combination with **2a**; see Supporting Information.

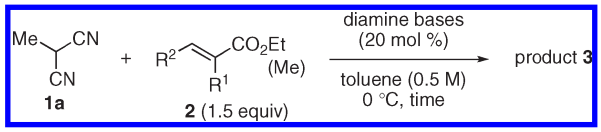
**Table 2.** Diamine-Catalyzed Conjugate Addition to Ethyl 2-Azido Acrylate (**2a**)[a]

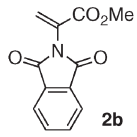
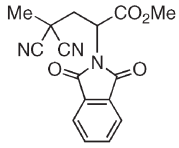
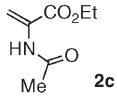
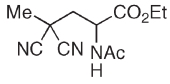
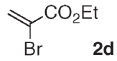
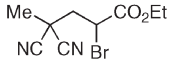
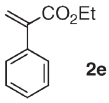
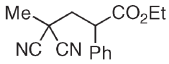
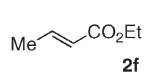
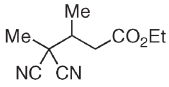
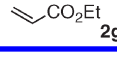
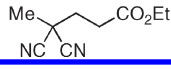



| entry | pre-nucleophiles | diamines | products | time, yield[b] |
|---|---|---|---|---|
| 1 |  **1b** | I |  **3ba** | 3 h, 86% |
| 2 |  **1c** | C |  **3ca** | 5 h, 82% |
| 3 |  **1d** | I |  **3ca** | 7 h, 80% |
| 4[c] |  **1e** | E |  **4ea** | 5 h, 60% |
| 5 |  **1f** | I |  **3fa** | 4 h, 98% |
| 6 |  **1g** | E |  **3ga** | 25 h, 82% (53:47)[d] |

[a] Reactions were carried out on the scale of 0.5 mmol of **1** and 1.5 equiv of vinyl azide **2a** in toluene (1 mL) at 0 °C under a $N_2$ atmosphere. [b] Isolated yields. [c] The reaction mixture was stirred at 0 °C until **1e** was consumed, before being heated at 40 °C for 10 h. [d] Diastereomer ratio determined by $^1$H NMR. The relative stereochemistry was not confirmed.

**Table 3.** 1,2-Diamine-Catalyzed Conjugate Addition of 2-Methylmalononitrile (**1a**) to Various Acrylates **2**[a]




| entry | electrophiles | diamines | product **3** | product time, yield[b] |
|---|---|---|---|---|
| 1 |  **2b** | D |  | **3ab**: 25 h, 87% |
| 2 |  **2c** | E |  | **3ac**: 24 h, 58% |
| 3 |  **2d** | I |  | **3ad**: 7 h, 96% |
| 4 |  **2e** | I |  | **3ae**: 7 h, 98% |
| 5 |  **2f** | C |  | **3af**: 7 days, 26% |
| 6 |  **2g** | I |  | **3ag**: 3 h, 99% |

[a] Reactions were carried out on the scale of 0.5 mmol of **1a** and 1.5 equiv of **2a** in toluene (1 mL) at 0 °C under a $N_2$ atmosphere. [b] Isolated yields.

give corresponding α-azido ester **3fa** in exellent yields (entry 5). Methyl 2-cyano-2-phenylacetate (**1g**) could also be utilized for this catalytic conjugate addition, providing **3ga** in good yields albeit with an almost 1:1 diastereoselectivity and a longer reacton time (25 h) (entry 6).[15]

Next, diamine-catalyzed conjugate additions of 2-methylmalononitrile (**1a**) to a series of acrylate derivatives were investigated, and the diamine catalyst realizing the best yield was shown for each acrylate in Table 3.[16,17] As 2-aminoacrylates, methyl 2-phthalimidoacrylate (**2b**)[18] and ethyl 2-acetoamidoacrylate (**2c**)[19] were examined instead of 2-azidoacrylate **2a** for the synthesis of α-amino acid derivatives. The reaction of 2-phthalimidoacrylate **2b** catalyzed by primary amine catalysts, ethylenediamine **D**, provided conjugate addition product **3ab** in good yield (entry 1), whereas, in the case of 2-acetoamidoacrylate (**2c**), the yields of conjugate addition product **3ac** were moderate (entry 2). Ethyl 2-bromoacrylate (**2d**) reacted with **1a** to give α-bromo ester **3ad** in 96% yield with propane-1,3-diamine **I** (entry 3). Ethyl 2-phenylacrylate

(15) The reactions of malononitrile were complicated by the formation of di- and monoalkylated products as well as polymelization of acrylate derivatives so that 2-substituted malononitriles and their derivatives were utilized for this study. Nucleophiles derived from 1,3-diketones and malonate esters resulted in no reaction under the present reaction conditions.

(16) Optimization of the reaction conditions by varying diamine catalysts has been done for each acrylate in combination with **1a**; see Supporting Information.

(17) An experimental procedure: Diamine (20 mol%) was added to a mixture of acrylates (0.75 mmol, 1.5 equiv) and a prenucleophile (0.5 mmol) in toluene (1 mL, 0.5 M) at 0 °C. The mixture was stirred under a $N_2$ atmosphere at 0 °C. Upon completion indicated by TLC, toluene was removed under reduced pressure and the crude mixture was subjected to column chromatography to yield conjugate addition products.

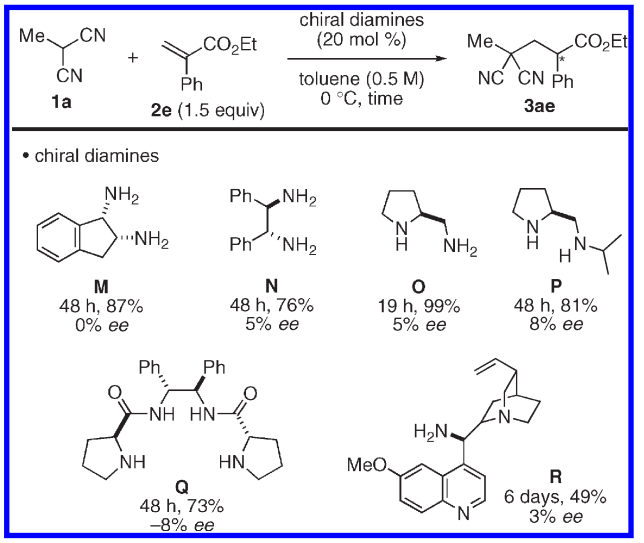
(18) For a report on enantioselective protonation of 2-phthalimidoacrylate (**2b**) by the reaction with thiols catalyzed by a chiral bicyclic guanidine, see: Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641.

(19) For a report on an NHC-catalyzed enantioselective Stetter reaction of ethyl 2-acetoamidoacrylate (**2c**), see: Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410.

(20) For a report of conjugate addition of malonates to methyl acrylate under the $Et_3N-LiClO_4$ catalyst system, see: Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44.

(21) For reviews on enantioselective protonation, see: (a) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653.

**Scheme 2.** Enantioselective Induction Using Chiral Diamines[a]




[a] Reactions were carried out on the scale of 0.5 mmol of **1a** and 1.5 equiv of **2a** in toluene (1 mL) at 0 °C under a $N_2$ atmosphere. Isolated yields.

(**2e**) resulted in a smooth reaction with **1a**, giving α-phenyl ester **3ae** in excellent yield (entry 4). It was found that *β*-substituents retarded the conjugate addition. For example, the reaction of ethyl crotonate (**2f**) was sluggish, providing ethyl 4,4-dicyano-3-methylpentanoate (**3af**) in 26% yield even after 7 days (entry 5). Finally, conjugate addition of **1a** to ethyl acrylate (**2g**) was tested,[20] where propane-1,3-diamine **I** could complete the reaction within 3 h, leading to the formation of **3ag** in almost quantitative yields (entry 6).

We finally explored a possibility for the construction of an α-chiral center in the conjugate addition of 2-methylmalononitrile (**1a**) to ethyl 2-phenylacrylate (**2e**) by using a series of chiral diamine catalysts (**M**−**R**) as shown in Scheme 2.[21] It was found that several chiral diamines such as (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine (**N**) and (*S*)-2-(*N*-aminomethyl)pyrrolidines (**O** and **P**) provided low but reproducible enantioselectivities (5−8% ee). Interestingly, $C_2$-symmetric bisprolinamide **Q**[22] showed reverse chiral induction (−8% ee). The reaction with diamine **R** derived from quinidine[23] was very sluggish. Although the obtained enantioselectivity was not practically valuable yet, these results might uphold the working hypothesis depicted in Scheme 1 including a certain interaction of the prenucleophile (Nu−H) and the acrylate through the acid−base complex of the prenucleophile and the diamine base.

In summary, we have developed a diamine-catalyzed intermolecular conjugate addition of α-cyano active methine nucleophiles to various acrylate derivatives. Further investigation on the detailed reaction mechanism and reaction scope as well as rational design of the catalysts based on the diamine functionality for enhancing enantio- and diastereoselectivity is currently underway and will be reported in due course.

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**Supporting Information Available.** Experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321.

(23) Brunner, H.; Bugler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699.