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COMMUNICATION

Synthesis of functionalized 2,3-dihydroisoxazoles by domino reactions in water and unexpected ring-opening reactions of 2,3-dihydroisoxazoles†‡

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α,α-Dicyanoolefins react with hydroxylamine to afford 2,3-dihydroisoxazoles (2,3-dihydroisoxazoles can be easily isolated by filtration) in excellent yields under mild and environmentally benign conditions. A one-pot reaction in tandem with an unexpected ring-opening of 2,3-dihydroisoxazoles has been developed as well.

2,3-Dihydroisoxazoles are an important class of heterocycles, widely present in a number of bioactive molecules.[1] In addition to serving as drug and agrochemical targets, 2,3-dihydroisoxazoles are also valuable as synthetic building blocks in organic synthesis since the N–O bond can be easily cleaved under mild reducing conditions.[2] For example, highly substituted 2,3-dihydroisoxazoles are particularly used as interesting starting materials in the synthesis of 1,3-amino alcohols[3–4] or 1,3-amino ketones[3–5] Moreover, the rearrangement reactions of 2,3-dihydroisoxazoles are well-known.[6] It is therefore unsurprising that the development of a new and efficient methodology for the synthesis of these materials continuously commands considerable attention. The most frequent synthetic methods used for the construction of 2,3-dihydroisoxazoles are of 1,3-dipolar cycloaddition reactions between nitrones and alkynes or metal acetylides over transition metals or Lewis acids as catalysts in the past years.[7] Recently, an Et_3N-catalyzed tandem reaction of electron-deficient 1,3-conjugated enynes with hydroxylamines for the construction of 2,3-dihydroisoxazoles has been developed by Zhang's group.[8] Although these methods have been used for years, there are significant drawbacks: transition-metal-catalyzed 1,3-dipolar cycloadditions often furnish regioisomeric mixtures of adducts and proceed in low yields.[7e,7g,7h] The success of these methods is often limited as in many cases the reaction conditions remain harsh.[7b,7d,7g,7h] Toxic transition-metal catalysts and organic solvents can cause significant air pollution, land contamination and water pollution.[7,8] Thus it remains highly desirable to develop a new synthetic method that can be carried out under milder conditions without using toxic transition-metal catalysts. Furthermore, the development of an efficient synthetic methodology for organic reactions, in the absence of organic solvents, is an important challenge toward reducing the amount of waste. An ideal organic reaction would proceed in an environmentally benign solvent, such as water. To address this important issue, here we would like to present a base-catalyzed domino reaction of electron-deficient α,α-dicyanoolefins with hydroxylamines, providing a facile, mild, efficient and environmentally benign approach to trisubstituted 2,3-dihydroisoxazoles. For the first time, we report the highly chemoselective unexpected ring-opening reactions of 2,3-dihydroisoxazoles to afford 2-cyano-α,β-unsaturated amides under mild conditions.

Recently, our group[9] and others[10] have demonstrated that electron-deficient α,α-dicyanoolefins are readily available and attractive precursors for the construction of various acyclic and cyclic compounds. Inspired by the recent reports,[9–10] we envisaged that 2,3-dihydroisoxazoles with multiple substitutions might be prepared from the corresponding electron-deficient α,α-dicyanoolefins and hydroxylamine by the new domino Michael addition/intramolecular cyclization reactions.

In an initial study, we studied the reaction of $NH_2OH{\cdot}HCl$ with α,α-dicyanoolefin **1a**, which can easily be prepared on a gram scale in excellent yields according to the reported procedure.[11] To our delight, 2,3-dihydroisoxazole **2a** was obtained in a yield of 78% when the reaction was carried out at pH ~ 8 in water at room temperature for 4 h (Table 1, entry 1). The yield was dramatically increased when the pH value increased (Table 1, entries 2–3). Interestingly, clean product **2a** was obtained when the pH values were in the region of 9–10. Surprisingly, both desired products 2,3-dihydroisoxazole **2a** and benzaldoxime **3a** were isolated when the pH value was increased (Table 1, entry 4). It was quite obvious that the elimination of malononitrile took place under these conditions. Only benzaldoxime **3a** was obtained when the pH value was above 12 (Table 1, entry 5). Therefore, the reaction condition (pH = 9–10) was chosen as our general strategy for the following work.

With the optimized conditions in hand, we then explored the scope of the domino reactions by employing various substituted

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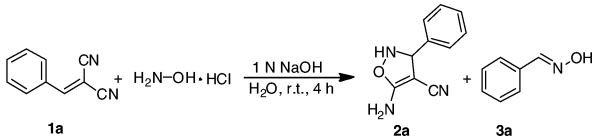
‡ Crystal data for **4a** $C_{10}H_8N_2O$ (172.18), monoclinic, space group $P2_1/n$, a = 10.3225(7) Å, b = 11.2447(8) Å, c = 16.7681(11) Å, U = 1776.5(2) Å^3, Z = 8, specimen 0.492 × 0.453 × 0.259 mm^3, T = 296(2)K, SIEMENS P4 diffractometer, absorption coefficient 0.086 mm^{-1}, reflections collected 26305, independent reflections 4096 [R(int) = 0.0497], refinement by full-matrix least-squares on F^2, data/restraints/parameters 4096/0/235, goodness-of-fit on F^2 = 1.010, final R indices [$I > 2\sigma(I)$] R_1 = 0.0483, wR_2 = 0.1209, R indices (all data) R_1 = 0.1016, wR_2 = 0.1477, largest diff. peak and hole 0.129 and -0.175 e Å^{-3}.

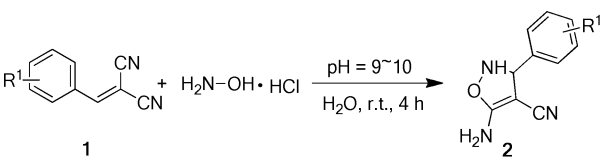
Table 1 Reaction of α,α-dicyanoolefin **1a** and $NH_2OH{\cdot}HCl$ under different conditions[a]

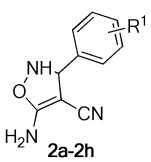


Entry	pH[b]	Yield (%) **2a**[c]	Yield (%) **3a**[c]
1	8	78	0
2	9	91	0
3	10	90	0
4	11	16	68
5	12	trace	75

[a] Unless otherwise noted, reaction performed with 1 mmol of **1a**, 10 mmol of $NH_2OH{\cdot}HCl$, in 5 mL water at room temperature for 4 h. [b] Testing with pH paper. [c] Isolated yield.

electron-deficient α,α-dicyanoolefins **1a–h**. The results are shown in Scheme 1. It is worthy of note here that a pale yellow precipitate was formed when the reactions were carried out at room temperature for 4 h and 2,3-dihydroisoxazoles were easily isolated by filtration, then washed with water to give the pure 2,3-dihydroisoxazoles in excellent yields. The domino reaction was also proven effective and convenient to prepare 2,3-dihydroisoxazoles on a large scale (>10 g, see Supplementary Information†). The reaction scope was quite broad with respect to α,α-dicyanoolefins **1**. Various substituted electron-deficient α,α-dicyanoolefins **1a–h** with different substitutions were investigated. The electronic effect was very marginal and remarkable yields were achieved (Scheme 1, **2a–h**) and α,α-dicyanoolefins with electron-withdrawing substituents on the *ortho*, *meta* or *para* positions afford 2,3-dihydroisoxazoles without affecting the yield (Scheme 1, **2d**, **2g–h**).

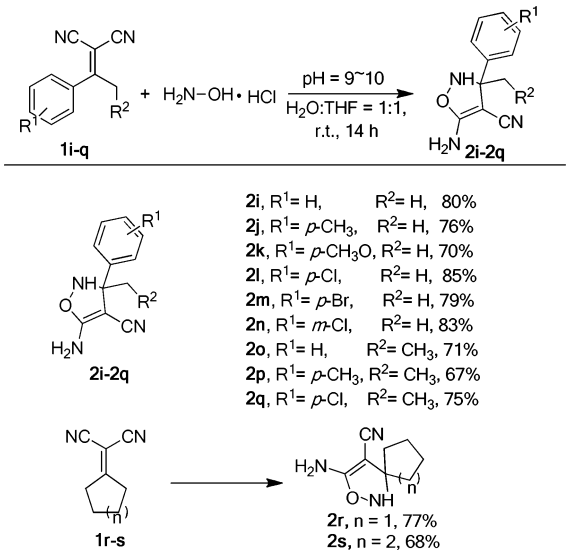




2a, R^1= H, 91%
2b, R^1= *p*-CH_3, 93%
2c, R^1= *p*-F, 90%
2d, R^1= *p*-Cl, 95%
2e, R^1= *p*-Br, 93%
2f, R^1= *p*-CF_3, 88%
2g, R^1= *m*-Cl, 95%
2h, R^1= *o*-Cl, 91%

Scheme 1 Synthesis of multifunctionalized 2,3-dihydroisoxazoles (**2a–h**).

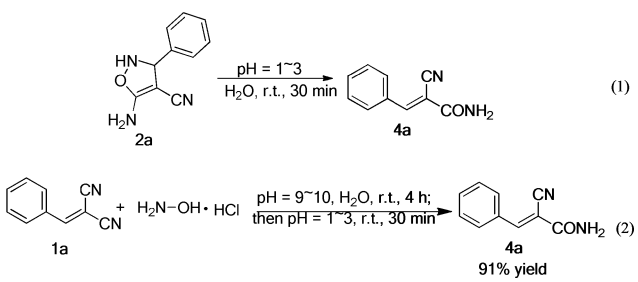
Other bulkier α,α-dicyanoolefins **1i–q** were also well tolerated to give good yields while a longer reaction time was required (Scheme 2). Although a sluggish reaction was observed even at room temperature due to the very low solubility of α,α-dicyanoolefins **1i–q** in water, gratifyingly, the domino reactions proceeded very well when THF and water were used in a 1 : 1 ratio under the same conditions, and moderate to good yields (67%–85%) were achieved after 14 h. Good yields were obtained in the domino reactions of $NH_2OH{\cdot}HCl$ with α,α-dicyanoolefins which



Scheme 2 Synthesis of multifunctionalized 2,3-dihydroisoxazoles (**2i–2q**) and spiro-2,3-dihydroisoxazoles (**2r–s**).

possess electron-withdrawing groups in the phenyl ring (**1l–n**, **1q**). An electron-donating substituent on aryl ring of α,α-dicyanoolefin substrates has a little effect on the yields (**1j–k**, **1p**). Interestingly, under the same conditions as aforementioned, for aliphatic cyclic substrates **1r–s**, the domino reactions proceeded very well to afford spiro-2,3-dihydroisoxazoles (**2r–s**).

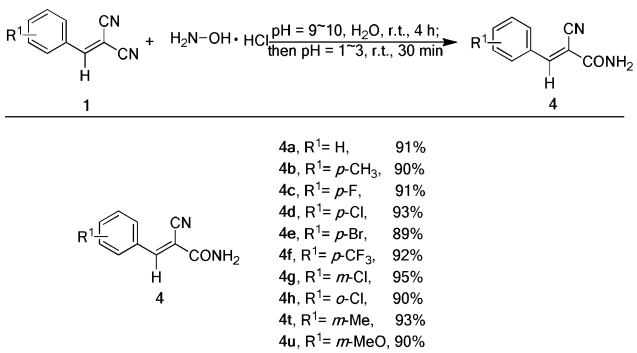
Having succeeded in synthesizing 2,3-dihydroisoxazoles and spiro-2,3-dihydroisoxazoles possessing multiple substitutions from various substituted electron-deficient α,α-dicyanoolefins and $NH_2OH{\cdot}HCl$ under mild conditions, we turned our attention to the possible synthesis of functional compounds by this new methodology. To our surprise, unexpected ring-opening product 2-cyano-3-phenyl-acrylamide **4a** was isolated in quantitative yield when 2,3-dihydroisoxazole **2a** was stirred in diluted hydrochloric acid (Scheme 3, (1)). From a synthetic point of view, one-pot procedures beginning with simple, readily available substrates provide ideal strategies in organic synthesis. It was envisioned that some reactions would be processed in one pot between α,α-dicyanoolefins and $NH_2OH{\cdot}HCl$. Therefore, we first investigated the reaction of α,α-dicyanoolefin **1a** with $NH_2OH{\cdot}HCl$ under the same conditions as described above. After stirring at room temperature for 4 h, 2,3-dihydroisoxazole **2a** was not separated. Afterwards, hydrochloric acid (2 N HCl) was added until the reaction pH was in the range of 1–3. After stirring at room temperature for another 30 min, unexpected ring-opening product



Scheme 3 Synthesis of 2-cyano-3-phenyl-acrylamide *via* one-pot tandem reaction.

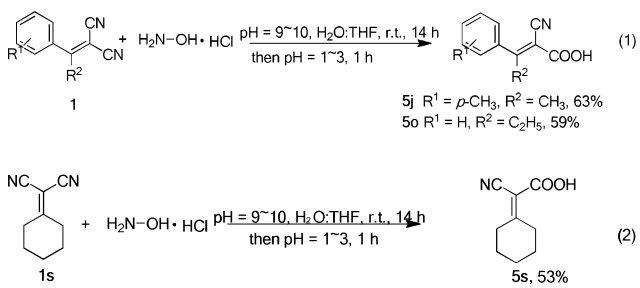
2-cyano-3-phenyl-acrylamide **4a** was isolated in a yield of 91% (Scheme 3, (2)). The structure and stereochemistry of **4a** were established by X-ray analysis.[12] It is obvious that highly chemoselective ring-opening reactions of 2,3-dihydroisoxazole **2a** to afford 2-cyano-3-phenyl-acrylamide **4a** took place under these conditions.

After the unexpected reactions of α,α-dicyanoolefins were investigated, more experiments were conducted to test the substrate scope of the one-pot process and to gain further insight with regard to the possible reaction mechanism. As shown in Scheme 4, a variety of α,α-dicyanoolefins with different structures were investigated. The electronic effect was also very marginal and excellent yields were achieved for substrates **1**. α,α-Dicyanoolefins with electron withdrawing substituents on the *ortho*, *meta* or *para* positions afford 2-cyano-3-aryl-acrylamides without affecting the yields (Scheme 4, **4d**, **4g–h**).



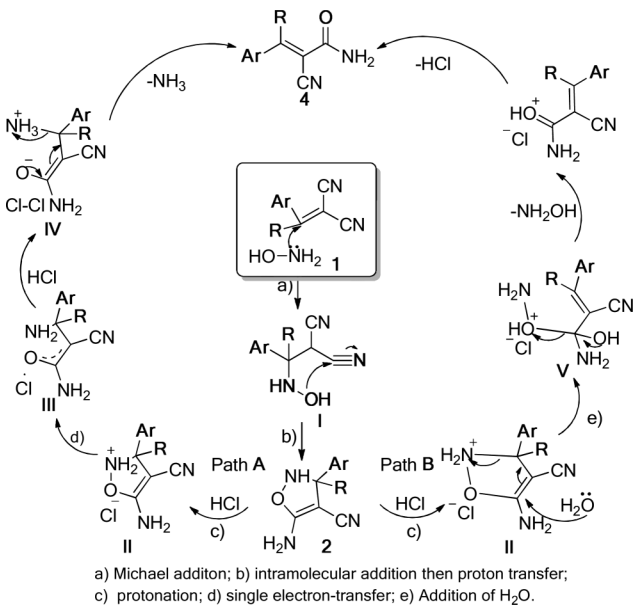
Scheme 4 Reaction scope of α,α-dicyanoolefins **1** in the one-pot tandem reaction.

Interestingly, under the same conditions as described above, for other bulkier α,α-dicyanoolefins (Scheme 5, **1j**, **1o**), 2-cyano-3-aryl-but-2-enoic acid derivatives **5j** and **5o** were isolated in good yields, respectively (Scheme 5, eq. 1). Apparently the unexpected ring-opening reactions took place, and a further hydrolysis of the amide group occurred to generate the observed acid products. Since the direct Knoevenagel reactions of unmodified ketones, especially for aryl ones, with 2-cyanoacetic acid, have been rarely reported to date,[13] the readily available and easily handled α,α-dicyanoolefins could act as versatile and highly reactive precursors of ketones in such reactions. In addition, for aliphatic cyclic substrate **1s**, hydrolyzed product **5s** was isolated in good yield (Scheme 5, eq. 2).



Scheme 5 One-pot tandem reaction of other bulkier α,α-dicyanoolefins **1** and $NH_2OH{\cdot}HCl$.

On the basis of the experimental observations, a possible mechanism was proposed to explain the one-pot tandem reactions. As shown in Scheme 6, the Michael reaction between the highly reactive α,α-dicyanoolefins **1** and hydroxylamine proceeded very well to afford the intermediates **I** under the basic conditions. 2,3-Dihydroisoxazoles **2** were readily obtained *via* an intramolecular addition of the OH group on the cyano moiety and proton transfer. Then 2,3-dihydroisoxazoles **2** were protonated, followed by a single electron-transfer (SET) mechanism[14] to afford open-ring products **4** (Path A). Open-ring products **4** were also obtained by addition of H_2O to intermediates **II**, then hydroxylamine was eliminated as a leaving group (Path B). Path A is more preferred than Path B by the DFT calculations.[15a]



Scheme 6 Plausible mechanism for the one-pot tandem reaction.

In summary, we have developed an extremely facile and mild synthesis of trisubstituted 2,3-dihydroisoxazoles, including spirocyclic compounds that are potentially relevant to natural product synthesis, by the reaction of hydroxylamine with α,α-dicyanoolefins **1** as well as developed a one-pot reaction in tandem with an unexpected ring-opening of 2,3-dihydroisoxazoles to afford 2-cyano-3-aryl-acrylamides and 2-cyanobut-2-enoic acid derivatives. Both reactions employ very simple and readily available substrates and tolerate a range of functional groups to produce substituted 2,3-dihydroisoxazoles, 2-cyano-3-aryl-acrylamides and 2-cyanobut-2-enoic acid derivatives with moderate to excellent yields. Additionally, the reactions can be carried out in water as a cheap and environmentally benign solvent, and a simple purification step provides the products in good yields. The method for the synthesis of trisubstituted 2,3-dihydroisoxazoles can be conducted on a larger scale (>10 g)[15b] at low cost making it an ideal alternative to existing methods. Two plausible mechanisms for this unprecedented ring-opening reaction were given. We anticipate that this work would arouse more interest in the chemistry of 2,3-dihydroisoxazoles. Further development of this reaction including studies on the reaction mechanism and scopes, is being pursued and will be reported in due course.

Acknowledgements

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Notes and references

1 (*a*) A. G. Habeeb, P. N. Praveen Rao and E. E. Knaus, *J. Med. Chem.*, 2001, **44**, 2921; (*b*) M. E. Fraley, R. M. Garbaccio, G. D. Hartman, Patent WO 2006023440, 2006.

2 (*a*) J. P. Freeman, *Chem. Rev.*, 1983, **83**, 241; (*b*) A. Padwa and G. S. K. Wong, *J. Org. Chem.*, 1986, **51**, 3125; (*c*) A. Padwa, U. Chiachio, D. N. Kline and J. Perumattan, *J. Org. Chem.*, 1988, **53**, 2238; (*d*) A. Padwa, W. H. Bullock, D. N. Kline and J. Perumattam, *J. Org. Chem.*, 1989, **54**, 2862; (*e*) E. Lopez-Calle, M. Keller and W. Eberbach, *Eur. J. Org. Chem.*, 2003, 1438; (*f*) T. Ishikawa, T. Kudoh, J. Yoshida, A. Yasuhara, S. Manabe and S. Saito, *Org. Lett.*, 2002, **4**, 1907; (*g*) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, C. Pardo, E. Saez and M. R. Torres, *J. Org. Chem.*, 2002, **67**, 7004; (*h*) P. Aschwanden, L. Kværnø, R. W. Geisser, F. Kleinbeck and E. M. Carreira, *Org. Lett.*, 2005, **7**, 5741; (*i*) W. V. Murray, D. Francois, A. Maden and I. Turchi, *J. Org. Chem.*, 2007, **72**, 3097; (*j*) D. P. Canterbury, I. R. Herrick, J. Um, K. N. Houk and A. J. Frontier, *Tetrahedron*, 2009, **65**, 3165; (*k*) D. P. Canterbury, A. J. Frontier, J. M. Um, P. H.-Y. Cheong, D. A. Goldfeld, R. A. Huhn and K. N. Houk, *Org. Lett.*, 2008, **10**, 4597; (*l*) N. Coşkun and M. Ceştin, *Tetrahedron*, 2010, **66**, 2053.

3 (*a*) R. A. Pilli and D. Russowsky, *J. Chem. Soc., Chem. Commun.*, 1987, 1053; (*b*) R. A. Pilli, D. Russowsky and L. C. Dias, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1213; (*c*) J. Barluenga, E. Aguilar, S. Fustero, B. Olano and A. L. Viado, *J. Org. Chem.*, 1992, **57**, 1219; (*d*) G. E. Keck and A. P. Truong, *Org. Lett.*, 2002, **4**, 3131.

4 (*a*) *Comprehensive Asymmetric Catalysis I–III*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, ed.; Springer-Verlag: Berlin, Heidelberg, 1999; (*b*) *Catalytic Asymmetric Synthesis*, 2nd ed.; I. Ojima, Ed.; Wiley-VCH: New York, 2000.

5 (*a*) D. J. Hart and D. C. Ha, *Chem. Rev.*, 1989, **89**, 1447; (*b*) M. Arend, B. Westermann and N. Risch, *Angew. Chem., Int. Ed.*, 1998, **37**, 1045; (*c*) A. Dondoni, A. Marra and A. Boscarato, *Chem.–Eur. J.*, 1999, **5**, 3562; (*d*) S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069; (*e*) M. S. Taylor, D. N. Zalatan, A. M. Lerchner and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 1313; (*f*) M. L. Kantam, V. Neeraja, B. Kavita, B. Neelima and S. Hussain, *Adv. Synth. Catal.*, 2005, **347**, 763; (*g*) A. A. Jafari, F. Moradgholi and F. Tamaddon, *Eur. J. Org. Chem.*, 2009, 1249.

6 (*a*) R. Huisgen, H. Giera and K. Polborn, *Liebigs Ann./Recl.*, 1997, **8**, 1691; (*b*) J. P. Freeman, *Chem. Rev.*, 1983, **83**, 241.

7 (*a*) P. Aschwanden, D. E. Frantz and E. M. Carreira, *Org. Lett.*, 2000, **2**, 2331; (*b*) M. Fabio, L. Ronzini and L. Troisi, *Tetrahedron*, 2008, **64**, 4979; (*c*) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry. Toward Heterocycles and Natural Products*, A. Padwa, W. H. Pearson, ed.; Wiley: New York, 2002; (*d*) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, C. Pardo, E. Sa'ez and M. R. Torres, *Org. Lett.*, 2002, **4**, 1463; (*e*) F. Benfatti, G. Cardillo, S. Contaldi, L. Gentilucci, E. Mosconi, A. Tolomelli, E. Juaristi and G. Reyes-Rangel, *Tetrahedron*, 2009, **65**, 2478; (*f*) F. Cantagrel, S. Pinet, Y. Gimbert and P. Y. Chavant, *Eur. J. Org. Chem.*, 2005, 2694; (*g*) D. P. Canterbury, A. J. Frontier, J. M. Um, P. H.-Y. Cheong, D. A. Goldfeld, R. A. Huhn and K. N. Houk, *Org. Lett.*, 2005, **7**, 5147; (*h*) O. Debleds, C. Dal Zotto, E. Vrancken, J.-M. Campagne and P. Retailleau, *Adv. Synth. Catal.*, 2009, **351**, 1991.

8 X. Yu, B. Du, K. Wang and J. Zhang, *Org. Lett.*, 2010, **12**, 1876.

9 (*a*) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Chem. Commun.*, 2006, 1563–1565; (*b*) J.-W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y.-C. Chen, Y. Wu, J. Zhu and J.-G. Deng, *Angew. Chem., Int. Ed.*, 2007, **46**, 389–392.

10 (*a*) T. B. Poulsen, C. Alemparte and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 11614; (*b*) T. B. Poulsen, M. Bell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2006, **4**, 63; (*c*) H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 4479 and references therein.

11 K. Guo, M. J. Thompson, T. R. K. Reddy, R. Mutter and B. Chen, *Tetrahedron*, 2007, **63**, 5300.

12 For X-ray crystal data of compound **4a**, see Supporting Information†.

13 (*a*) G. Fronza, C. Fuganti and S. Serra, *Eur. J. Org. Chem.*, 2009, 6160; (*b*) Y. Moussaoui and R. B. Salem, *C. R. Chim.*, 2007, **10**, 1162.

14 (*a*) U. Chiacchio, A. Rescifina, M. A. Chiacchio, G. Romeo and R. Romeo, *J. Org. Chem.*, 2003, **68**, 3718; (*b*) L. Eberson, *Adv. Phys. Org. Chem.*, 1982, **18**, 79; (*c*) A. Pros, *Acc. Chem. Res.*, 1985, **18**, 212.

15 See Supplementary Information for (*a*) DFT Calculations; (*b*) Photo of the reactions of **1a** (15.4 g, 0.1 mol) with $NH_2OH.HCl$†.