

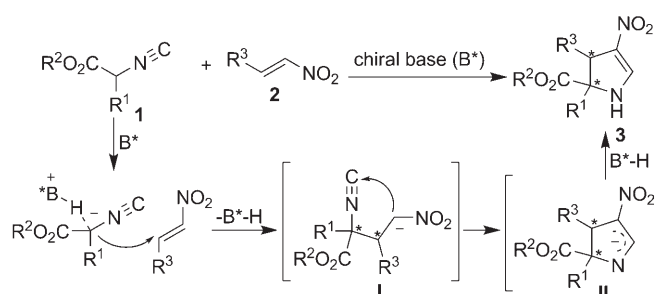
Organocatalytic Asymmetric Formal [3+2] Cycloaddition Reaction of Isocyanoesters to Nitroolefins Leading to Highly Optically Active Dihydropyrroles**

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Heterocyclic compounds containing a chiral pyrrolidine motif commonly appear in natural alkaloids and pharmaceutically active substances, and serve as building blocks commonly used for total syntheses; therefore there has been great demand for highly efficient asymmetric synthetic methods to access these compounds.^[1,2] Optically active 2,3-dihydropyrroles are important unsaturated heterocyclic compounds that can not only be transformed into multisubstituted pyrrolidines for the synthesis of chiral building blocks, but can also be applied to the total synthesis of natural products.^[3] The synthetic approaches to access enantioenriched pyrrolidines include chiral-auxiliary-assisted asymmetric synthesis and a number of transition-metal-catalyzed asymmetric dipolar addition reactions.^[2] However, organocatalytic approaches to access chiral pyrrolidines are scarce^[4] despite the growth in asymmetric organocatalysis in modern organic synthesis.^[5] Moreover, the asymmetric catalytic synthesis of chiral 2,3-dihydropyrroles remains elusive and the discovery of catalytic asymmetric reactions that yield optically active 2,3-dihydropyrroles is an important challenge. Over 30 years ago, cycloaddition reactions of metalated isocyanides to α,β -unsaturated carbonyl and nitrile compounds were reported to generate racemic 2,3-dihydropyrroles.^[6] An enantioselective version of this transformation may provide a method for direct access to chiral dihydropyrroles and would therefore be valuable in the synthesis of chiral building blocks and related alkaloids.^[2] In contrast to the long history of nonasymmetric variants,^[6] enantioselective, catalytic cycloaddition reactions of isocyanoesters with electron-deficient olefins are not yet

available. Herein, we report the first catalytic asymmetric cycloaddition reaction of isocyanoesters^[7] to nitroolefins by using alkaloid-derived bases to form highly functionalized 2,3-dihydropyrroles with excellent enantioselectivities (up to > 99% *ee*).

Our mechanistic proposal for the formal cycloaddition reaction catalyzed by a chiral base is shown in Scheme 1. The



Scheme 1. Proposed mechanism for the asymmetric cycloaddition reactions of isocyanoesters to nitroolefins catalyzed by a chiral base.

chiral base could promote an asymmetric Michael addition of isocyanoesters **1** to electron-deficient olefins, such as nitroolefins **2**, by activating the acidic α -carbon atom of **1** to generate intermediates **I**. Subsequent intramolecular cyclization reactions of intermediates **I** afforded precursor 1,2-dihydropyrroles **II**, which may be converted into dihydropyrrole **3** after protonation.^[6]

Cinchona alkaloids and their derivatives have been revealed as efficient organocatalysts for many asymmetric reactions,^[8] particularly for a variety of asymmetric C-nucleophilic addition reactions in which the basic functionalities of the alkaloid activates acidic α -carbon pronucleophiles (Figure 1).^[9–12] Surprisingly, to the best of our knowledge, isocyanoesters have not yet been used as nucleophiles in these reactions, or in other organic base-catalyzed nucleophilic addition reactions. Despite this, we still believed that cinchona alkaloids and their derivatives might be able to activate isocyanoesters by deprotonation in consideration of the sufficient acidity of the α -hydrogen atom in isocyanoesters **1** and in light of the earlier successes.^[9–12] Thus, in the presence of cinchona alkaloid derivatives the asymmetric formal cycloaddition of isocyanoesters to nitroolefins may proceed by the proposed mechanism (Scheme 1) and lead to the formation of optically active 2,3-dihydropyrroles.

We first examined a cycloaddition reaction of methyl α -phenylisocyano acetate (**1a**) to nitroalkene **2a** in CH_2Cl_2 at

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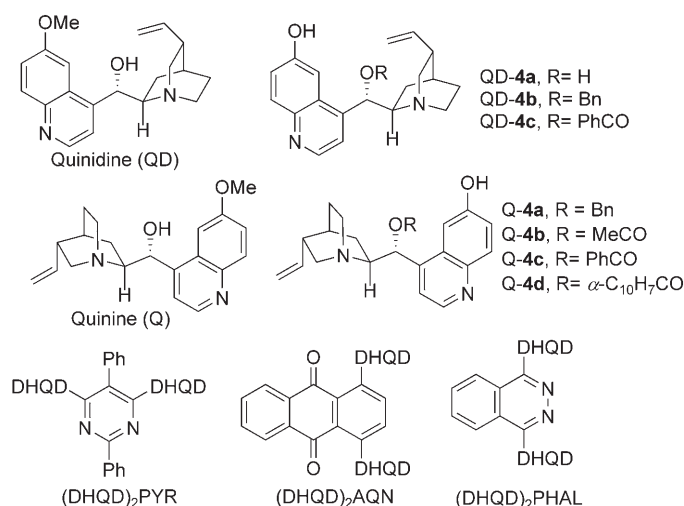


Figure 1. Organocatalysts used in this study.

room temperature in the presence of 20 mol % of naturally available quinidine. However, the reaction gave the desired product in only 48 % yield with poor diastereo- and enantioselectivity after three days (Table 1, entry 1). No significant enhancement in the yield was achieved when the reaction was carried out at 35 °C (Table 1, entry 2). Although quinine provided a high overall yield, low diastereo- and enantioselectivities were obtained for the major diastereomer of **3a** (Table 1, entry 3). Neither (DHQD)₂AQN, (DHQD)₂PYR, nor (DHQD)₂PHAL served as an efficient and highly stereoselective organocatalyst (Table 1, entries 4–6). Notably,

cinchona alkaloids bearing a C6'-hydroxy group can serve as a bifunctional organocatalyst,^[12] and they showed much higher stereoselectivity than their parent molecules (Table 1, entries 7–13). Of the 6'-hydroxy cinchona alkaloids screened, **Q-4c** was the best catalyst and afforded **3a** in 68 % yield, 19:1 d.r., and 97 % *ee* (Table 1, entry 12). Slightly higher enantio- and diastereoselectivities were observed for the reaction carried out in chloroform, but the product was isolated in a lower yield (Table 1, entry 14). Very low conversion occurred when the reaction was conducted in toluene, albeit with a high *ee* value (Table 1, entry 15). Increasing the reaction temperature enhanced the reaction rate, but it was deleterious to the diastereo- and enantioselectivities (Table 1, entry 16).

The cycloadditions of methyl α -phenylisocyno acetate (**1a**) with a variety of nitroolefins were investigated under the optimized reaction conditions (Table 2); the nitroolefins included those bearing electron-withdrawing and electron-donating substituents on the aryl ring and aliphatic nitroalkenes. High enantioselectivities ranging from 91 % to more than 99 % *ee* and synthetically useful diastereoselectivities were observed for all the nitrostyrenes tested; the selectivities depend on the steric and electronic features of the substituents (Table 2, entries 1–9). Electron-deficient aryl substituents facilitate the cycloaddition with excellent stereoselectivity (Table 2, entries 1–5 and 8–9). Electron-rich aryl nitroolefins also underwent smooth cycloaddition reactions with

Table 2: Cycloadditions of methyl α -phenylisocyno acetate (**1a**) with various nitroolefins.^[a]

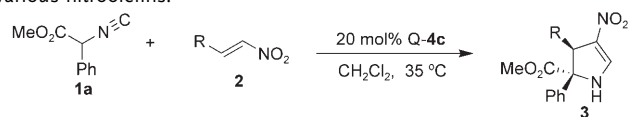


Table 1: Catalyst screening and optimization of reaction conditions.^[a]

Entry	Catalyst	Solvent	T [°C]	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1	QD	CH ₂ Cl ₂	25	48	2:1	21 (22) ^[e]
2	QD	CH ₂ Cl ₂	35	40	4:1	27 (37)
3	Q	CH ₂ Cl ₂	25	70	3:1	25 (80) ^[e]
4	(DHQD) ₂ AQN	CH ₂ Cl ₂	25	33	5:1	0 (0) ^[f]
5	(DHQD) ₂ PYR	CH ₂ Cl ₂	25	44	2:1	4 (43)
6	(DHQD) ₂ PHAL	CH ₂ Cl ₂	35	30	4:1	4 (14) ^[f]
7	QD-4a	CH ₂ Cl ₂	35	40	4:1	87 (33)
8	QD-4b	CH ₂ Cl ₂	35	41	11:1	96
9	QD-4c	CH ₂ Cl ₂	35	51	10:1	94
10	Q-4a	CH ₂ Cl ₂	35	42	10:1	98
11	Q-4b	CH ₂ Cl ₂	35	46	19:1	96
12	Q-4c	CH ₂ Cl ₂	35	68	19:1	97
13	Q-4d	CH ₂ Cl ₂	35	50	> 20:1	96
14	Q-4c	CHCl ₃	35	31	> 20:1	99
15	Q-4c	PhCH ₃	35	9	> 20:1	98
16	Q-4c	CHCl ₃	50	66	3:1	94

[a] The reaction of **1a** (0.45 mmol), **2a** (0.3 mmol), and a catalyst in solvent (1.0 mL) was stirred for 24 h unless indicated otherwise. [b] Yields of isolated products. [c] Determined by ¹H NMR spectroscopy of the crude product. [d] Determined by HPLC analysis and *ee* values are shown in parentheses for the minor diastereomer. [e] Run for 3 days. [f] Run for 4 days.

Entry	3	R	t [h]	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1	3b	4-BrC ₆ H ₄ (2b)	30 (29)	74 (52)	> 20:1 (> 20:1)	96 (96)
2	3c	4-ClC ₆ H ₄ (2c)	29 (30)	75 (65)	8:1 (> 20:1)	91 (98)
3	3d	4-FC ₆ H ₄ (2d)	28	61	14:1	96
4	3e	4-CNC ₆ H ₄ (2e)	29	82	10:1	95
5	3f	4-CF ₃ C ₆ H ₄ (2f)	29	68	10:1	98
6	3g	4-MeC ₆ H ₄ (2g)	29	59	8:1	96
7	3h	2-naphthyl (2h)	106	60	4:1	91
8	3i	3-ClC ₆ H ₄ (2i)	24	69	11:1	97
9	3j	3-NO ₂ C ₆ H ₄ (2j)	56	61	7:1	> 99
10	3k	α -C ₄ H ₃ S (2k)	29	63	8:1	98
11	3l	α -C ₁₀ H ₇ (2l)	22 (28)	86 (79)	8:1 (> 20:1)	97 (96)
12	3m	β -C ₁₀ H ₇ (2m)	48	66	5:1	95
13	3n	3,5-Br ₂ C ₆ H ₃ (2n)	47	66	7:1	98
14	3o	Cy (2o)	125	52	8:1	93
15	3p	Et (2p)	134	51	10:1	97

[a] Conditions: **1a** (0.45 mmol), **2** (0.3 mmol), and **Q-4c** (0.06 mmol) in CH₂Cl₂ (1.0 mL). The results in parentheses were obtained with 20 mol % **QD-4c** for opposite enantiomers. Cy = cyclohexyl. [b] Yields of isolated products. [c] Determined by ¹H NMR spectroscopy of crude product. [d] Determined by HPLC analysis.

91–96% *ee* (Table 2, entries 6 and 7), although a prolonged reaction was needed in the case of **2h** (Table 2, entry 7). Generally high enantioselectivities were attained with nitroolefins bearing a heterocyclic, naphthyl, or a disubstituted phenyl group (Table 2, entries 10–13, 95–98% *ee*). Alkyl substituted nitroalkenes also furnished **3o** and **3p** with high diastereo- and enantioselectivities, respectively (Table 2, entries 14 and 15). Notably, QD-4c afforded opposite enantiomers of the products with high *ee* values (Table 2, entries 1, 2, and 11).

Investigations into the scope of α -substituted isocyanooesters was carried out by using **2b** and **2l** as the reaction partners under the optimized conditions (Table 3). A cyclization of benzyl α -phenylisocyno acetate (**1b**) with **2l** occurred in

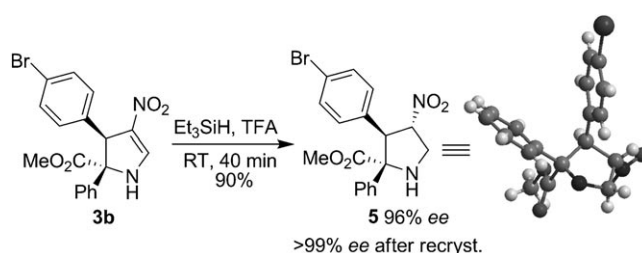
Table 3: Cycloadditions of α -substituted isocyanooesters (**1**) with various nitroolefins.^[a]

Entry	3	R ¹	R ²	2	<i>t</i> [h]	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1	3q	Bn	Ph	2l	44	73	20:1	97
2	3r	Et	Ph	2l	44	85	8:1	92
3	3r	Et	Ph	2l	31	78	> 20:1	91 ^[e]
4	3s	Me	PhCH ₂	2l	92	64	5:1	90
5	3t	Me	4-MeOC ₆ H ₄	2b	88	60	> 20:1	97
6	3u	Me	4-AcOC ₆ H ₄	2b	24	99	6:1	90

[a] Conditions: **1** (0.45 mmol), **2** (0.3 mmol), and QD-4c (0.06 mmol) in CH₂Cl₂ (1.0 mL). [b] Yields of isolated products. [c] Determined by ¹H NMR spectroscopy of crude product. [d] Determined by HPLC analysis. [e] The opposite enantiomer was obtained with 20 mol% QD-4c.

73% yield with a 20:1 d.r. and 97% *ee* (Table 3, entry 1). A comparably lower stereoselectivity was obtained in the case of ethyl α -phenylisocyno esters (Table 3, entry 2). Once again, QD-4c provided the opposite enantiomer with comparable *ee* values (Table 3, entries 2 and 3). Notably, methyl α -benzylisocyno acetate underwent reaction to furnish **3s** in 64% yield with 5:1 d.r. and 90% *ee* (Table 3, entry 4). Moreover, isocyanooesters substituted with an electron-rich phenyl group at the α carbon successfully reacted with **2b** to give high stereochemical outcomes (Table 3, entries 5 and 6). However, the α -unsubstituted alkylisocyno acetate failed to undergo the cycloaddition, indicating that the substituent is crucial for the reaction to succeed.^[13]

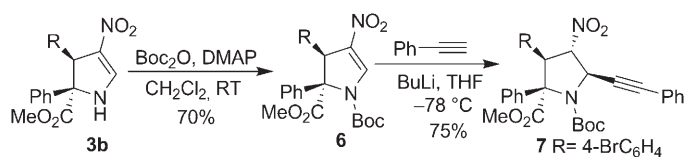
The relative and absolute configurations of **3b** were assigned by X-ray crystallographic analysis of optically pure compound **5**, which was prepared from **3b** by reduction with triethylsilane in trifluoroacetic acid and subsequent recrystallization from a solvent mixture of isopropanol and hexane (Scheme 2). The structure confirmed the (2*R*,3*R*) assignment of the newly formed stereogenic centers in **3b**. Notably, compound **5** and its structural analogues could be obtained by similar reductions of **3** to give α,α -disubstituted amino esters,



Scheme 2. Stereoselective reduction of the dihydropyrrole and X-ray crystallographic structure of **5**.TFA = trifluoroacetic acid.

important building blocks for the synthesis of biologically active substances.^[14] The presence of a nitro group also allows these compounds to be transformed into synthetically useful molecules.^[15]

The 2,3-dihydropyrroles (**3**) contain multiple functionalities and can therefore be transformed into structurally diverse heterocycles by Michael addition reactions with organometallics. For example, 2,3-dihydropyrrole **3b** was first protected with a *tert*-butoxycarbonyl (Boc) group by exposure to di-*tert*-butyl dicarbonate (Boc₂O) and 4-dimethylaminopyridine (DMAP), and then treated with phenylethynyl lithium (generated in situ from phenylacetylene and *n*-butyllithium) to undergo a conjugate addition to yield pyrrolidine **7** containing four stereogenic centers, including a quaternary stereogenic carbon center, with high stereochemical outcome (Scheme 3). The carbon–carbon double bond



Scheme 3. The preparation of pyrrolidines by Michael addition of phenylethynyl lithium to Boc-protected dihydropyrrole **6**.

and nitro group make pyrrolidine **7** structurally flexible and thus allow it to be converted into other chiral heterocyclic building blocks. The transformation shown in Scheme 3, together with the diastereoselective reduction shown in Scheme 2, enhances the importance of the current asymmetric cycloaddition in organic synthesis.

In conclusion, we have disclosed the first asymmetric catalytic cycloaddition reaction of α -substituted isocyanooesters with nitroolefins by cinchona alkaloid derivatives to yield 2,3-dihydropyrroles with high diastereo- and enantioselectivities (up to > 20:1 d.r., > 99% *ee*). This reaction provides a convenient method to access multiply substituted dihydropyrroles and related heterocyclic compounds in high optical purity. The applications of this asymmetric cycloaddition in the synthesis of structurally diverse pyrrolidines was demonstrated by performing a diastereoselective reduction and a Michael addition with phenylethynyl lithium. As isocyanooesters frequently serve as reactants in many organic reactions,^[7b,16] this work might facilitate the creation of other new

organocatalytic procedures related to isocyanooesters. Our investigation on related fields is actively underway.

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- [1] W. H. Pearson in *Studies in Natural Product Chemistry*, Vol. 1 (Ed.: Atta-Ur-Rahman), Elsevier, New York, **1998**, p. 323.
- [2] a) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484; d) V. Nair, T. D. Suja, *Tetrahedron* **2007**, *63*, 12247.
- [3] For recent examples, see: a) J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.-L. Wong, H.-J. Chen, A. K. Courtney, S. F. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 8584; b) S. B. Herzon, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 5342.
- [4] J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.
- [5] a) B. List, *Chem. Rev.* **2007**, *107*(12), special issue for organocatalysis; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; c) K. N. Houk, B. List, *Acc. Chem. Res.* **2004**, *37*(8), special issue for organocatalysis.
- [6] a) T. Saegusa, Y. Ito, H. Kinoshita, S. Tomita, *J. Org. Chem.* **1971**, *36*, 3316; b) U. Schollkopf, K. Hantke, *Liebigs Ann. Chem.* **1973**, 1571.
- [7] Seminal work on the enantioselective aldol reaction between isocyanooesters and carbonyl compounds: a) Y. Ito, M. Samura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405. For a review, see: b) M. Sawamura, Y. Ito, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **1993**, pp. 367.
- [8] a) Y. Chen, P. McDaid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965; b) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985; c) S.-K. Tian, Y. Chen, J. F. Huang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621.
- [9] a) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256; b) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896; c) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120; d) T. B. Poulsen, C. Alemparte, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 11614; e) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191; f) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048.
- [10] a) H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732; b) T. Mandal, S. Samanta, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 943.
- [11] a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057; b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238; c) M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672; d) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; e) D. Xue, Y.-C. Chen, Q.-W. Wang, L.-F. Cun, J. Zhu, J.-G. Deng, *Org. Lett.* **2005**, *7*, 5293; f) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; g) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652.
- [12] a) H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107; *Angew. Chem. Int. Ed.* **2005**, *44*, 105; c) H. Li, J. Song, F. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948; d) F. Wu, H. Li, F. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961; *Angew. Chem. Int. Ed.* **2006**, *45*, 947; e) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301; f) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928; g) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem.* **2006**, *118*, 5088; *Angew. Chem. Int. Ed.* **2006**, *45*, 4966; h) B. Wang, F. Wu, Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768; i) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364.
- [13] The reaction of methylisocyano acetate with **2k** gave a complex product mixture that did not contain the desired compound.
- [14] V. J. Hruby, C. Slate in *Advances in Amino acid Mimetics and Peptidomimetics* (Ed.: A. Abell), JAI, Greenwich, **1999**, pp. 191–220.
- [15] a) N. Ono, *The nitro group in organic synthesis*, Wiley-VCH, New York, **2001**; b) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137.
- [16] *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienayme), Wiley-VCH, Weinheim, **2005**.