Organocatalysis

DOI: 10.1002/anie.201001644

Organocatalytic Michael Addition of Aldehydes to Protected 2-Amino-1-Nitroethenes: The Practical Syntheses of Oseltamivir (Tamiflu) and Substituted 3-Aminopyrrolidines**

*Shaolin Zhu, Shouyun Yu, You Wang, and Dawei Ma**

The 1,2-diamino moiety can be frequently found as a substructure in pharmaceutical molecules. Substituted 3-aminopyrrolidines also belong to one of the most popular classes in this family. Bioactive compounds that contain these heterocycles include: bacterial peptide deformylase inhibitor **1**,[1] NK2 receptor antagonist **2**,[2] 11-β-hydroxysteroid dehydrogenase 1 inhibitor **3**,[3] and the clinically used fluoroquinolone antibiotic Vigamox **4** (Figure 1). Probably the most famous 1,2-diamine-containing compound is oseltamivir (Tamiflu, **5**), which has received enormous attention from the synthetic community because a more practical and economic route for preparing this antiflu drug is highly desired.[4,5] Although a number of enantioselective methods have been reported for the construction of 1,2-diamines, the development of conceptually different synthetic alternatives is still of great interest.

Recently, there has been great progress in the organocatalytic Michael addition reactions of aldehydes to nitroolefins.[6] However, most of the attention has been devoted to exploring new catalyst systems in order to improve the reaction efficiency and selectivity;[7] attempts to extend the reaction scope by employing functionalized nitroolefins are rare.[5g,7m,8] We have reported that β nitroacrylates are suitable substrates for the catalyzed Michael additions of *O*-TMS-protected diphenylprolinol to aldehydes,[7m] which led to the efficient formation of cyclic β-amino acids. Soon after that, Hayashi and co-workers developed an elegant synthesis of Tamiflu using (*E*)-*tert*-butyl 3-nitroacrylate as a Michael acceptor.[5g] In their procedure, the ester moiety of the β nitroacrylate was subsequently transformed into an acetylamino group. Considering that this conversion requires three steps, and uses the toxic and hazardous sodium azide as a reagent, we decided to investigate organocatalytic Michael reactions of protected 2-amino-1-nitroethenes with aldehydes. If these transformations take place, we will be able to develop a general, facile approach for the synthesis of 1,2-diamines, such as Tamiflu and 3-aminopyrrolidines.

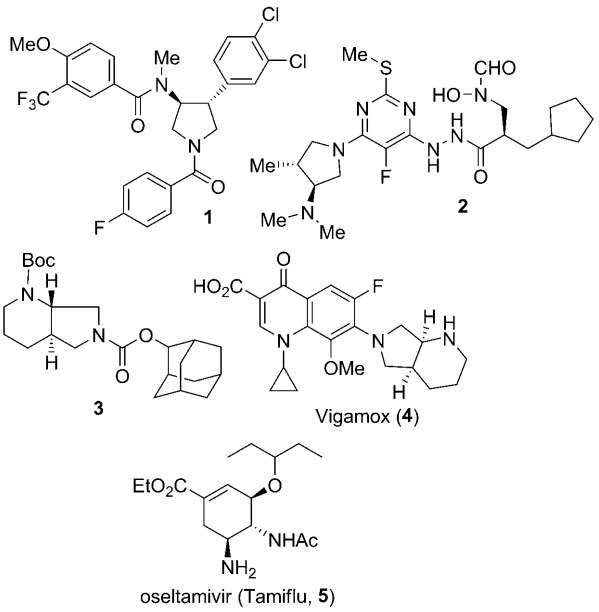


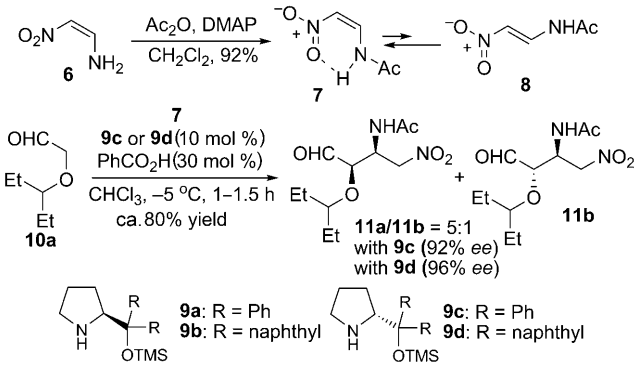
Figure 1. Pharmaceutically important compounds with 1,2-diamine moiety.

With this idea in mind, we prepared (*Z*)-2-nitroethenamine **6** from nitromethane according to the procedure reported by Krówczyński and Kozerski (63% yield over two steps).[9] Treatment of **6** with acetic anhydride and DMAP afforded enamide **7** in 92% yield as fine crystals (Scheme 1). Only the *Z* isomer was formed, owing to strong intramolecular hydrogen bonding in the product. Initially, we expected that **7** could isomerize into its *E* isomer (**8**) under suitable reaction conditions,[10] and then subsequently react with aldehydes to give the desired adducts. Accordingly, the reaction of **7** with 2-(pentan-3-yloxy)acetaldehyde **10a** was carried out in the presence of 10 mol% of **9c** and 30 mol% of benzoic acid. The reaction in chloroform was complete in 1 hour, affording the adduct in excellent enantioselectivity (92% *ee* for the major isomer) and moderate diastereoselectivity (*syn*/*anti* = 5:1, Scheme 1). The enantioselectivity could be further increased to 96% *ee* by using the more-bulky catalyst **9d**. Next, we

[*] S. Zhu, Dr. S. Yu, Prof. Dr. D. Ma
State Key Laboratory of Bioorganic & Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences, 354 Fenglin Lu
Shanghai 200032 (P.R. China)
Fax: (+86) 21-6416-6128
E-mail: madw@mail.sioc.ac.cn
Y. Wang
Department of Chemistry, Fudan University
220 Handan Lu, Shanghai 200433 (P.R. China)

[**] The authors are grateful to the National Basic Research Program of China (973 Program, grant 2010CB833200), and to the Chinese Academy of Sciences and the National Natural Science Foundation of China (20632050, 90713047, and 20921091) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001644.

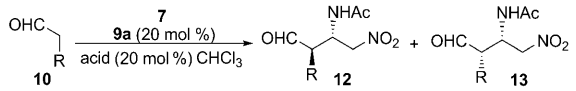


Scheme 1. Synthesis of nitroolefin **7** and its Michael addition with aldehyde **10a** catalyzed by *O*-TMS protected diphenylprolinols **9**. TMS = trimethylsilyl, DMAP = 4-(dimethylamino)pyridine.

attempted to convert the major isomer **11a** into oseltamivir (for the reaction sequence, see Scheme 4), and surprisingly found that the final product was the enantiomer of oseltamivir. This result indicated that **11a** is the (2*S*,3*R*) isomer, not the (2*R*,3*S*) isomer that was predicted according to the transition-state model for Michael additions to simple nitroolefins.[7]

When 3-methylbutanal was used as a Michael donor, another interesting result was observed: *anti* adduct **12a** was determined to be the major product (Table 1, entry 1). However, the diastereoselectivity was not satisfactory. As only one recent example of the *anti*-selective asymmetric Michael reaction of aldehydes and nitroolefins has been reported,[11] we decided to try to enhance the *anti*/*syn*-isomeric ratio by changing the reaction conditions. After several experiments, we were pleased to discover that higher selectivity could be obtained by adding 4 Å molecular sieves to the reaction, using acetic acid as the additive, and slightly reducing the reaction temperature (Table 1, entry 2). Other aldehydes were then examined under these optimized reaction conditions, and they generally provided the *anti* adducts as the major products (Table 1, entries 3–5). The enantioselectivities for the *anti* adducts was excellent, although in most cases the corresponding *syn* adducts had lower *ee* values (however, their absolute configuration is not clear). Intramolecular hydrogen bonding presumably plays a key role in this undesired observation, as evident from the fact that reaction of 3-methylbutanal with **7** in methanol still gave *syn*-adduct **13a** as the major product (Table 1, entry 6).

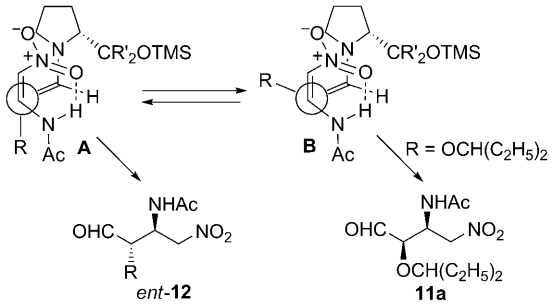
Table 1: Organocatalytic Michael of *cis*-olefin **7** with aldehydes.[a]



Entry	*T* [°C]	*t* [h]	Product	Yield [%][b]	*anti*/*syn* ratio[c]	*ee* [%][d]
1	−5	12	**12a**: R = *i*Pr	90[e]	3:1	94 (74)
2	−10	9		98	7:1	98 (84)
3	−10	2.5	**12b**: R = Et	95[f]	9:1	98 (96)
4	−10	1.5	**12c**: R = Bn	93	6:1	93 (41)
5	−10	3	**12d**: R = $(CH_2)_3Cl$	80	4:1	94 (55)
6	25	3	**12a**: R = *i*Pr	91[g]	1:1.4	68 (94)

[a] Reaction conditions: **7** (0.2 mmol), aldehyde (0.4 mmol), **9a** (0.04 mmol), HOAc (0.04 mmol), 4 Å M.S. (50 mg), $CHCl_3$ (0.4 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. The values in parentheses are for the *syn* isomer. [e] $PhCO_2H$ was used as the additive and 4 Å M.S. was absent. [f] 5 mol% catalyst was used. [g] Methanol was used as the solvent and 4 Å M.S. was absent.

Although further experiments are required for a detailed mechanistic investigation of this unusual stereoselectivity, tentative proposals are outlined in Scheme 2. These possible

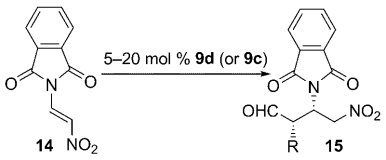


Scheme 2. Possible reaction pathway for Michael addition of nitroolefin **6** with aldehydes.

pathways are based on the acyclic synclinal transition-state model for enamine-based Michael additions, as proposed by Seebach and Goliński.[12] We realized that isomerization of **7** did not occur in chloroform, because the intramolecular hydrogen bond was too strong. As a result, **7** might directly interact with *E* enamines to form transition-state **A**, which in turn gave the *anti*-selective adducts. However, there should be a marked steric repulsion between the R group and the amido moiety in transition-state **A**. When R was the more bulky $OCH(CH_2CH_3)_2$ group, the steric repulsion was very high, which predominantly led to reaction of the *Z* enamine[13] with **7**. This model could be used to rationalize the absolute configuration of *syn*-adduct **11a**, which was different to the absolute configuration of the products that were generated from interaction of *E* nitroolefins with *E* enamines.

As it is difficult to convert **7** into its *trans* isomer (**8**), we decided to obtain the corresponding *trans* olefins by removing the intramolecular hydrogen bond through the introduction of another N substituent. Accordingly, exposure of amine **6** to a solution of phthaloyl dichloride and triethylamine in methylene chloride afforded **14** in 90% yield (for experimental details, see the Supporting Information). Next, we investigated the Michael reaction of **14** with *n*-butyraldehyde under different reaction conditions (Table 2). In the presence of 5 mol% **9c**, the reaction proceeded well in chloroform to afford the desired *syn* adduct (**15a**) with good yield and 99% *ee* (Table 2, entry 1). The diastereoselectivity could be improved by changing the solvent to acetonitrile (Table 2, entry 2), and further increased by reducing the reaction temperature (Table 2, entry 3). The highest ratio of *syn*/*anti* isomers (14:1) was observed when the catalyst was

Table 2: Organocatalytic Michael addition of *trans*-olefin **14** with aldehydes.[a]



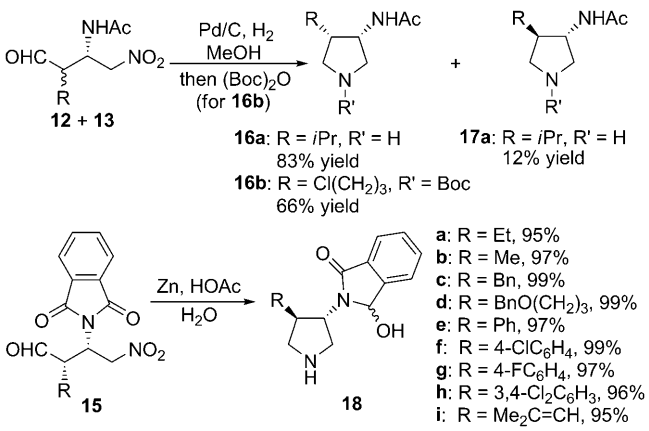
Entry	*t* [h]	Product	Yield [%][b]	*syn*/*anti* ratio[c]	*ee* [%]
1	25	**15a**: R = Et	90[d]	3:1	99
2	2.5		99	5.4:1	99
3	1.3		99	6.7:1	99
4	3.5		99	14:1	99
5	3.5		99	14:1	99
6	3.5	**15b**: R = Me	95	10:1	99
7	7	**15c**: R = Bn	99	14:1	99
8	4	**15d**: R = $(CH_2)_3OBn$	99	12:1	99
9	1.5	**15e**: R = Ph	99[e]	26:1	97
10	2.5	**15f**: R = 4-ClC_6H_4	93[f]	11:1	92
11	4.5	**15g**: R = 4-FC_6H_4	87[f]	12:1	93
12	6	**15h**: R = 3,4-$Cl_2C_6H_3$	92[f]	9:1	88
13	2	**15i**: R = CH=CMe_2	98[f]	9:1	97

[a] Reaction conditions: **14** (0.2 mmol), aldehyde (0.3 mmol, 0.4 mmol for entries 1-4), 5 mol% **9d** (or **9c** for entries 1-3, 9, and 13), 25 mol% HOAc (or $PhCO_2H$ for entries 1 and 2), MeCN (0.4 mL), 0°C (or RT for entries 1 and 2); *ee* was determined by HPLC of the major isomer on a chiral stationary phase. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] $CHCl_3$ as solvent. [e] 10 mol% catalyst was used. [f] 20 mol% catalyst was used.

switched to **9d** and acetic acid was used as an additive (Table 2, entry 4). Reducing the amount of aldehyde to 1.5 equivalents gave the same result under these conditions (Table 2, entry 5).

Exploration of the scope of the reaction revealed that a considerable number of aldehydes were compatible with these optimized reaction conditions (Table 2, entries 6–13), thereby providing their corresponding *syn* adducts in good yields and excellent stereocontrol. This benefit allowed us to introduce diverse substituents at the γ position of the nitro group.

With *anti*-adducts **12** and *syn*-adducts **15** in hand, we next attempted their transformation into substituted 3-aminopyrrolidines (Scheme 3). The Pd/C-catalyzed direct hydrogenation of a mixture of **12a** and **13a** proceeded smoothly in methanol, affording acyl-protected 3-aminopyrrolidine **16a** and its 4-epimer **17a** in almost quantitative combined yield. Hydrogenation of a mixture of **12d** and **13d**, followed by protection with $(Boc)_2O$ (Boc = *tert*-butoxycarbonyl) afforded **16b** as the major isomer in 66% yield (the corresponding *trans* isomer was not pure, and therefore its yield was not measured). However, when **15** were subjected to direct hydrogenation, only moderate yields of the phthaloyl-protected 3-aminopyrrolidines were obtained, owing to side-reactions. Eventually, we found that **15** could be transformed into **18** (the N substituent could be deprotected using $NaBH_4$ reduction)[14] in excellent yields by treating with zinc and acetic acid. Interestingly, when these conditions were applied to *anti*-adducts **12a** and **13a**, **16a** and **17a** were isolated in a 1:1 ratio, thus implying that racemization (through a cyclic

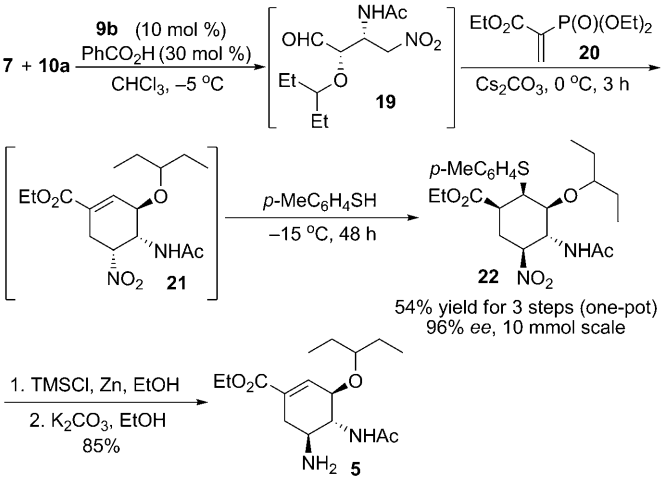


Scheme 3. Conversion of Michael adducts into the corresponding substituted 3-aminopyrrolidines.

imine intermediate) took place during this transformation. These results indicate that the stereochemistry of these adducts has a great influence on the reduction/reductive amination process.

It is notable that our protected 3-aminopyrrolidines are very useful building blocks for assembling some bioactive compounds. For example, **16b**, **18b**, **18d**, and **18h** could potentially be converted into the diamine parts of Vigamox **4**, NK2 receptor antagonist **2**, 11-β-hydroxysteroid dehydrogenase 1 inhibitor **3**, and bacterial peptide deformylase inhibitor **1**, respectively. The deprotected diamines of **18e**–**18g** also form the core units for a class of dual NK1/NK3 antagonists that could be useful for the treatment of positive and negative symptoms in schizophrenia,[15] whilst **18a** could be applied in the preparation of some Factor Xa inhibitors that have potential for the treatment of Alzheimer's disease.[16]

The synthetic usage of our methodology is further illustrated by the synthesis of oseltamivir, as outlined in Scheme 4. Michael addition of aldehyde **10a** to the olefin **7**, catalyzed by 10 mol% **9b** produced crude adduct **19** (approx. 80% yield, *syn*/*anti* = 5:1). Next, we planned to convert adduct **19** into **22** by using a similar strategy as reported by



Scheme 4. Synthesis of (−)-oseltamivir.

Hayashi and coworkers.[5g] Accordingly, reaction of crude **19** with vinylphosphonate **20** in the presence of Cs_2CO_3 provided cyclized product **21**, which was directly treated with *para*-toluenethiol to deliver ester **22** and its isomer. This one-pot reaction was carried out on a 10 mmol scale and ester **22** was isolated in 54% overall yield (3 steps) and 96% *ee*; its structure was confirmed by single crystal X-ray analysis.[17] After reduction of the nitro moiety of **22** with zinc and trimethylsilyl chloride, treatment with K_2CO_3 in methanol furnished oseltamivir **5** in 85% yield. Importantly, only two separation steps were necessary during this five-step synthesis, which makes our procedure very competitive as a practical route for the preparation of this clinically used drug.

In conclusion, we have demonstrated that protected 2-nitro-ethenamine could undergo organocatalytic Michael additions to aldehydes to provide 1,2-diamine precursors. The phthaloyl-protected 2-nitroethenamine exists in the *E* form and gives the Michael adducts with the usual stereochemistry, like other simple nitroolefins. However, acyl-protected 2-nitroethenamine exists in the *Z* form owing to a strong intramolecular hydrogen bond, thus delivering the Michael adducts with an unusual stereochemistry. These unexpected results suggest that other possible transition-states in the enamine-based Michael addition of nitroolefins to aldehydes could become a reality. This fact, together with the observation that electron-rich nitroolefins **7** and **14** could serve as the Michael acceptors for organocatalytic Michael additions, will stimulate further investigations on the exploration of the scope of these reactions. More importantly, our studies offer a very efficient and practical approach for assembling substituted 1,2-diamines, illustrated by the successful synthesis of some substituted 3-aminopyrrolidines and (−)-oseltamivir.

Experimental Section

In a typical procedure, the aldehyde (0.4 mmol) and HOAc (5–20 mol%) were added to a suspension of catalyst **9** (5–20 mol%), (*Z*)-*N*-(2-nitrovinyl)acetamide (0.2 mmol), and 4 Å M.S. (powder, 50 mg) in anhydrous chloroform (0.4 mL) at −10 °C. The reation mixture was stirred until the *Z*-nitroalkene was completely consumed, as monitored by ^{1}H NMR spectroscopy. The reaction mixture was directly loaded on a column of silica gel and purified by eluting with 1.2:1–1:1 petroleum ether/ethyl acetate to afford the Michael adducts. The *syn*/*anti* ratio was determined by ^{1}H NMR and the enantiomeric excess (*ee*) was determined after purification by HPLC on a chiral phase.

Received: March 19, 2010
Published online: May 17, 2010

Keywords: aldehydes · aminopyrrolidines · asymmetric synthesis · Michael addition · organocatalysis

[1] C. Bissantz, P. Jablonski, H. Knust, A. Koblet, A. Limberg, M. Nettekoven, H. Ratni, C. Riemer, US 2009312327, **2009**.
[2] D. A. Claremon, L. Zhuang, Y. Ye, S. B. Singh, C. M. Tice, WO 2009131669, **2009**.
[3] D. Qin, B. Norton, X. Liao, A. N. Knox, Y. Fang, J. Lee, J. C. Dreabit, S. B. Christensen, A. B. Benowitz, K. M. Aubart, WO 2009061879, **2009**.
[4] For a review, see: a) J. Magano, *Chem. Rev.* **2009**, *109*, 4398; b) V. Farina, J. D. Brown, *Angew. Chem.* **2006**, *118*, 7488; *Angew. Chem. Int. Ed.* **2006**, *45*, 7330.
[5] For selected leading references, see: a) M. Karpf, R. Trussardi, *J. Org. Chem.* **2001**, *66*, 2044; b) Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310; c) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312; d) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2007**, *119*, 5836; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; e) T. Mita, N. Fukuda, F. X. Roca, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 259; f) B. M. Trost, T. Zhang, *Angew. Chem.* **2008**, *120*, 3819; *Angew. Chem. Int. Ed.* **2008**, *47*, 3759; g) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304; h) B. Sullivan, I. Carrera, M. Drouin, T. Hudlicky, *Angew. Chem.* **2009**, *121*, 4293; *Angew. Chem. Int. Ed.* **2009**, *48*, 4229; i) M. Karpf, R. Trussardi, *Angew. Chem.* **2009**, *121*, 5871; *Angew. Chem. Int. Ed.* **2009**, *48*, 5760; j) H. Osato, I. L. Jones, A. Chen, C. L. L. Chai, *Org. Lett.* **2010**, *12*, 60.
[6] For reviews, see: a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; b) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065.
[7] a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; c) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147; d) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; e) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; f) Y. Xu, W. Zhou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418; g) J. Wang, H. Li, B. Lou, L. Zu, H. Guo, W. Wang, *Chem. Eur. J.* **2006**, *12*, 4321; h) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093; i) C. Palomo, S. Vera, A. Mielgo, E. Gomez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984; j) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; k) S. Mossé, A. Alexakis, *Org. Lett.* **2006**, *8*, 3577; l) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; m) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555; *Angew. Chem. Int. Ed.* **2008**, *47*, 545; n) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871; o) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610; p) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem.* **2008**, *120*, 4797; *Angew. Chem. Int. Ed.* **2008**, *47*, 4719; q) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800; *Angew. Chem. Int. Ed.* **2008**, *47*, 4722; r) Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50.
[8] a) O. Andrey, A. Vidonne, A. Alexakis, *Tetrahedron Lett.* **2003**, *44*, 7901; b) E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, *Org. Lett.* **2006**, *8*, 6135.
[9] A. Krówczyński, L. Kozerski, *Synthesis* **1983**, 489.
[10] J. L. Chiara, A. Gómez-Sánchez, J. Bellanato, *J. Chem. Soc. Perkin Trans. 2* **1992**, 787.
[11] H. Uehara, C. F. Barbas, *Angew. Chem.* **2009**, *121*, 10032; *Angew. Chem. Int. Ed.* **2009**, *48*, 9848.
[12] D. Seebach, J. Goliński, *Helv. Chim. Acta* **1981**, *64*, 1413.
[13] It is known that Michael addition of ketones with nitroolefins could proceed through Z-enamine-based transition-states to afford *anti* adducts in some cases. See: a) Ref. [7c]; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; c) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; d) T. Mandal, C.-G. Zhao, *Angew. Chem.* **2008**, *120*, 7828; *Angew. Chem. Int. Ed.* **2008**, *47*, 7714.

[14] a) J. O. Osby, M. G. Martin, B. Ganem, *Tetrahedron Lett.* **1984**, *25*, 2093; b) S. Luo, C. A. Zificsak, R. P. Hsung, *Org. Lett.* **2003**, *5*, 4709.
[15] C. Bissantz, T. Hoffmann, P. Jablonski, H. Knust, M. Nettekoven, H. Ratni, X. Wu, WO 2008128891, **2008**.
[16] K. Gerlach, H. Priepke, R. Pfau, W. Wienen, A. Schuler-Metz, G. Dahmann, WO 2007009963, **2007**.
[17] CCDC 768990 (**15a**), CCDC 768991 (**15c**), and CCDC 768992 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

