

Regioselective Synthesis of γ -Amino Esters, Nitriles, Sulfones, and Pyrrolidinones by Nickel-Catalyzed Reductive Coupling of Aldimines and Activated Alkenes**

Chien-Hung Yeh, Rajendra Prasad Korivi, and Chien-Hong Cheng*

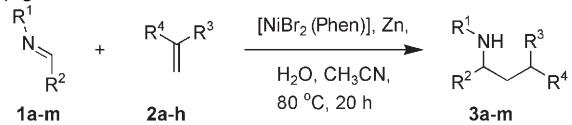
The transition-metal-catalyzed regioselective coupling of two organic π components via a five-membered metallacycle intermediate is one method for the construction of C–C bonds and the synthesis of molecules with multiple functional groups. Among these reactions, the reductive coupling of alkyne/alkyne^[1a] alkene/alkyne,^[1b,c,i,j] and alkene/alkene^[1a] couples has been widely explored by us and others. Similarly, the coupling of alkene/carbonyl^[1d] and alkyne/carbonyl^[1e–h] couples catalyzed by metal complexes has more recently also attracted attention. In comparison, the use of an imine derivative as one of the π components has only rarely been explored.^[2,3] Rhodium-^[2a–c] and organo-catalyzed^[2d,e] coupling reactions of conjugated alkenes with activated imines were found to give Baylis–Hillman-type products in which a C–C bond was formed between the α -carbon atom of the alkene and the carbon atom of the imine. There is no report of an analogous metal-catalyzed coupling reaction occurring at the β -carbon atom of the alkene.^[3] Our efforts to develop methods for the reductive coupling of two π components^[1b,c,4a] prompted us to investigate the coupling reaction of conjugated alkenes and imines. Herein, we report an efficient ene–imine reductive coupling reaction catalyzed by a nickel–1,10-phenanthroline complex to give various substituted γ -amino esters,^[5i,j] γ -aminonitriles,^[5k,l] γ -aminosulfones, and pyrrolidinones.^[5] These products are all γ -aminobutyric acid (GABA) derivatives, which are known to exhibit a wide range of biological properties^[6] and have found various industrial applications.^[6] In contrast to the base-^[2d] and metal-catalyzed reactions, our ene–imine coupling reaction yields saturated products in which a C–C bond is formed at the β -carbon atom of conjugated alkenes.

The success of the reductive ene–imine coupling reaction depends greatly on the choice of the ligand and metal. When 4-fluorobenzaldimine **1a** was treated with ethyl acrylate in acetonitrile in the presence of [CoI₂(dppe)] (dppe = 1,2-bis(diphenylphosphanyl)ethane) or [NiBr₂(dppe)], Zn, and H₂O at 80 °C, only a trace of the reductive coupling product

3a was observed. Fortunately, when we changed the catalyst to [NiI₂(phen)], [NiBr₂(bipy)], [NiCl₂(bipy)], or [NiBr₂(phen)] (phen = 1,10-phenanthroline, bipy = 2,2'-bipyridine), the expected product **3a** was formed in yields of 55, 75, 37, or 99%, respectively. The yields of **3a** were determined by integration of the ¹H NMR signals, using mesitylene as the internal standard. The nickel complex [NiBr₂(tmeda)] (tmeda = tetramethylethylenediamine), which has an electron-rich nitrogen ligand, did not give the desired product. Also, phenanthroline or zinc alone did not catalyze the reaction. Surprisingly, these studies show that phosphines are not suitable ligands in the present catalytic reaction, but that bipyridine-type ligands, particularly phen, are essential.

We studied the scope of the reductive coupling reaction under the optimized reaction conditions shown in Table 1. The reaction of imines **1b**, **1a**, and **1c** with acrylate derivatives

Table 1: Nickel-catalyzed reductive coupling reaction of imines and conjugated alkenes.^[a]

			
Entry	Imine: R ¹ , R ²	Ene: R ³ , R ⁴	Yield [%] ^[b]
1	1a : Ph, 4-FC ₆ H ₄	2a : CO ₂ Et, H	3a 85
2 ^[c,d]	1b : Ph, Ph	2a	3b 73
3	1a	2b : CO ₂ tBu, H	3c 61
4 ^[c,e]	1c : Ph, 4-MeOC ₆ H ₄	2a	3d 74
5 ^[c,e]	1d : 4-BuC ₆ H ₄ , 4-MeOC ₆ H ₄	2a	3e 88
6 ^[e]	1e : 4-MeOC ₆ H ₄ , Ph	2c : CO ₂ Me, H	3f 71
7	1e	2d : CO ₂ Me, Me	3g 65
8	1f : 4-MeOC ₆ H ₄ , cyclohexyl	2c	3h 52
9 ^[c]	1a	2e : CN, H	3i 86
10 ^[c]	1e	2e	3j 84
11 ^[c]	1g : R ¹ = R ² = 4-MeOC ₆ H ₄	2e	3k 75
12	1e	2f : CN, Me	3l 79
13	1f	2e	3m 64
14	1e	2g : SO ₂ C ₆ H ₄ , H	3n 67
15	1h : 4-MeOC ₆ H ₄ , H	2e	3o 63
16	1i : 4-MeOC ₆ H ₄ , C $\equiv$ C(CH ₂) ₄ CH ₃	2e	3p 65
17	1j : 4-MeOC ₆ H ₄ , 2-furyl	2e	3q 68

[a] All reactions were carried out under nitrogen (1 atm) using imine (0.25 mmol), acrylate (0.75 mmol), [NiBr₂(phen)] (0.0125 mmol), H₂O (0.50 mmol), and Zn (0.75 mmol) at 80 °C for 20 h. [b] Yield of isolated product. [c] No chromatography procedures were required for purification of the product. [d] Reaction time: 12 h. [e] Reaction time: 16 h.

[*] C.-H. Yeh, Dr. R. Prasad Korivi, Prof. Dr. C.-H. Cheng
Department of Chemistry, National Tsing Hua University
Hsinchu, 30043 (Taiwan)
Fax: (+886) 3572-4698
E-mail: chcheng@mx.nthu.edu.tw
Homepage: <http://mx.nthu.edu.tw/~chcheng/>

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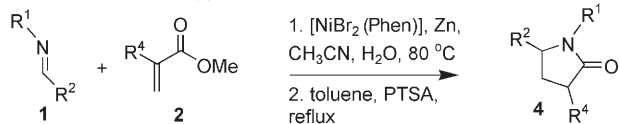
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proceeded smoothly to give amino ester derivatives **3b–d** in good yields (Table 1, entries 2–4). When imines **1d** and **1e** were used, the corresponding γ -amino derivatives **3e** and **3f** were obtained in yields of 88 and 71 %, respectively (Table 1, entries 5 and 6). Replacement of H₂O by D₂O in the reaction of **1e** with **2c** gave deuterated product [D]-**3f** with 68 % deuteration at the carbon atom α to the ester group. Treatment of methyl methacrylate (**2d**) with imine **1e** afforded a diastereomeric mixture of the corresponding amino ester derivatives in 65 % yield (diastereomeric ratio 2:1; Table 1, entry 7). When imine **1f** derived from cyclohexanecarboxaldehyde was used with acrylate **2c**, product **3h** was obtained in 52 % yield (Table 1, entry 8).

The scope of the reaction was further extended by using acrylonitrile derivatives in place of the acrylates. When imines **1a**, **1e**, and **1g** were employed in the reaction with acrylonitrile **2e**, γ -aminonitriles **3i**, **3j**, and **3k** were obtained in yields of 86, 84, and 75 %, respectively (Table 1, entries 9–11). Treatment of methyl-substituted acrylonitrile **2f** with **1e** gave a mixture of γ -aminonitrile diastereomers **3l** in yields of 37 and 42 % (Table 1, entry 12). The reaction of imine **1f** with **2e** resulted in the corresponding nitrile derivative **3m** in 64 % yield (Table 1, entry 13). These results indicate that acrylonitrile derivatives give higher product yields than their acrylate analogues (Table 1, entry 8 versus 13). Nitrile derivatives can also be used for the preparation of acids, aldehydes, and amines. Enzyme-based catalytic^[7] methods have been developed to prepare various chiral derivatives from nitriles for industrial application. Vinyl sulfone **2g** reacted smoothly with imine **1e** to provide **3n** in 67 % yield (Table 1, entry 14). The reaction of aldimine **1h** derived from formaldehyde, as well as of **1i** and **1j** with **2e** also proceeded smoothly to provide γ -aminobutyronitriles **3o–q** in good yield (Table 1, entries 15–17). The present study shows that a variety of imines can be used along with a wide range of conjugated alkenes.

The present catalytic reaction was utilized for the synthesis of pyrrolidinones (Table 2). After completion of the catalytic reductive coupling reaction of **1** with acrylate **2c**, the mixture was filtered, and the acetonitrile was removed under vacuum. The resulting crude product was heated in toluene with *para*-toluenesulfonic acid (PTSA) to give the corresponding pyrrolidinone. The 4-FC₆H₄CHO imine **1a** converted smoothly into pyrrolidinone **4a** in 75 % yield (Table 2, entry 1). When *N*-phenylbenzalimine **1b** was used, the corresponding diphenylpyrrolidinone **4b** was isolated in 64 % yield (Table 2, entry 2). Imines **1c** and **1g** derived from 4-MeOC₆H₄CHO reacted with **2c** under similar reaction conditions to give pyrrolidinones **4c** and **4d** in yields of 74 and 85 %, respectively (Table 2, entries 3 and 4). When imine **1e** prepared from 4-MeOC₆H₄NH₂ was used for the reaction, the expected pyrrolidinone derivative **4e** was obtained in 77 % yield (Table 2, entry 5). These results indicate that slightly better yields of the pyrrolidinones can be obtained when the phenyl groups on the imine are substituted with a *p*-methoxy group. Apart from aromatic benzaldehydes, imines **1f** and **1j** prepared from cyclohexanecarboxaldehyde and 2-furylaldehyde, respectively, can be utilized in the reaction, albeit with lower yields of the corresponding pyrrolidinones (Table 2,

Table 2: Formation of pyrrolidinone derivatives.^[a]

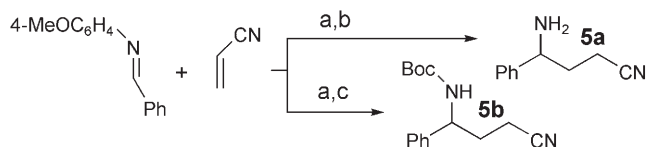
					
Entry	1	R ¹ , R ²	2	Prod. 4	Yield [%] ^[b]
1	1a	Ph, 4-FC ₆ H ₄	2c	4a	75
2	1b	Ph, Ph	2c	4b	64
3 ^[c]	1c	Ph, 4-MeOC ₆ H ₄	2c	4c	74
4 ^[c]	1g	R ¹ = R ² = 4-MeOC ₆ H ₄	2c	4d	85
5 ^[c]	1e	4-MeOC ₆ H ₄ , Ph	2c	4e	77
6	1f	4-MeOC ₆ H ₄ , cyclohexyl	2c	4f	45
7	1j	4-MeOC ₆ H ₄ , 2-furyl	2c	4g	49
8	1k	4-MeOC ₆ H ₄ , 	2c	4h	87
9	1k	4-MeOC ₆ H ₄ , 	2d	4i , 4i'	35, 42
10	1l	4-MeOC ₆ H ₄ , 3,4,5-(MeO) ₃ C ₆ H ₄	2c	4j	62

[a] The reaction was carried out under similar conditions as shown in Table 1 for 20 h, then the catalyst, zinc, and acetonitrile were removed. The residue was heated at 120 °C in toluene (2.0 mL) and PTSA (0.0250 mmol) for 4 h. [b] Yield of isolated product. [c] Chromatography was not necessary for the isolation of the products.

entries 6 and 7). The aromatic imine derived from piperonal gives the desired product **4h** in excellent yield (Table 2, entry 8). Under similar reaction conditions, methyl methacrylate reacted with **1k** to yield a mixture of the *trans*- and *cis*-pyrrolidinone derivatives *trans*-**4i** and *cis*-**4i'** in yields of 35 and 42 %, respectively, (Table 2, entry 9). These two isomers could be separated by column chromatography and the structures were assigned by comparing the chemical shifts in the NMR spectra with those of reported^[8a,b] compounds with similar skeletons.

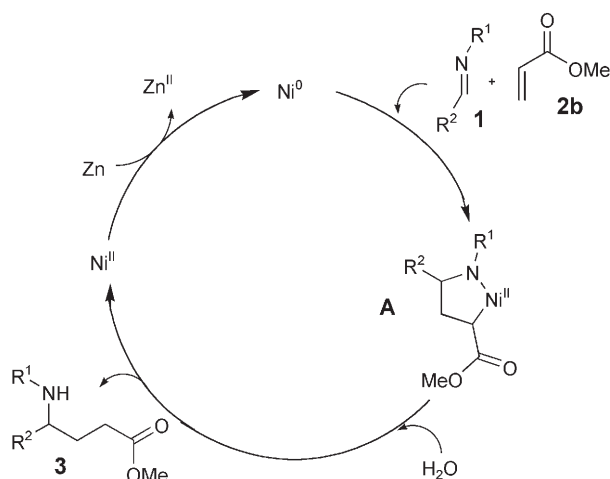
The catalytic reaction can also be applied to the synthesis of γ -aminonitrile **5a** and Boc-protected derivative **5b** (Scheme 1) in yields of 64 and 85 %, respectively, by following the reported procedure^[9] after the catalytic reaction. The Boc group in the latter can be removed to give **5a** in excellent yield.^[9]

A possible mechanism for the formation of γ -amino derivatives in this reaction is shown in Scheme 2. The reaction is initiated by the reduction of Ni^{II} to Ni⁰ by zinc powder. Coordination of the imine and acrylate to the nickel center results in the formation of azanickelacycle **A**, which undergoes hydrolysis to give the γ -amino derivative and a Ni^{II} species. The nickel(II) species is further reduced by zinc to



Scheme 1. Synthesis of protected and free nitrogen compounds.

a) [NiBr₂(phen)], Zn, H₂O, CH₃CN, 80 °C; b) CAN; c) CAN, (Boc)₂O. CAN = cerium ammonium nitrate, Boc = *tert*-butoxycarbonyl.



Scheme 2. Plausible pathway for the formation of γ -amino derivatives.

regenerate the Ni^0 species for the next cycle. The formation of five-membered azanickelacycles from imines and alkynes similar to **A** were described recently by Ogoshi et al.^[10a] Many other five-membered metallacycles^[11] containing an oxygen atom^[10b,c] or only carbon atoms^[11b–c] were observed or proposed as key catalytic intermediates. The formation of a nickelacycle by the addition of two π components is generally regioselective, with the carbon atom having an electron-drawing functionality near to the metal center.^[4,12] This mechanism explains the regioselectivity of the present reductive coupling product. Alternatively, the acrylate first interacts with Ni^0 to give an oxy- π -allylnickel(II) intermediate.^[11f–h] A β -coupling reaction of the oxy- π -allyl group with the imine followed by hydrolysis would lead to the final γ -amino derivative. This pathway can not be totally excluded.

We have demonstrated a simple and convenient nickel-catalyzed ene-imine reductive coupling reaction for the synthesis of γ -amino derivatives using zinc powder as the reducing agent and water as the proton source. The coupling reaction occurs at the β -carbon atom of the conjugated alkene, in contrast to the known coupling reactions at the α -carbon atom.^[2c–e,13] The catalytic reaction is a simple and efficient method for the synthesis^[5m] of GABA derivatives. The active nickel catalyst requires bipyridine or phenanthroline instead of the commonly used phosphine ligands. In addition, this nickel-catalyzed reaction can generate one to two new stereocenters in the products, and thus is potentially useful for enantioselective synthesis. Studies in this direction are underway.

Experimental Section

Representative procedure for the synthesis of 4b: A screw-cap sealed tube initially fitted with a septum (15 mL) containing $[\text{Ni}(\text{phen})\text{Br}_2]$ (0.01250 mmol) and zinc powder (0.75 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled acetonitrile (1.0 mL), imine **1b** (0.25 mmol), ethyl acrylate (0.75 mmol), and H_2O (0.50 mmol) were added and the reaction mixture was stirred at 80°C for 20 h. After filtration of the zinc, the acetonitrile was removed under vacuum, toluene (2.0 mL) was added along with PTSA (0.0250 mmol), and the mixture was kept at 120°C for 4 h. After

completion of the reaction, the mixture was cooled and diluted with dichloromethane. Et_3N (0.05 mmol) was added and the mixture was filtered and then concentrated. Separation on a column of silica gel using hexane/ EtOAc as the eluent gave pure diphenylpyrrolidinone product **4b** in 64% yield. ^1H NMR δ = 1.97–2.02 (m, 1 H), 2.58–2.64 (m, 2 H), 2.72–2.77 (m, 1 H), 5.22–5.25 (m, 1 H), 7.04 (t, J = 7.2 Hz, 1 H), 7.19–7.24 (m, 5 H), 7.29 (t, J = 7.2 Hz, 2 H), and 7.39 ppm (d, J = 8.0 Hz, 2 H); ^{13}C NMR δ = 29.2, 31.2, 63.9, 122.2, 124.9, 125.9, 127.7, 128.6, 128.9, 138.1, 141.2, and 174.9 ppm; HRMS (EI^+) 237.1158 (calcd for $\text{C}_{16}\text{H}_{15}\text{NO}$: 237.1154); IR (KBr): 1381, 1497, 1697, and 2947 cm^{-1} .

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- [1] a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980–3998; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908; b) C.-C. Wang, P. S. Lin, C.-H. Cheng, *J. Am. Chem. Soc.* **2002**, *124*, 9696–9697; c) H. T. Chang, T. Jayanth, C.-C. Wang, C.-H. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 12032–12041; d) C.-Y. Ho, T. F. Jamison, *Angew. Chem.* **2007**, *119*, 796–799; *Angew. Chem. Int. Ed.* **2007**, *46*, 782–785; e) K. M. Miller, W.-S. Huang, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443; f) R. R. Huddleston, H.-Y. Jang, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 11488–11489; g) J. R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16040–16041; h) M.-Y. Ngai, A. Barchuk, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 280–281; i) D. K. Rayabarapu, C.-H. Cheng, *Chem. Eur. J.* **2003**, *9*, 3164–3169; j) D. K. Rayabarapu, C.-H. Cheng, *Acc. Chem. Res.* **2007**, *40*, 971–983.
- [2] a) J.-R. Kong, C.-W. Cho, M. J. Krische, *J. Am. Chem. Soc.* **2005**, *127*, 11269–11276; b) E. Skucas, J.-R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 7242–7243; c) S. A. Garner, M. J. Krische, *J. Org. Chem.* **2007**, *72*, 5843–5846; d) N. Utsumi, H. Zhang, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2007**, *119*, 1910–1912; *Angew. Chem. Int. Ed.* **2007**, *46*, 1878–1880; e) J. A. Townes, M. A. Evans, J. Queffelec, S. J. Tayler, J. P. Morken, *Org. Lett.* **2002**, *4*, 2537–2540.
- [3] a) T. Shono, N. Kise, N. Kunimi, R. Nomura, *Chem. Lett.* **1991**, 2191–2194.
- [4] a) H.-T. Chang, T. Jayanth, C.-H. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 4166–4167; b) R. P. Korivi, C.-H. Cheng, *Org. Lett.* **2005**, *7*, 5179–5182; c) R. P. Korivi, C.-H. Cheng, *J. Org. Chem.* **2006**, *71*, 7079–7082.
- [5] a) P. Renaud, C. Olliver, P. Panchaud, *Angew. Chem.* **2002**, *114*, 3610–3612; *Angew. Chem. Int. Ed.* **2002**, *41*, 3460–3462; b) H. Kagoshina, T. Okamura, T. Akiyama, *J. Am. Chem. Soc.* **2001**, *123*, 7182–7183; c) I. Ryu, K. Matsu, S. Minakata, M. Komatsu, *J. Am. Chem. Soc.* **1998**, *120*, 5838–5839; d) S. Serna, I. Tellitu, E. Dominguez, I. Moreno, R. SanMartin, *Org. Lett.* **2005**, *7*, 3073–3076; e) G.-Y. Li, J. Chen, W.-Y. Yu, W. Hong, C.-M. Che, *Org. Lett.* **2003**, *5*, 2153–2156; f) L. E. Overman, T. P. Remarchuk, *J. Am. Chem. Soc.* **2002**, *124*, 12–13; g) L. Biasutto, E. Marotta, U. DeMarchi, M. Zoratti, C. Paradisi, *J. Med. Chem.* **2007**, *50*, 241–253; h) S. Stepane, M. Eric, B. Philippe, EP 1580186 (A1), **2005**; i) V. G. DeVries, E. E. Largis, T. G. Miner, *J. Med. Chem.* **1983**, *26*, 1411–1421; j) B. Milan, D. Hong, E. Steven, K. Aaron, US 2007072860 (A1); k) C. Leisenl, P. Langguth, B. Herbert, C. Pressler, A. Koggel, H. S. Langguth, *Pharm. Res.* **2003**, *20*, 772–778.
- [6] a) B. Wu, K. Kuhen, T. N. Nguyen, D. Ellis, B. Anaclerio, X. He, K. Yang, D. Karanewsky, H. Yin, K. Wolf, K. Bieza, J. Caldwell, Y. He, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3430–3433; b) D. Niri, G. Fossati, M. Zanda, *ChemMedChem* **2006**, *1*, 175–180; c) R. B.

- Login, *Encyclopedia of Polymer Science and Technology*, Wiley, New York, **2004**; d) piracetam, doxapram, and cotine are widely used pyrrolidinone drugs.
- [7] a) A. Schmid, J. S. Dordick, B. Hauer, A. Kiener, M. Wubbolts, B. Wiltolt, *Nature* **2001**, *409*, 258–268; b) H. E. Schoemaker, D. Mink, M. G. Wubbolts, *Science* **2003**, *299*, 1694–1697.
- [8] a) C. Denhez, E. Pindinelli, C. Granito, L. D. Vitis, *ARKIVOC* **2006**, *vi*, 161–173; b) C. Denhez, J. L. Vasse, D. Harakat, J. Szymoniak, *Tetrahedron: Asymmetry* **2007**, *18*, 424–434.
- [9] a) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508–6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360–6362; b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; c) G. Hughes, M. Kimura, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258; d) A. Suzuki, M. Mae, H. Amii, K. Uneyama, *J. Org. Chem.* **2004**, *69*, 5132–5134.
- [10] a) S. Ogoshi, H. Ikeda, H. Kurosawa, *Angew. Chem.* **2007**, *119*, 5018–5020; *Angew. Chem. Int. Ed.* **2007**, *46*, 4930–4932; b) S. K. Chowdhury, K. K. D. Amarasinghe, M. J. Heeg, J. Montgomery, *J. Am. Chem. Soc.* **2000**, *122*, 6775–6776; c) K. K. D. Amarasinghe, S. K. Chowdhury, M. J. Heeg, J. Montgomery, *Organometallics* **2001**, *20*, 370–372.
- [11] a) M. McLaughlin, M. Takahashi, G. C. Micalizio, *Angew. Chem.* **2007**, *119*, 3986–3988; *Angew. Chem. Int. Ed.* **2007**, *46*, 3912–3914; b) J.-C. Hsieh, C.-H. Cheng, *Chem. Commun.* **2005**, *19*, 2459–2461; c) M.-S. Wu, M. Shanmugasundaram, C.-H. Cheng, *Chem. Commun.* **2003**, 718; d) A. Jeevanandam, R. P. Korivi, I.-W. Huang, C.-H. Cheng, *Org. Lett.* **2002**, *4*, 807–810; e) H.-T. Chang, M. Jegannathan, C.-H. Cheng, *Org. Lett.* **2007**, *9*, 505–508; f) J. R. Johnson, P. S. Tully, P. B. Mackenzie, M. Sabat, *J. Am. Chem. Soc.* **1991**, *113*, 6172–6177; g) B. A. Grisso, J. R. Johnson, P. B. Mackenzie, *J. Am. Chem. Soc.* **1992**, *114*, 5160–5165; h) L.-C. Wang, H.-Y. Jang, Y. Roh, V. Lynch, A. J. Schultz, X. Wang, M. Krische, *J. Am. Chem. Soc.* **2002**, *124*, 9448–9453.
- [12] a) K.-J. Chang, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **2004**, *69*, 4781–4787; b) D. K. Rayabarapu, C.-H. Cheng, *J. Am. Chem. Soc.* **2002**, *124*, 5630.
- [13] a) M. Shi, Y.-M. Xu, *Angew. Chem.* **2002**, *114*, 4689–4692; *Angew. Chem. Int. Ed.* **2002**, *41*, 4507–4510; b) M. Shi, Y.-M. Xu, Y.-L. Shi, *Chem. Eur. J.* **2005**, *11*, 1794–1802; c) P. Ribiere, N. Y. Bhatnagar, J. Martinez, F. Lamaty, *QSAR Comb. Sci.* **2004**, *23*, 911–914.