DOI: 10.1002/ejoc.201301421

Ytterbium(III)-Catalyzed Addition Reaction of Alkynyltrifluoroborate Salts to α-Imino Esters: Efficient Synthesis of β-Unsaturated α-Amino Esters

Hélio A. Stefani,*[a] Flávia Manarin,[a] Amna N. Khan,[a] and Stanley N. S. Vasconcelos[a]

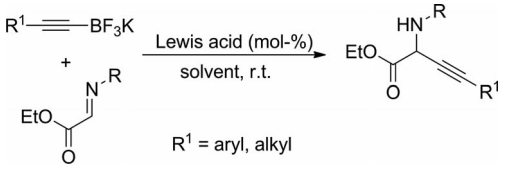
Keywords: Synthetic methods / Lewis acids / Schiff bases / Alkynes / Boron / Ytterbium

We describe the development of a mild and efficient method for the preparation of β-unsaturated α-amino esters through the ytterbium triflate catalyzed addition of potassium alkynyltrifluoroborate salts to imino esters. The synthetic viability of this protocol was supported by its high yields, short reaction times, and efficiency with regard to the scope of the substrates.

Introduction

β-Unsaturated α-amino acid derivatives are nonproteinogenic amino acids that are found in biologically active compounds and are isolated from natural products.[1] These optically active amines are used to generate pharmaceutically important compounds and are also utilized in organic syntheses as resolving agents, as chiral auxiliaries for asymmetric transformations, and as useful intermediates. In particular, β-alkynyl α-amino acids such as FR-900130,[1g,1h] which is isolated from *Streptomyces catenulae*,[2] have been shown to have antimicrobial activity against Gram-positive bacteria. Therefore, significant efforts have been made to develop new strategies to synthesize these structures. Among the available methods, one of the reliable approaches involves the addition of terminal alkynes to α-imino esters using different catalysts.[3]

α-Imino esters are an alternative synthon for α-amino acid derivatives.[4] This class of compounds has been utilized in a number of organic transformations. Although difficulties arise in the addition of imines because of the poor electrophilicity of the azomethine carbon, the high applicability of α-imino esters stems from the enhanced electrophilicity of the imine carbon as a result of the adjacent ester functionality.[5] Trifluoroborates have materialized as a potent alternative to the corresponding boronic acids because of their easy preparation and remarkable stability towards air and moisture.[6] To the best of our knowledge, there are no reports that describe the Lewis acid catalyzed addition of alkynyltrifluoroborate salts to α-imino esters. Therefore, as part of our ongoing studies to search for new carbon–carbon bond forming processes that use potassium organotrifluoroborate compounds,[7] we designed a simple, mild, and efficient method to synthesize of β-alkynyl α-amino esters (Scheme 1).



Scheme 1. General reaction.

Results and Discussion

Initially, we evaluated the reaction between α-imino ester **1a** (as the acceptor) and potassium phenylethynyltrifluoroborate salt **2a** (as the nucleophile) in the presence of various Lewis acids (10 mol-%) in dichloromethane at room temperature under a nitrogen atmosphere (see Table 1). Imino esters such as **1a** are more stable than their corresponding imines, and the resulting products can easily be deprotected under mild conditions by using cerium ammonium nitrate (CAN).[8]

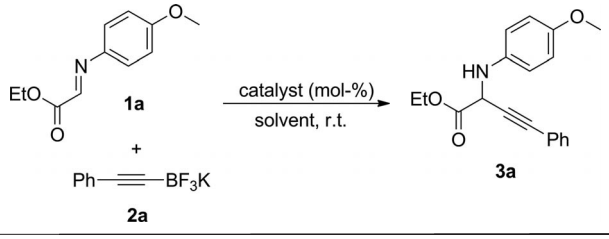
In the absence of any Lewis acid catalyst, the reaction proceeded to give only 20% yield of **3a** (see Table 1, Entry 1). Therefore, we attempted to use a Lewis acid catalyst to promote the reaction. Seven Lewis acids were viable options for this purpose, but $Yb(OTf)_3$ gave the best yield of product and was chosen as the ideal catalyst for the addition reaction (see Table 1, Entries 2–8). The use of lanthanide triflates $Ln(OTf)_3$ in organic synthesis has been widely researched because of their efficiency as Lewis acid catalysts and their low environmental impact.[9]

Several solvents, which include tetrahydrofuran (THF), toluene, nitromethane, and 1,4-dioxane, were investigated, and all provided moderate to good yields. Dichloromethane was revealed as the best choice and provided the product in

[a] Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo,
Av. Prof. Lineu Prestes 580, São Paulo, SP 05508-000, Brazil
E-mail: hstefani@usp.br
http://www.fcf.usp.br/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301421.

Table 1. Screening of Lewis acids for the addition of alkynyltrifluoroborate salts to α-imino esters.



Entry	Catalyst[a]	Solvent	Time[b]	% Yield
1	–	CH_2Cl_2	12	20
2	$Sc(OTf)_3$	CH_2Cl_2	12	45
3	$Yb(OTf)_3$	CH_2Cl_2	1	81
4	$Cu(OTf)_2$	CH_2Cl_2	24	trace
5	$InBr_3$	CH_2Cl_2	12	20
6	$MnCl_2$	CH_2Cl_2	12	42
7	$FeCl_3$	CH_2Cl_2	3	35
8	$In(OTf)_3$	CH_2Cl_2	1	71
9	$Yb(OTf)_3$	THF	12	75
10	$Yb(OTf)_3$	toluene	2	41
11	$Yb(OTf)_3$	CH_3NO_2	2	73
12	$Yb(OTf)_3$	dioxane	12	64
13[c]	$Yb(OTf)_3$	CH_2Cl_2	3	66

[a] All the reactions were carried out with 10 mol-% of the catalyst. [b] Time in hours. [c] 5 mol-% of catalyst.

a high yield of 81% (see Table 1, Entry 3). We also investigated a lower catalyst loading (5 mol-%), but this resulted in a decrease in the product yield (seer Table 1, Entry 13).

To gain further insight into the reaction, in situ Fourier transform infrared spectroscopy (FTIR)[10] was used to monitor its progress. The main region of interest is in the range of 1690–1590 cm^{-1}, in which the C=N stretching vibrations of an imine are located. At t = 7 min, the potassium alkynyltrifluoroborate salt was introduced to the reaction medium, and the intensity of the C=N band rapidly decreased (around 40 min.), which is associated with the consumption of imine. Figure 1 shows the decrease of the characteristic peak at 1595 cm^{-1}, which corresponds to the C=N bond. The results can also be analyzed by a trends curve, in which the reactant (imine) decreased in concentration after the addition of the catalyst and RBF_3K partner (see Supporting Information).

We evaluated the scope and generality of the reaction by using different α-imino esters (0.5 mmol) and potassium alkynyltrifluoroborate salts (0.6 mmol) with $Yb(OTf)_3$ (10 mol-%) as the catalyst in dichloromethane (5 mL) at room temperature (see Table 2). A wide range of alkynyltrifluoroborate salts with different substituents successfully underwent the reaction under Yb^{III} catalysis with α-imino ester **1a**. Alkynyltrifluoroborates that contain an aryl substituent with an electron-withdrawing or -donating group underwent addition to the α-imino ester in a short reaction time to give the product in a satisfactory yield (see Table 2, Entries 1–7). Even the naphthyl-substituted substrate gave the desired product in good yield (80%) in 30 min of reaction time (see Table 2, Entry 8).

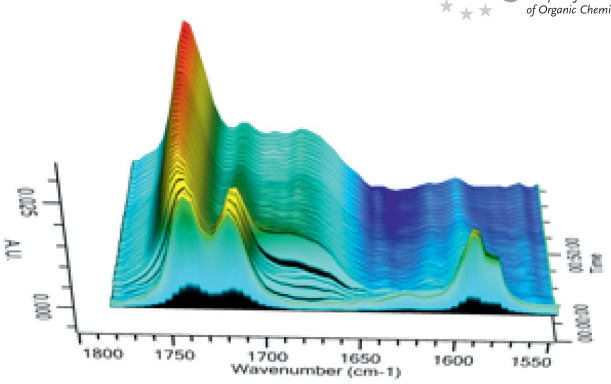


Figure 1. Three-dimensional plot of the IR monitoring data.

We also examined alkyl-substituted alkynyltrifluoroborate salts, and these reactions proceeded to give the highest yields in comparison to the other reactions (see Table 2, Entries 9–12). The trimethylsilylethynyltrifluoroborate salt gave a poor yield of product despite repeating the reaction three times (see Table 2, Entry 13). The resulting compound **3m** represented an attractive target precursor to ethynylglycine, as the trimethylsilyl group could easily be converted into a terminal alkyne by using a fluoride source such as tetra-*n*-butylammonium fluoride (TBAF).[11]

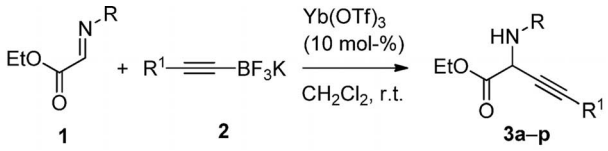
Finally, we investigated different substituents on the imine substrate, and the reactions gave the desired products in moderate to good yields (see Table 2, Entries 14–16). All products were obtained as oils. We also demonstrated that increasing the scale 10-fold to 5.0 mmol led to a comparable yield (77% of product **3a**; for comparison, see Table 2).

Although data in the literature[4a,5a] show that there are three possible modes of reactivity between organometallic reagents and imino esters, that is, at C of C=N, at N of C=N, or in some cases at the C of CO_2Et, we did not observe this. Instead, the side product that was obtained was a solid, and the ^1H NMR spectroscopic data showed that there was a substitution at the aromatic ring. An examination of this side product is currently in progress in our laboratory.

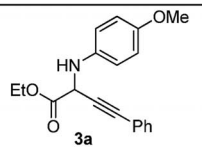
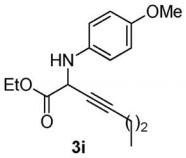
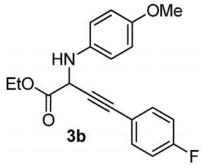
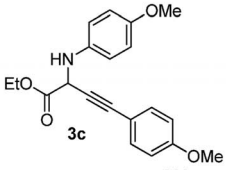
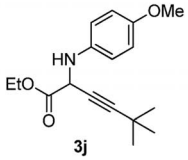
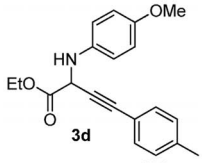
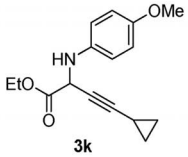
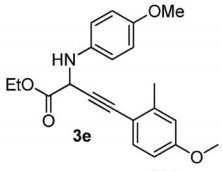
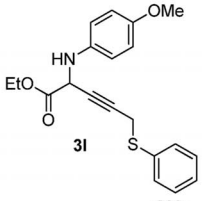
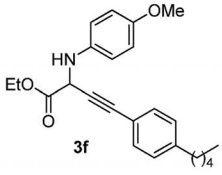
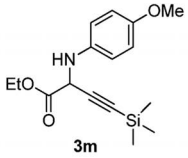
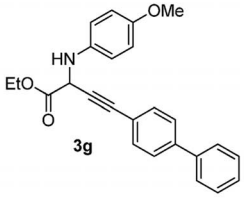
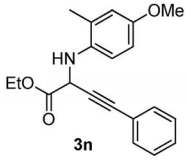
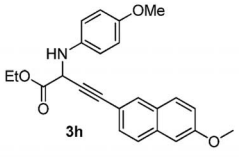
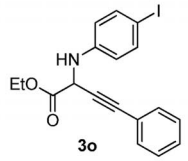
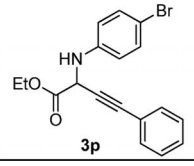
With respect to the reaction mechanism, it is known that potassium organotrifluoroborates are more reactive upon activation by a Lewis acid, which converts them into the corresponding organodifluoroborane intermediates.[12] Several Lewis acids and fluorophiles have been reported as viable precursors to this intermediate dihaloborane.[13] Thus, a possible catalytic cycle for the Yb^{III}-catalyzed alkynylation is proposed in Scheme 2.

In the first step of the proposed mechanism, the electrophilic organodifluoroborane intermediate that is generated in situ by the reaction between the corresponding organotrifluoroborate salt **2** and a Lewis acid defluoridating agent formed nitrogen–boron complex[14] I with the α-imino ester. This complexation facilitates the migration of the alkynyl group from the boron to C=N bond to form intermediate II. Finally, the propargylic amine is formed, and the active Yb^{III} triflate is regenerated.

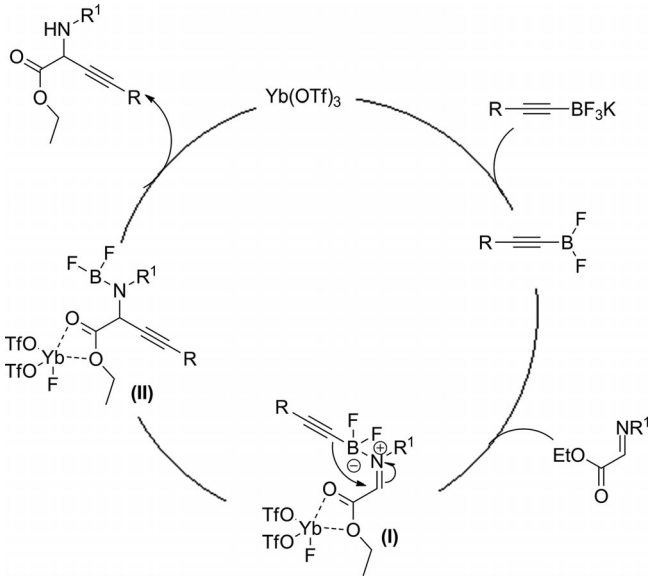
Table 2. Addition of alkynyltrifluoroborates to α-imino esters catalyzed by ytterbium (III).[a]



1a, R = 4-OMe(C_6H_4) **1c**, R = 4-I(C_6H_4)
1b, R = 2-Me-4-OMe(C_6H_3) **1d**, R = 4-Br(C_6H_4)

Entry	Product	Reaction time (min)	Yield (%)[a]	Entry	Product	Reaction time (min)	Yield (%)[a]
1	 **3a**	60	81	9	 **3i**	60	84
2	 **3b**	40	77				
3	 **3c**	30	65	10	 **3j**	120	77
4	 **3d**	30	87	11	 **3k**	50	90
5	 **3e**	60	60	12	 **3l**	90	95
6	 **3f**	45	80	13	 **3m**	120	50
7	 **3g**	30	82	14	 **3n**	90	86
8	 **3h**	30	80	15	 **3o**	60	55
				16	 **3p**	60	78

[a] Yields are given for isolated products.



Scheme 2. Proposed mechanism.

An interesting aspect of using rare earth metal triflates[15] is that the catalyst can be easily recovered from the reaction medium and recycled. This prompted us to evaluate the possibility of reusing the $Yb(OTf)_3$ in our reactions. In this regard, the catalyst was separated from the reaction medium by simple filtration, washed with dichloromethane, and dried at 70 °C for 2 h. This process was repeated two times to afford the desired product in 81% (first run), 75% (second run), and 50% (third run).

Conclusions

In summary, we have developed a practical approach for the synthesis of β-unsaturated α-amino acid derivatives through the alkynylation of imino esters with ytterbium triflate as the catalyst. The reaction is general and efficient with respect to the scope of substrates. Furthermore, the catalyst can be easily recovered and then reused.

Experimental Section

General Methods: All reactions were carried out under nitrogen. All compounds were characterized by using ^1H and ^{13}C NMR spectroscopy as well as ESI-MS. Copies of the ^1H and ^{13}C NMR spectra can be found in the Supporting Information. The ^1H and ^{13}C NMR spectroscopic data were recorded with a 300 MHz instrument. The chemical shifts (δ) for the ^1H NMR experiments are reported in parts per million (ppm) and measured relative to the signals for TMS (δ = 0.00 ppm). The chemical shifts for the ^{13}C NMR spectra are reported in ppm relative to deuterated chloroform (δ =77.23 ppm), unless otherwise stated, and all data were recorded using ^1H decoupling. Solvents and reagents were analytical grade or the highest grade commercially available and were used without further purification. The reactions were monitored by in situ Fourier transform infrared (FTIR) spectroscopy using a Mettler Toledo ReactIR 15 that was fitted with an articulated arm and a diamond probe.

General Procedure for Yb^{III}-Catalyzed Addition Reaction of Alkynyltrifluoroborate Salts to α-Imino Esters: Ytterbium triflate (10 mol-%, 0.030 g) was added to a stirred solution of α-imino ester (0.5 mmol, 0.103 g) in CH_2Cl_2 (5 mL). Potassium trifluoroborate (0.6 mmol) was then added, and the reaction mixture was stirred at room temperature until there was total consumption of the starting material. Afterwards, the reaction mixture was extracted with NaOH (0.5 N). The organic phase was dried using $MgSO_4$, and the solvent was removed under reduced pressure.

Ethyl 2-(4-Methoxyphenylamino)-4-phenylbut-3-ynoate (3a): (0.125 g, 81% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 2 H), 7.30–7.24 (m, 3 H), 6.77 (dd, J = 9.0 Hz, 4 H), 4.94 (s, 1 H), 4.30 (q, J = 7.1 Hz, 2 H), 3.74 (s, 3 H), 1.32 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 153.3, 139.4 (2 C), 131.8, 128.5 (2 C), 128.1, 122.1, 116.0 (2 C), 114.7 (2 C), 84.3, 84.2, 62.3, 55.6, 50.6, 14.0 ppm. HRMS: calcd. for $C_{19}H_{19}NO_3$ $[M + H]^+$ 310.1437; found: 310.1435.

Supporting Information (see footnote on the first page of this article): Experimental details and analytical data for all new compounds as well as the ^1H and ^{13}C NMR spectra.

Acknowledgments

The authors gratefully acknowledge the São Paulo Research Foundation (FAPESP; fellowship to F. M., 2010/15677-58, grant number 2012/00424-2) for financial support and The National Council for Scientific and Technological Development (CNPq) for a fellowship (308.320/2010-7, to H. A. S.).

[1] a) Y. Li, M.-H. Xu, *Org. Lett.* **2012**, *14*, 2062–2065; b) G. Dardenne, J. Casimir, M. Marlier, P. O. Larsen, *Phytochemistry* **1974**, *13*, 1897–1900; c) D. B. Berkowitz, E. Chisowa, J. M. McFadden, *Tetrahedron* **2001**, *57*, 6329–6343; d) R. R. Rando, *Biochemistry* **1974**, *13*, 3859–3863; e) B. W. Metcalf, K. Jund, *Tetrahedron Lett.* **1977**, *18*, 3689–3692; f) C. Danzin, P. Casara, N. Claverie, B. W. Metcalf, *J. Med. Chem.* **1981**, *24*, 16–20; g) D. B. Berkowitz, W.-J. Jahng, M. L. Pedersen, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2151–2156; h) Y. Kuroda, M. Okuhara, T. Goto, E. Igushi, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiot.* **1980**, *33*, 125–131; i) Y. Kuroda, M. Okuhara, T. Goto, E. Igushi, M. Kohsaka, H. Aoki, H. Himanaka, *J. Antibiot.* **1980**, *33*, 132–136.

[2] a) R. M. Williams, D. J. Aldous, S. C. Aldous, *J. Chem. Soc. Perkin Trans. 1* **1990**, 171–172.

[3] a) J.-X. Ji, A. Yeung, J. Wu, C. W. Yip, A. S. C. Chan, *Adv. Synth. Catal.* **2004**, *346*, 42–44; b) Z. Shao, J. Wang, K. Ding, A. S. C. Chan, *Adv. Synth. Catal.* **2007**, *349*, 2375–2379; c) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906; d) F. Peng, Z. Shao, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 465–468; e) J.-X. Ji, J. Wu, L. Xu, C.-W. Yip, K. H. Lam, A. S. C. Chan, *Pure Appl. Chem.* **2006**, *78*, 267–274; f) Z. Shao, A. S. C. Chan, *Synthesis* **2008**, *18*, 2868–2870.

[4] a) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19; b) Q. Kang, Z.-A. Zhao, S.-L. You, *Org. Lett.* **2008**, *10*, 2031–2034; c) S. Basra, M. W. Fennie, M. C. Kozlowski, *Org. Lett.* **2006**, *8*, 2659–2662; d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; e) J. Chen, X. Lu, W. Lou, Y. Ye, H. Jiang, W. Zeng, *J. Org. Chem.* **2012**, *77*, 8541–8548.

[5] a) J. S. Dickstein, M. C. Kozlowski, *Chem. Soc. Rev.* **2008**, *37*, 1166–1173; b) K. P. Chiev, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry* **2002**, *13*, 2205–2209.

[6] a) S. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288–325; b) G. A. Molander, R. Figueroa, *Aldrichim. Acta* **2005**, *38*, 49–56;

c) H. A. Stefani, R. Cella, A. S. Vieira, *Tetrahedron* **2007**, *63*, 3623–3658.
[7] a) H. A. Stefani, R. Cella, A. S. Vieira, *Tetrahedron* **2007**, *63*, 3623–3658; b) H. A. Stefani, M. F. Z. J. Amaral, G. Reyes-Rangel, J. V. Caporali, E. Juaristi, *Eur. J. Org. Chem.* **2010**, *33*, 6393–6403; c) A. S. Vieira, R. L. O. R. Cunha, C. F. Klitzke, J. Zukerman-Schpector, H. A. Stefani, *Tetrahedron* **2010**, *66*, 773–779; d) M. Weber, F. V. Singh, H. A. Stefani, M. W. Paixão, *Tetrahedron Lett.* **2009**, *50*, 4324–4327.
[8] a) D. R. Kronenthal, C. Y. Han, M. K. Taylor, *J. Org. Chem.* **1982**, *47*, 2765–2768; b) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431–432.
[9] a) L. Wu, M. Shi, *Chem. Eur. J.* **2011**, *17*, 13160–13165; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217; c) S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1997**, *62*, 232–233.
[10] E. Le Gall, S. Sengmany, C. Hauréna, E. Léonel, T. Martens, *J. Organomet. Chem.* **2013**, *736*, 27–35.
[11] a) M. Jurícek, P. H. J. Kouwer, J. Rehák, J. Sly, A. E. Rowan, *J. Org. Chem.* **2009**, *74*, 21–25; b) V. Fiandanese, D. Bottalico, G. Marchese, A. Punzi, F. Capuzzolo, *Tetrahedron* **2009**, *65*, 10573–10580.
[12] a) J.-P. Tremblay-Morin, S. Raeppel, F. Gaudette, *Tetrahedron Lett.* **2004**, *45*, 3471–3474; b) K. A. Tehrani, S. Stas, B. Lucas, N. Kimpe, *Tetrahedron* **2009**, *65*, 1957–1966.
[13] a) E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin, M. R. Schrimpf, *J. Org. Chem.* **1995**, *60*, 3020–3027; b) D. S. Matteson, G. Y. Kim, *Org. Lett.* **2002**, *4*, 2153–2155; c) G. A. Molander, J. Raushel, N. M. Ellis, *J. Org. Chem.* **2010**, *75*, 4304–4306.
[14] J. A. Bishop, S. Lou, S. E. Schaus, *Angew. Chem.* **2009**, *121*, 4401; *Angew. Chem. Int. Ed.* **2009**, *48*, 4337–4340.
[15] a) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Eur. J. Org. Chem.* **2002**, 1562–1565; b) M. Curini, F. Epifano, F. Maltese, M. C. Marcotullio, *Eur. J. Org. Chem.* **2003**, 1631–1634; c) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227–2302.

Received: September 17, 2013
Published Online: December 11, 2013

