ORGANIC LETTERS

2010
Vol. 12, No. 24
5740−5743

Friedel−Crafts Acylation of Pyrroles and Indoles using 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) as a Nucleophilic Catalyst

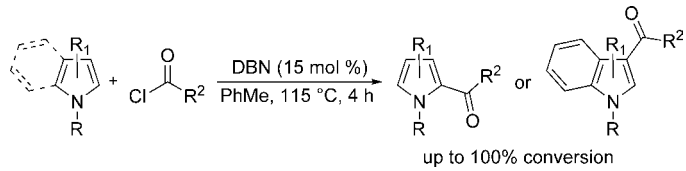
James E. Taylor, Matthew D. Jones, Jonathan M. J. Williams, and Steven D. Bull*

Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, United Kingdom

s.d.bull@bath.ac.uk

Received October 21, 2010

ABSTRACT



1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) has been shown to be an effective catalyst for the regioselective Friedel−Crafts *C*-acylation of pyrroles and indoles in high yields. A detailed mechanistic study implies that DBN is acting as a nucleophilic organocatalyst, with the X-ray crystal structure of a key *N*-acyl-amidine intermediate having been determined for the first time.

Substituted pyrroles and indoles are found in many natural products and biologically active compounds.[1] However, their synthesis remains challenging, with syntheses often suffering from poor regioselectivity and/or low yields due to oxidative degradation.[2] Traditionally, stoichiometric amounts of Lewis acids have been used for the Friedel−Crafts acylation of pyrroles and other heteroaromatic compounds,[3,4] while recently metal-based catalytic methods have also proven successful.[5]

Organocatalysts have been used previously for the *O*-acylation of alcohols and amines, with a few examples of intramolecular organocatalytic *C*-acylations having been reported.[6,7] However, to the best of our knowledge, organocatalysts have never been used for the direct intermolecular *C*-acylation of aromatic substrates. We now report the development of a high yielding and regioselective organocatalytic methodology for the *C*2-acylation of *N*-protected pyrroles and *C*3-acylation of *N*-protected indoles.

Initially, we screened a range of organocatalysts for the acylation of commercially available *N*-methylpyrrole (**1**) with

(1) Joule, J. A.; Mills, K.; Smith, D. F. *Heterocyclic Chemistry*, 3rd ed.; Stanley Thornes: Cheltenham, 1998.

(2) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110.

(3) Olah, G. A. *Friedel-Crafts Chemistry*; Wiley-Interscience: New York, 1973.

(4) (a) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214–3219. (b) Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451–5457. (c) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485–1487. (d) Ottoni, O.; Neder, A. D. F.; Dias, A. K. B.; Cruz, R. P. A.; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005–1007. (e) Yadav, J. S.; Reddy, B. V. S.; Kondaji, G.; Srinivasa Rao, R.; Praveen Kumar, S. *Tetrahedron Lett.* **2002**, *43*, 8133–8135. (f) Yeung, K. S.; Farkas, M. E.; Qiu, Z. L.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 5793–5795. (g) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720–5723. (h) Kantam, M. L.; Ranganath, K. V.; Sateesh, M.; Kumar, K. B. S.; Choudary, B. M. *J. Mol. Catal. A: Chem.* **2005**, *225*, 15–20. (i) Alvaro, V. F. D.; Brigas, A. F.; Derouane, E. G.; Lourenco, J. P.; Santos, B. S. *J. Mol. Catal. A: Chem.* **2009**, *305*, 100–103. (j) Huffman, J. W.; Smith, V. J.; Padgett, L. W. *Tetrahedron* **2008**, *64*, 2104–2112.

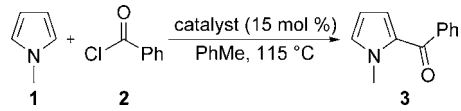
(5) (a) Komoto, I.; Matsuo, J.; Kobayashi, S. *Top. Catal.* **2002**, *19*, 43–47. (b) Su, W.; Wu, C.; Su, H. *J. Chem. Res.* **2005**, 67–68. (c) He, F.; Wu, H. Y.; Chen, J. X.; Su, W. K. *Synth. Commun.* **2008**, *38*, 255–264.

(6) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

(7) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369. (c) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934. (d) Thomson, J. E.; Rix, K.; Smith, A. D. *Org. Lett.* **2006**, *8*, 3785–3788. (e) Joannesse, C.; Simal, C.; Concellon, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900–2907. (f) Joannesse, C.; Johnston, C. P.; Concellon, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 8914–8918. (g) Steglich, W.; Hofle, G. *Tetrahedron Lett.* **1970**, 4727–4730. (h) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425–5430.

10.1021/ol1025348
Published on Web 11/15/2010

Table 1. Catalyst Screen for the Acylation of *N*-Methylpyrrole (**1**)[a]



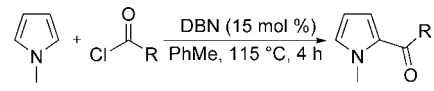
entry	catalyst	time/h	conversion (%)[b,c]
1	–	1.5	30
2	DMAP	1.5	31
3	DABCO	1.5	34
4	Imidazole	1.5	33
5	Pyridine	1.5	45
6	DBU	1.5	60
7	DBN	1.5	72
8	DBN	4	95 (73)
9	–	8	87 (57)

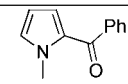
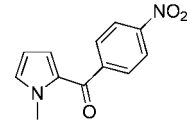
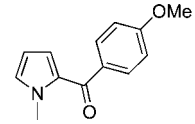
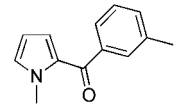
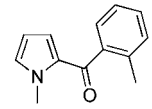
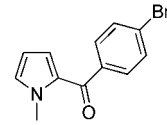
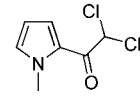
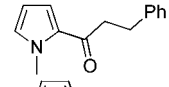
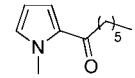
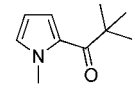
[a] Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**2**).[9] [b] Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c] Isolated yields by column chromatography in parentheses.

benzoyl chloride (**2**) in toluene at reflux (Table 1). Traditional nucleophilic acylation catalysts, such as 4-(dimethylamino)pyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), and imidazole, showed little catalytic activity, while pyridine only gave a small rate increase (Table 1, entries 2−5). However, the use of bicyclic amidines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) gave a significant rate increase (Table 1, entries 6 and 7),[8] with a 72% yield of 2-benzoyl-*N*-methylpyrrole **3** being formed after only 1.5 h using 15 mol % DBN. Further optimization using DBN showed that increasing the reaction time to 4 h gave essentially complete conversion into acyl pyrrole **3** as a single regioisomer (Table 1, entry 8). This compares with an uncatalysed acylation reaction that took 8 h to proceed to 87% conversion affording acyl pyrrole **3** in only 57% isolated yield.

The generality of this acylation protocol was then tested using a range of acyl chlorides (**4**) for the acylation of *N*-methylpyrrole (**1**) (Table 2). The reaction with substituted benzoyl chlorides tolerates both strongly electron-withdrawing (*p*-NO_2) and electron-donating (*p*-OMe) substituents in the acyl chloride, with complete conversion being observed in both cases (Table 2, entries 2 and 3). Aryl substituents were well tolerated, with *o*-toluoyl chloride giving 100% conversion after 4 h, whereas *m*-toluoyl chloride required 8 h to proceed to completion. (Table 2, entries 4 and 5). The presence of halo substituents was also tolerated, with reactions using *p*-bromobenzoyl chloride and dichloroacetyl chloride giving complete conversion and good isolated yields (Table 2, entries 6 and 7). Next, the reaction was tested on alkyl acyl chlorides, which were found to be just as active, with hydrocinnamoyl chloride and heptanoyl chloride giving complete conversion and good isolated yields (Table 2,

Table 2. Acylation of *N*-Methylpyrrole (**1**) with a Range of Acyl Chlorides[a]



entry	R	conversion (%)[b,c]
1		95 (73)
2		100 (74)
3		100 (66)
4[d]		100 (76)
5		100 (63)
6		100 (70)
7		100 (80)
8		100 (70)
9		100 (82)
10[d]		71 (63)

[a] Reactions performed on a 1 mmol scale using 1.2 mmol acyl chloride. [b] Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c] Isolated yields by column chromatography in parentheses. [d] Eight hour reaction time.

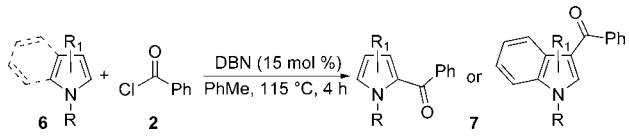
(8) Amidines such as DBU and DBN have traditionally been used as bases in organic reactions; however, there are a number of reports of their use as nucleophilic catalysts in a wide variety of reactions, see: (a) Ghosh, N. *Synlett* **2004**, 574–575. (b) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794. (c) Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477. (d) Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669–3670. (e) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312. (f) Shieh, W.-C.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188–2191. (g) Lohmeijer, B. G. G.; Pratt, R. C.; Leibfarth, F.; Logan, J. W.; Long, D. A.; Dove, A. P.; Nederberg, F.; Choi, J.; Wade, C.; Waymouth, R. M.; Hedrick, J. L. *Macromolecules* **2006**, *39*, 8574–8583. (h) Zhang, W.; Shi, M. *Org. Biomol. Chem.* **2006**, *4*, 1671–1674. (i) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37–40. (j) Price, K. E.; Larrivee-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003–2006. (k) Yang, X.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1499–1502. (l) Larrivee-Aboussafy, C.; Jones, B. P.; Price, K. E.; Hardink, M. A.; McLaughlin, R. W.; Lillie, B. M.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2010**, *12*, 324–327. (m) Birman, V. B.; Uffman, E. W.; Hui, J.; Li, X. M.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227. (n) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537.

(9) An initial screen of solvents, equivalents of acyl chloride, and catalyst loading revealed these to be the best conditions.

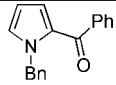
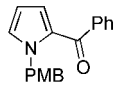
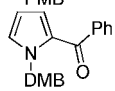
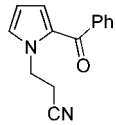
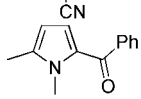
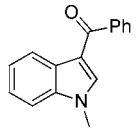
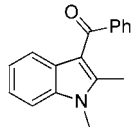
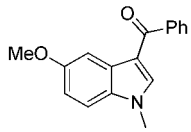
entries 8 and 9). However, the bulkier pivaloyl chloride proved more sluggish, requiring 8 h to proceed to a reduced 71% conversion (Table 2, entry 10).

These acylation conditions were then applied to a number of substituted pyrroles using benzoyl chloride (**2**) as the standard acylating agent. Acylation reactions were found to be successful for all of the *N*-alkyl pyrroles investigated, with *N*-benzyl-, *N*-*p*-methoxybenzyl- (PMB), *N*-dimethoxybenzyl- (DMB), and *N*-cyanoethyl- pyrroles all successfully acylated with high conversions and reasonable isolated yields (Table 3, entries 1−4).[10] The acylation reaction was also shown to tolerate ring substitution with 2-methyl-*N*-methylpyrrole being acylated with 100% conversion (Table 3, entry 5). Given the success of these pyrrole *C*-acylation reactions, we applied our acylation protocol to *N*-methylindoles. Pleasingly, *N*-methylindole was regioselectively acylated in its precedented *C*3 position, albeit in a lower 65% isolated yield (Table 3, entry 6). The acylation reaction proceeded more smoothly with 1,2-dimethylindole, with complete conversion and an 88% isolated yield being obtained (Table 3, entry 7). However, acylation of indoles was shown to be sensitive to the presence of substituents in their benzenoid ring, with 5-methoxy-*N*-methylindole acylated in only 57% conversion (Table 3, entry 8).

Table 3. Acylation of Pyrroles and Indoles with Benzoyl Chloride (**2**)[a]



6 2 7

entry	product	conversion (%)[b]
1		86 (56)
2		100 (79)
3		87 (62)
4		94 (73)
5		100 (63)
6		65 (54)
7		100 (88)
8		57 (40)

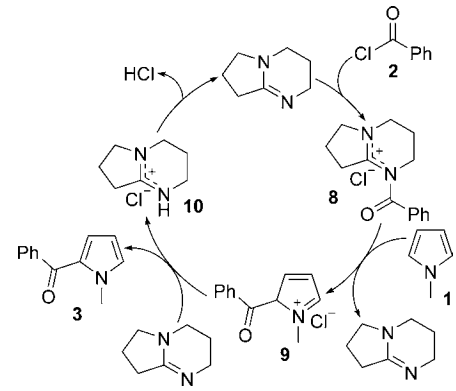
[a] Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**2**). [b] Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c] Isolated yields, by column chromatography, in parentheses. [d] Attempts to increase the levels of conversion by increasing reaction times to greater than 4 h led to a drop in yield of the corresponding indole product.

We next decided to probe the mechanism of the acylation reaction to confirm that DBN was acting as a nucleophilic catalyst to activate the acyl chloride toward electrophilic attack. First, we ruled out the possibility that DBN was increasing the rate of reaction by acting as a base to rearomatize the acylated pyrrole intermediate **9**.

This was confirmed by performing a kinetic-isotope experiment where it was found that the rates of acylation for both *N*-benzylpyrrole and *N*-benzyl-D_4-pyrrole were the same, implying that proton transfer is not involved in the rate-determining step.[11] We also confirmed that the reaction was not catalyzed by adventitious HCl generated in the reaction, since carrying out the acylation reaction in a saturated solution of HCl in toluene did not increase the rate of reaction.

Given this evidence, a potential catalytic mechanism was proposed as shown in Scheme 1, which involves the addition of pyrrole to an *N*-acyl-DBN intermediate **8**. In order to prove this hypothesis it was decided to attempt to isolate the proposed *N*-acyl-DBN intermediate **8** (Scheme 1). Therefore, a 1:1 mixture of DBN and benzoyl chloride (**2**) was stirred in chloroform-D and the resulting solution analyzed. High-resolution mass-spectrometry confirmed the presence of a positively charged ion with the correct molecular weight for the *N*-acyl-DBN intermediate **8** that exhibited a carbonyl resonance in the infrared at 1709 cm^{-1}. ^{1}H NMR spectroscopic analysis of this solution showed that a single complex had been

Scheme 1. Proposed Mechanism for the DBN Catalyzed *C*-Acylation of *N*-Methylpyrrole (**1**)



(10) These *N*-substituents have all been used as protecting groups for pyrroles, with protocols available for their removal see: Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531–11563.

(11) See Supporting Information for full details.

formed whose spectrum was consistent with the formation of *N*-acyl-DBN **8**, while no resonances corresponding to free DBN were observed. The aromatic protons of its benzoyl fragment were shifted approximately 0.2 ppm upfield, while the signals for the protons of the amidine fragment were shifted downfield. The largest shifts (approximately 0.7 ppm downfield) were observed for the three pairs of protons adjacent to the two nitrogen atoms of **8**, suggesting that the positive charge of the complex was distributed between both nitrogen atoms. Importantly, formation of a quantitative amount of this *N*-acyl-DBN species (**8**) has been observed in the ^{1}H NMR spectrum of a sample of the standard acylation reaction (in $CDCl_3$) when 15 mol % of the catalyst is used, with no resonances corresponding to any free DBN being observed.

Attempts to obtain X-ray quality crystals of the *N*-acyl-DBN **8** salt with chloride as counterion were unsuccessful. However, exchanging the counterion for tetraphenylborate allowed suitable crystals to be obtained for X-ray crystallographic analysis (Figure 1).[12a] This structure confirmed that the acyl fragment

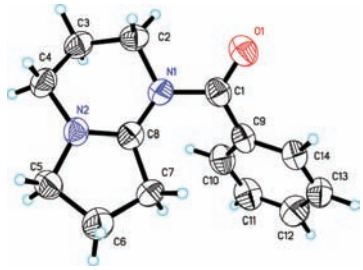


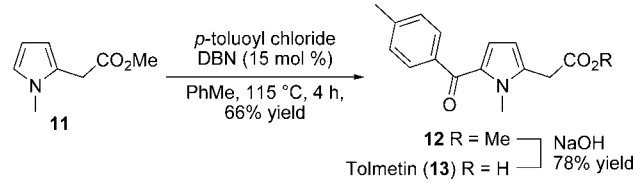
Figure 1. X-ray crystal structure of the *N*-acyl-DBN reveals a 36.1° angle between the carbonyl and the amidine ring. Tetraphenylborate counterion not shown for clarity.

was attached to N1, with the N1−C8 bond length of 1.349 Å and the N2−C8 bond length of 1.310 Å implying that the positive charge is delocalized over both nitrogen atoms. Interestingly, the carbonyl group lies out of the plane of the delocalized system, with an angle of 36.1° between the N1−C8−N2 and N1−C1−O1 planes (Figure 1). The fact that the carbonyl group of *N*-acyl-DBN (**8**) lies out of the plane may explain why DBN exhibits catalytic activity, while traditional acyl transfer catalysts such as DMAP or pyridine showed little activity in these acylation reactions (Table 1). Crystal structures of *N*-acyl-DMAP and 2,3-dihydroimidazo-[1,2-a]pyridine systems reveal that the acyl group and the pyridine fragment lie in the same plane.[12] This is advantageous when an anhydride is used as the acyl source, as the planar *N*-acyl-catalyst is stabilized and thus the equilibrium between the anhydride and catalyst is favored toward the acylated intermediate.[13] However, in our case, DBN reacts quantitatively with an acyl chloride to afford an *N*-acyl-DBN intermediate whose "out of plane" carbonyl group is less conjugated, which may explain its increased reactivity toward nucleophilic attack.

To confirm that complex **8** was a catalytically active intermediate, a stoichiometric amount was reacted with *N*-methylpyrrole (**1**), which gave the corresponding acyl pyrrole **3** in quantitative yield. It seems reasonable to suggest that intermediate **9** is rearomatized by deprotonation by DBN to form acyl pyrrole **3** and DBN hydrochloride **10**. We speculate that the DBN hydrochloride (**10**) formed in this step must be able to dissociate into free DBN and HCl at these temperatures, with the equilibrium of this dissociation process being driven toward formation of free amidine catalyst by the low solubility of HCl in toluene. This hypothesis is supported by the fact that our acylation conditions release HCl gas from solution over the course of the reaction, while DBN hydrochloride (**10**) can also serve as a catalytic precursor in these acylation reactions.

The effectiveness of the acylation protocol has been demonstrated with a synthesis of Tolmetin (**13**), a nonsteroidal anti-inflammatory drug whose pyrrole skeleton contains a *C*2 *p*-toluoyl substituent.[14] Application of our DBN catalyzed conditions to pyrrole ester **11**, using 1.2 equivalents of *p*-toluoyl chloride and 15 mol % DBN at reflux in toluene for 4 h gave acylated product **12** in 100% conversion, which on hydrolysis gave Tolmetin (**13**) in 78% isolated yield.

Scheme 2. Tolmetin Synthesis



In conclusion, we have developed the first organocatalytic Friedel−Crafts acylation reaction for the regioselective synthesis of *C*2-acyl pyrroles and *C*3-acyl indoles. Detailed mechanistic studies and characterization of the key *N*-acyl-DBN intermediate suggest that DBN functions as a nucleophilic catalyst in these reactions. We are currently investigating other amidine based catalysts, with the aim of broadening the scope of the acylation reaction to other aromatic compounds and providing further rate enhancements.

Acknowledgment. J.E.T. thanks the University of Bath for funding.

Supporting Information Available: Experimental details, spectroscopic data, details of mechanistic experiments, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1025348

(12) (a) King, J. A.; Bryant, G. L. *J. Org. Chem.* **1992**, *57*, 5136–5139. (b) Lohse, C.; Hollenstein, S.; Laube, T. *Angew. Chem., Int. Ed.* **1991**, *30*, 1656–1658. (c) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836–13837.

(13) (a) Held, I.; Villinger, A.; Zipse, H. *Synthesis* **2005**, *9*, 1425–1430. (b) Xu, S. J.; Held, I.; Kempf, D.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751–4757. (c) Lutz, V.; Glatthaar, J.; Wurtele, C.; Serafin, M.; Hausmann, H.; Schreiner, P. R. *Chem.—Eur. J.* **2009**, *15*, 8548–8557.

(14) Reddy, L. A.; Chakraborty, S.; Swapna, R.; Bhalerao, D.; Malakondaiah, G. C.; Ravikumar, M.; Kumar, A.; Reddy, G. S.; Naram, J.; Dwivedi, N.; Roy, A.; Himabindu, V.; Babu, B.; Bhattacharya, A.; Bandichhor, R. *Org. Process Res. Dev.* **2010**, *14*, 362–368.