Decarboxylative C–H Activation

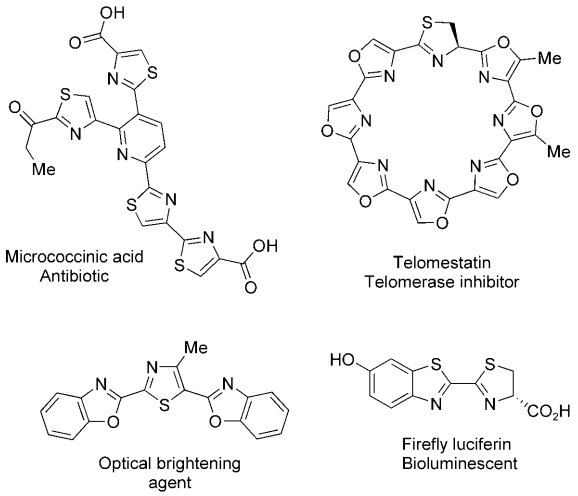
DOI: 10.1002/anie.200906921

Decarboxylative C–H Cross-Coupling of Azoles**

*Fengzhi Zhang and Michael F. Greaney**

The use of carboxylic acids as functional handles for transition metal catalyzed cross-coupling reactions is a fast growing area of research.[1] Pioneering work has established that metal-mediated decarboxylation affords organometallic intermediates that can participate in palladium-catalyzed C–C bond-forming processes such as the Heck reaction[2] and cross-coupling reactions with aryl halides (Steglich,[3] Miura,[4] Goossen,[5] and Forgione[6]).[7] The concept has recently been extended to the C–H activation field. Glorius and co-workers have demonstrated the intramolecular decarboxylative C–H activation of *ortho*-phenoxy benzoic acids for the synthesis of dibenzofurans,[8] whereas Crabtree and co-workers and Larrosa and co-workers have described the intermolecular cross-coupling of *ortho*-substituted benzoic acids with anisole and indoles, respectively.[9,10] The union of two emerging areas of catalytic C–C bond-forming chemistry, both of which eschew preformed organometallic substrates, holds great potential for new bond-forming strategies in synthesis. The reaction would be particularly powerful for the synthesis of polyheteroaromatic compounds. The regiocontrolled union of heteroaromatics, requiring no significant prefunctionalization and proceeding under catalytic conditions, could lead to dramatically streamlined syntheses of this fundamental compound class. To investigate this possibility, we have developed an intermolecular decarboxylative C–H cross-coupling between oxazoles and thiazoles with the rapid synthesis of functionalized polyazoles.

In recent years, azole heterocycles have proven to be useful substrates for the development of synthetic and mechanistic C–H arylation chemistry.[11] Oxazoles, thiazoles, and imidazoles are important heterocyclic components of bioactive natural products, pharmaceuticals, and functional materials, making their efficient synthesis of great interest (Scheme 1).[12] The development of new C–H arylation methods is particularly apposite for this class of heterocycle, as the stoichiometric amounts of organometallic reagents required in classic cross-coupling reactions are difficult to prepare at certain positions on the azole ring.[13] In contrast, carboxylate groups are commonly found in both synthetic and naturally occurring azole structures, and represent versatile synthetic handles for regioselective cross-coupling reactions.



Scheme 1. Representative azole structures.

The development of such a decarboxylative C–H arylation reaction would constitute a novel and convenient entry point into biologically active polyheteroaromatic structures.

We first established reaction conditions for the decarboxylative C–H coupling of thiazole **1a** with oxazole **2a**. We were pleased to discover that the reaction was viable using $Pd(OAc)_2$ in dioxane/DMSO in the presence of stoichiometric amounts of silver or copper salts and a ligand (Table 1).

The 2,5-linked bis(azole) **3a** was formed along with two side products, the homocoupled oxazole **4** and the decarboxylated starting thiazole. Small amounts of the decarboxylation product were always observed, as the thiazole was used in excess during the optimization process. The principal challenge in optimization centered upon increasing the yields of **3a** at the expense of the undesired homocoupling product **4**.

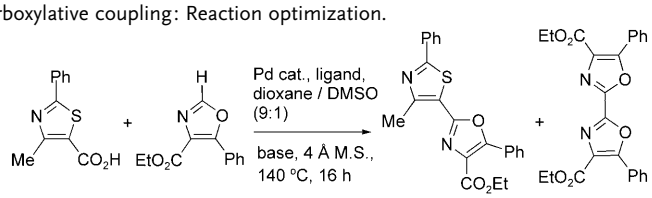
The screening of ligands established that various sterically hindered monodentate phosphines (Table 1, entries 1–2) and dipyridyl ligands (entry 3) together with silver carbonate led to the production of **3a** in modest yield and selectivity. Ethyl nicotinate was more effective (entry 4), and sterically hindered bidentate bis(dicyclohexylphosphino)ethane (entry 5) provided the best selectivity with a 22:1 ratio in favor of **3a**, and the product was isolated in 51% yield. A combination of the cheaper copper carbonate and the dcpe ligand proved best, providing similar yields of **3a**, although the overall selectivity was lower than that for silver carbonate (entry 9). Other copper and silver salts showed no improvement over their respective carbonate salts (entries 6–8). Fine tuning of the ligand to palladium ratio provided optimized product yields of 64% (entry 11) and 77% (entry 12). Control experiments run in the absence of palladium, copper or silver carbonate, and the ligand were all negative.[14]

[*] Dr. F. Zhang, Dr. M. F. Greaney
School of Chemistry, University of Edinburgh
King's Buildings, West Mains Rd., Edinburgh, EH9 3JJ (UK)
Fax: (+44) 131-650-4743
E-mail: michael.greaney@ed.ac.uk

[**] We thank the EPSRC for funding (Leadership Fellowship to MFG) and the EPSRC mass spectrometry service at the University of Swansea.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906921.

Table 1: Decarboxylative coupling: Reaction optimization.



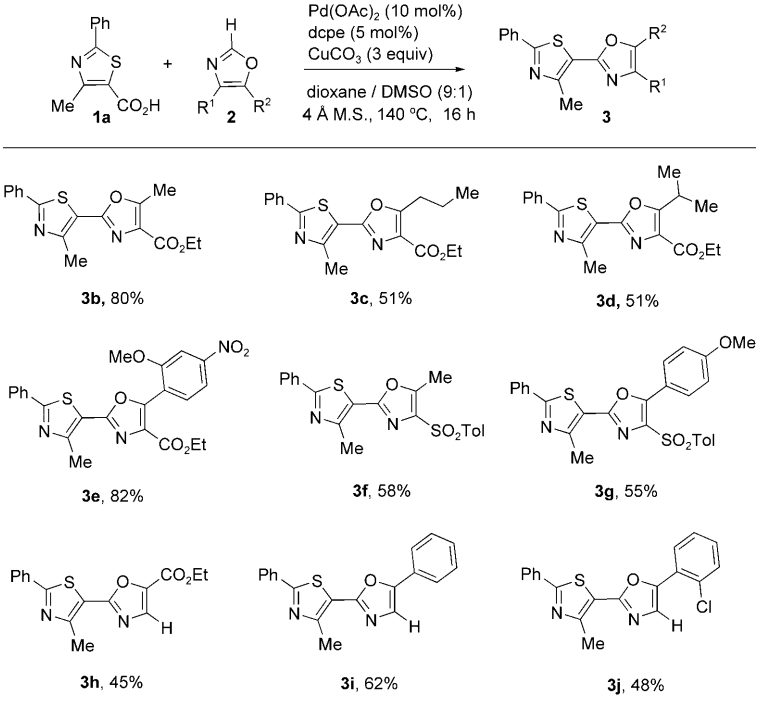
Entry[a]	$Pd(OAc)_2$ [mol%]	Ligand (mol%)	Base	**3a**/**4**[b]	Yield of **3a** [%][b]
1[c]	10	SPhos (10)	Ag_2CO_3	2:1	34
2[c]	10	*t*BuXPhos (10)	Ag_2CO_3	3:1	31
3[c]	10	2,2′-dipyridyl (10)	Ag_2CO_3	4:1	33
4[c]	10	ethyl nicotinate (10)	Ag_2CO_3	8:1	57
5[c]	10	dcpe (10)	Ag_2CO_3	22:1	68 (51)[d]
6	10	dcpe (10)	$AgNO_3$	–	0
7	10	dcpe (10)	Cu_2O	–	0
8	10	dcpe (10)	AgOAc	3:1	34
9	10	dcpe (10)	$CuCO_3$	8:1	64
10	10	dcpe (20)	$CuCO_3$	8:1	51[d]
11	10	dcpe (5)	$CuCO_3$	5:1	75 (64)[d]
12	20	dcpe (10)	$CuCO_3$	10:1	82 (77)[d]

[a] Reaction conditions: Thiazole **1** (1.5 equiv), oxazole **2** (1 equiv), catalytic $Pd(OAc)_2$, base (3 equiv), and 4 Å molecular sieves (100 mg) in dioxane/DMSO (9:1, 1.5 mL, 0.2 M). Reactions were carried out on a 0.1 mmol scale and heated to 140 °C for 16 hours in a sealed tube. [b] Ratio and yield determined by NMR spectroscopy of the crude raection mixture by using an internal standard. [c] Performed in DMSO. [d] Yield of isolated product. dcpe = bis(dicyclohexylphosphino)ethane, DMSO = dimethyl sulfoxide, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, *t*BuXPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl.

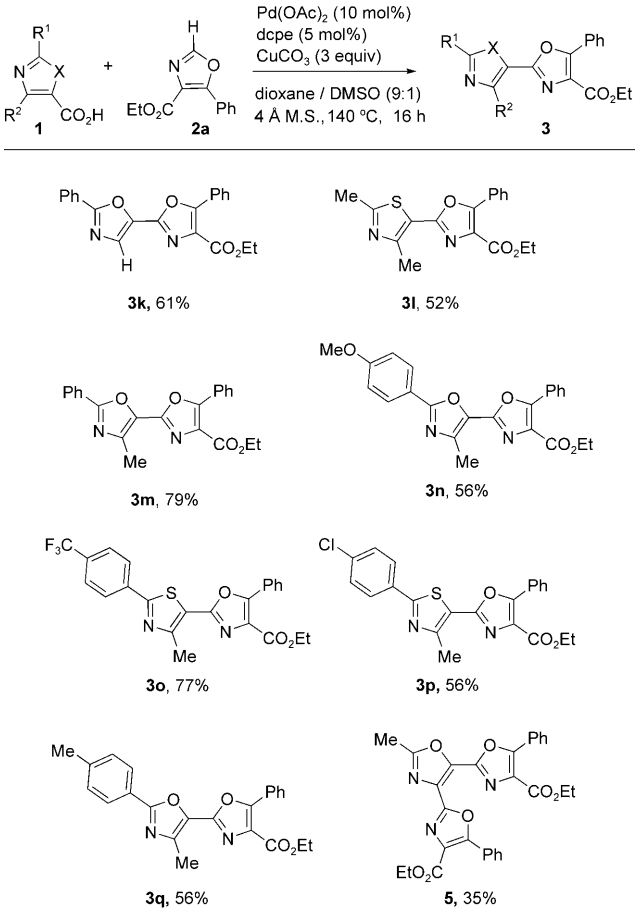
With an optimized process for the coupling of thiazole **1a** with oxazole **2a**, we next examined the scope of the reaction for bis(azole) synthesis. Using copper carbonate as the base, we first varied the C–H component in the cross-coupling reaction using a variety of oxazoles (Scheme 2). The 4-substituted ester and sulfone derivatives proved to be good substrates — they could be prepared by simple literature methods, the electron-withdrawing group promoted the reaction, and it was also present as a functional handle in the coupled product **3** for additional elaboration (see below). Yields for these bis(azole)s ranged from moderate to very good (45%–82%), and featured both alkyl (Scheme 2; **3b**, **3c**, **3d**, and **3f**), and aryl (Scheme 2; **3e** and **3g**) substituents at the 5-position. Esters (Scheme 2; **3b–3e** and **3h**), sulfones (Scheme 2; **3f** and **3g**), nitro (Scheme 2; **3e**), and chloro (Scheme 2, **3j**) groups were tolerated in the reaction, therefore providing sites for additional elaboration of the heteroaromatic products.

Regiocontrol for oxazoles containing two C–H bonds proved difficult as mixtures of products were obtained because of the difficulty in discriminating between the 2- and 5-positions. The facility of the electron-rich azole 5-position to undergo palladation is well-known, as exemplified in a number of direct arylation systems.[11] Oxazoles containing C–H bonds at C2 and C4, however, proved to be viable substrates. The C4 position is known to be quite unreactive towards C–H activation, as it is lacking in both nucleophilicity and acidity.[15] We could employ monosubstituted oxazoles, having either ester or aryl groups at the 5-position, in the decarboxylative cross-coupling reactions to afford bis(azole)s **3h**, **3i**, and **3j** in 45%, 62%, and 48% yields, respectively.

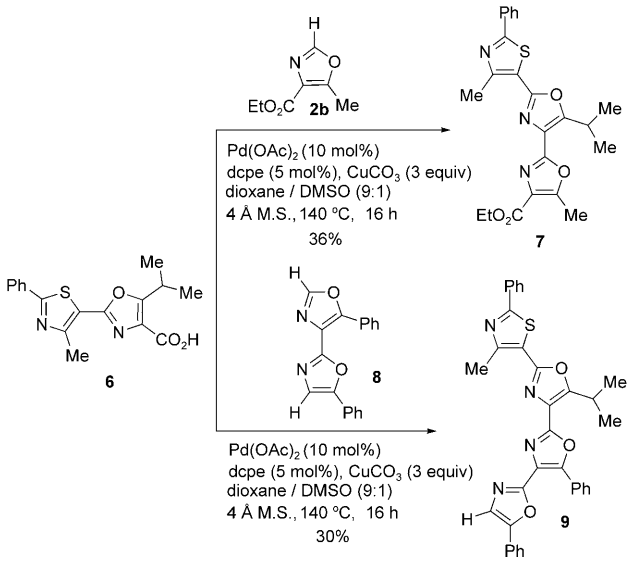
We prepared a selection of 2- and 4-substituted oxazoles, and thiazole-5-carboxylic acids to investigate the substrate scope for the acid component (Scheme 3). We placed a small group at C4 (Me or H), to avoid undue steric hindrance during the decarboxylation event. A variety of alkyl and aryl substituents were tolerated at C2 for both the oxazole and thiazole components, affording a range of bis(azole)s (**3k–q**) in 52%–79% yield. The C4 position on the acid component could be unsubstituted, with bis(oxazole) **3k** being formed in 61% yield. The isomeric C4-carboxylic acids with no substitution at C5 again proved to be problematic in terms of multiple arylations. As an example, we could isolate the novel trisoxazole **5** in 35% yield by treating **2a** with 2-methyloxazole-4-carboxylic acid. A decarboxylative coupling with **2a** at the 4-position is accompanied by a



Scheme 2. Substrate scope: C–H component.



Scheme 3. Substrate scope: CO_2H component.

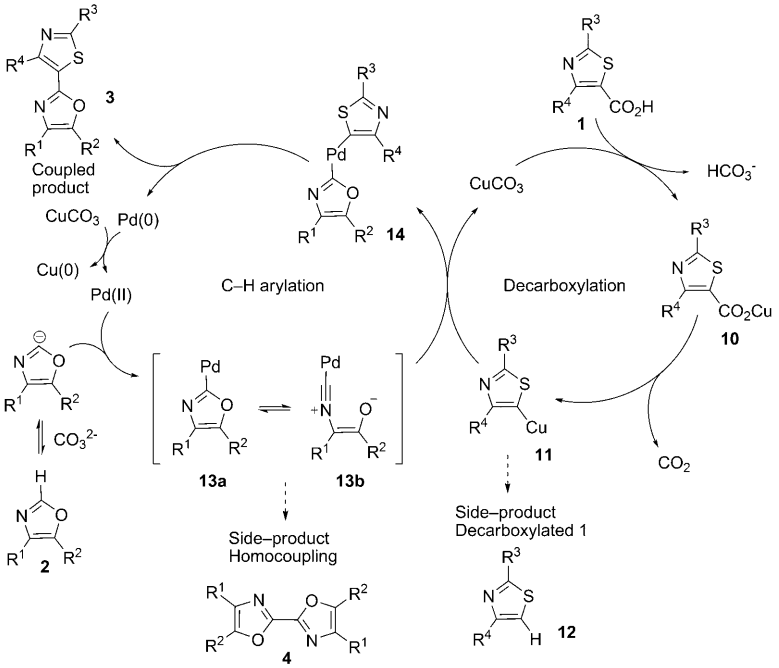


Scheme 4. Tris- and tetrakisazole synthesis.

second oxidative C–H/C–H coupling with **2a** at the 5-position.

The carboxylic ester group in many of the bis(azole) products presents a useful handle to repeat the decarboxylative cross-coupling in a second C–C bond-forming reaction. Preliminary efforts for this coupling are shown in Scheme 4. Ester **3d** could be hydrolyzed into the carboxylic acid **6** without any problem, and then used in a coupling reaction with oxazole **2b** to afford trisazole **7** in 36% yield. Subsequently, a coupling with bis(oxazole) **8**[16] produced the tetrazole **9** in 30% yield. Although the yields are modest, the synthesis of such 2,5-linked tris- and tetrakisazole structures have not been reported in the literature to date. Literature syntheses of analogous 2,4-linked polyoxazoles have involved multistep (>12 steps), linear routes frequently using peptide chemistry.[12] Our current approach is extremely quick, modular, and convergent, and has scope for optimization.

Mechanistically, the decarboxylative coupling may be considered in terms of a silver- or copper-catalyzed decarboxylation cycle and a C–H arylation cycle (Scheme 5). Decarboxylation using metal carbonates is well-established in the literature, with a number of recent advancements taking place as part of decarboxylative cross-coupling investigations.[10,17] We confirmed that thiazole acid **1a** underwent smooth decarboxylation when treated with stoichiometric amounts of copper carbonate, in the absence of palladium, under the optimized reaction conditions, producing 2-phenyl-4-methylthiazole in 87% yield. The thiazoyl cuprate **11** must intercept the C2-palladated intermediate **13** in the arylation cycle for successful coupling. Palladation at the azole 2-position with Pd^{II} salts has been rigorously demonstrated in the benzoxazole series by Sánchez and



Scheme 5. Possible mechanism for the decarboxylative cross-coupling reaction.

Zhuravlev,[18] as well as being implicit in a range of oxazole C2-directed arylation systems with aryl halides.[11]

We confirmed that oxazole **2a** undergoes deprotonation with copper carbonate in DMSO at 140 °C with a deuterium exchange reaction. Interestingly, the well-known ability of 2-oxazole anions to undergo ring-opening possibly allows the isonitrile isomer **13b** to act as a palladated intermediate. Transmetallation with cuprate **11** would then afford the palladium intermediate **14** which can reductively eliminate Pd^0 to produce the coupled product **3**. Oxidation of Pd^0 with excess Cu^{II} then restarts the catalytic cycle. The replacement of excess copper salts with cheaper and more environmentally friendly oxidizing agents is conceivable for this step, and will form part of our future work in the area.

In conclusion, we have developed a novel decarboxylative C–H arylation reaction that features the intermolecular union of two azole heteroarenes. The prevalence of carboxylate groups in simple azole building blocks enables the rapid synthesis of functionalized bis(azole)s and their higher congeners, without any prefunctionalization chemistry being necessary.

Experimental Section

Typical procedure for the synthesis of 2-(4-Methyl-2-phenyl-thiazol-5-yl)-5-phenyl-oxazole-4-carboxylic acid ethyl ester, (**3a**):

An oven-dried microwave tube was charged with thiazole **1a** (99 mg, 0.45 mmol, 1.5 equiv), copper carbonate (199 mg, 0.90 mmol, 3 equiv), palladium acetate (13.4 mg, 0.06 mmol 20 mol%), dcpe (12.7 mg, 0.03 mmol, 10 mol%), and 4 Å molecular sieves (100 mg). The reaction vessel was then flushed with nitrogen three times. A solution of oxazole **2a** (65 mg, 0.30 mmol, 1 equiv) in dioxane/DMSO (1.5 mL, 9:1, 0.2 M) was then added to the above mixture. The resulting mixture was stirred in a preheated oil bath at 140 °C for 16 hours before being cooled to room temperature, filtered and washed with EtOAc (50 mL). The resulting organic solution was washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and then the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc from 10:1 to 4:1) to give the coupled product **3a** as a pale yellow solid (96 mg, 77% yield); M.p. 154–156 °C; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 8.07$–8.11 (m, 2H), 7.96–7.99 (m, 2H), 7.45–7.51 (m, 6H), 4.45 (q, 2H, $J = 7.1$ Hz), 1.43 (s, 3H), 1.42 ppm (t, 3H $J = 7.1$ Hz); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 168.2$ (C), 162.0 (C), 155.8 (C), 154.9 (C), 154.6 (C), 132.9 (C), 130.8 (CH), 130.4 (CH), 129.1 (2×CH), 128.5 (2 × CH), 128.4 (2×CH), 128.2 (C), 126.8 (C), 126.7 (2×CH), 117.9 (C), 61.5 (CH_2), 17.5 (CH_3), 14.2 ppm (CH_3); IR (film): $\tilde{\nu} = 2972$, 1718, 1560, 1492, 1215, 1090, 770, 712, 689 cm^{-1}; HRMS (ESI) *m/z*: calc for $C_{22}H_{19}N_2O_3S$: 391.1111 $[M+H]^+$; found: 391.1117.

Received: December 8, 2009
Published online: March 16, 2010

Keywords: catalysis · cross-coupling · C–H activation · heterocycles · palladium

[1] For reviews, see: a) S. M. Bonesi, M. Fagnoni, A. Albini, *Angew. Chem.* **2008**, *120*, 10172–10175; *Angew. Chem. Int. Ed.* **2008**, *47*, 10022–10025; b) L. J. Goossen, N. Rodriguez, K. Goossen, *Angew. Chem.* **2008**, *120*, 10172–10175; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; c) O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395–1397; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373–1375.

[2] A. G. Myers, D. Tanaka, M. R. Mannion, *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251.

[3] C. Peschko, C. Winklhofer, W. Steglich, *Chem. Eur. J.* **2000**, *6*, 1147–1152.

[4] T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287.

[5] L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664.

[6] P. Forgione, M. C. Brochu, M. St Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351.

[7] For recent applications, see: a) M. Miyasaka, K. Hirano, T. Satoh, M. Miura, *Adv. Synth. Catal.* **2009**, *351*, 2683–2688; b) L. J. Goossen, B. Zimmermann, C. Linder, N. Rodriguez, P. P. Lange, J. Hartung, *Adv. Synth. Catal.* **2009**, *351*, 2667–2674; c) L. J. Goossen, C. Linder, N. Rodriguez, P. P. Lange, *Chem. Eur. J.* **2009**, *15*, 9336–9349; d) M. Miyasaka, A. Fukushima, T. Satoh, K. Hirano, M. Miura, *Chem. Eur. J.* **2009**, *15*, 3674–3677; e) H. P. Bi, L. Zhao, Y. M. Liang, C. J. Li, *Angew. Chem.* **2009**, *121*, 806–809; *Angew. Chem. Int. Ed.* **2009**, *48*, 792–795; f) L. J. Goossen, B. Zimmermann, T. Knauber, *Angew. Chem.* **2008**, *120*, 7211–7214; *Angew. Chem. Int. Ed.* **2008**, *47*, 7103–7106; g) L. J. Goossen, N. Rodriguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249; h) J. M. Becht, C. Le Drian, *Org. Lett.* **2008**, *10*, 3161–3164; i) M. Nakano, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1851–1854; j) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159–1162; k) J. M. Becht, C. Catala, C. Le Drian, A. Wagner, *Org. Lett.* **2007**, *9*, 1781–1783; l) L. J. Goossen, N. Rodriguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833; m) D. Tanaka, A. S. P. Romeril, A. G. Myers, *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333; n) D. Tanaka, A. G. Myers, *Org. Lett.* **2004**, *6*, 433–436.

[8] C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195.

[9] A. Voutchkova, A. Coplin, N. E. Leadbeater, R. H. Crabtree, *Chem. Commun.* **2008**, 6312–6314.

[10] J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506–5509.

[11] For a recent review, see: L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826.

[12] E. Riego, D. Hernández, F. Albericio, M. Álvarez, *Synthesis* **2005**, 1907–1922.

[13] M. Schnürch, R. Flasik, A. Farooq Khan, M. Spina, M. D. Mihovilovic, P. Stanetty, *Eur. J. Org. Chem.* **2006**, 3283–3307.

[14] See the Supporting Information.

[15] B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826–1834.

[16] E. Ferrer Flegeau, M. E. Popkin, M. F. Greaney, *J. Org. Chem.* **2008**, *73*, 3303–3306.

[17] a) P. Lu, C. Sanchez, J. Cornella, I. Larossa, *Org. Lett.* **2009**, *11*, 5710–5713; b) J. Cornella, C. Sanchez, D. Banawa, I. Larrosa, *Chem. Commun.* **2009**, 7176–7178; c) L. J. Goossen, C. Linder, N. Rodriguez, P. P. Lange, A. Fromm, *Chem. Commun.* **2009**, 7173–7175; d) L. J. Goossen, F. Manjolinho, B. A. Khan, N. Rodriguez, *J. Org. Chem.* **2009**, *74*, 2620–2623; e) L. J. Goossen, W. R. Thiel, N. Rodriguez, C. Linder, B. Melzer, *Adv. Synth. Catal.* **2007**, *349*, 2241–2246.

[18] R. S. Sánchez, F. A. Zhuravlev, *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825.

