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ARTICLE

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A Practical Synthesis of Biaryls via a Thermal Decarboxylative Pd-Catalyzed Cross-Coupling Reaction Operating at Moderate Temperature

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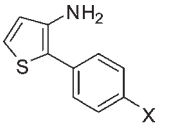
Supporting Information

ABSTRACT: The palladium-catalyzed decarboxylative cross-coupling of aminothiophene carboxylate and 1-bromo-4-chlorobenzene to produce 3-amino-2-(4-chlorophenyl)thiophene (**2**) is described. The cross-coupling proceeds under relatively mild conditions using catalytic Pd(0) and TBAB. Through use of a mixed-solvent system of DMF and NMP, it was possible to operate the cross-coupling system at 80 °C. An assessment of carbon dioxide liberation, which provides insight into the reaction operating parameters, is also discussed.

INTRODUCTION

The metal-catalyzed decarboxylative cross-coupling of aryl halides and triflates with arene carboxylic acids has recently received considerable attention as an attractive tool for biaryl formation.[1−13] In contrast to traditional coupling methods, the decarboxylative coupling process eliminates the need to prepare organometallic reagents, which require the use of stoichiometric amounts of organometallic compounds. In addition, the carboxylic acid coupling partners are readily available. Reported applications of the palladium-catalyzed decarboxylative coupling reaction involve copper as a cocatalyst or require microwave technology, and generally temperatures of 130−170 °C are necessary to promote the reaction. During a synthesis design development, the decarboxylative cross-coupling methodology was developed for preparing key intermediate **1**.

For our development needs, multigram quantities of 3-amino-2-(4-chlorophenyl)thiophene or the bromo analog (**1** or **2**, see Figure 1) were required. Compounds **1** and **2** are versatile intermediates as they offer opportunities for further functionalization utilizing the amino group, along with cross-coupling at the aryl halide.[14−19] During the early stages of a program that utilizes these synthesis building blocks, **1** was prepared via a six-step synthesis (Scheme 1). Starting from 4-bromophenyl ethyl acetate (**3**), NBS bromination provided benzylic bromide **4** which was reacted with 1-thiopropionic acid to provide adduct **5**. Fischer esterification of **5** resulted in diester **6**, and a Dieckmann condensation of **6** provided the 4-oxotetrahydrothiophene-5-carboxylate, **7**. Ester **7** was hydrolyzed and then decarboxylated



X = Br, **1**
X = Cl, **2**

Figure 1

to prepare ketone **8**. The final reaction in the sequence for preparing **2** was formation of the aminothiophene unit by reacting **8** with hydroxyl amine. On a pilot-plant scale, this synthesis approach was telescoped such that steps 1−4 were combined to give **7** in a 40−50% yield. Greater than 100 kg of intermediate **1** was prepared in this fashion.

When the synthesis was considered as a commercial route, the major drawback was the many transformations required to prepare biaryl **1** or **2** (six transformations). Although telescoping of steps minimized isolated intermediates, the many transformations resulted in seven days' cycle time for the synthesis, an area we wanted to address during route selection activities to prepare compound **1** or **2**.

Among the alternate synthesis approaches that were considered was the application of a one step decarboxylative cross-coupling methodology to prepare **1**. This alternative was selected

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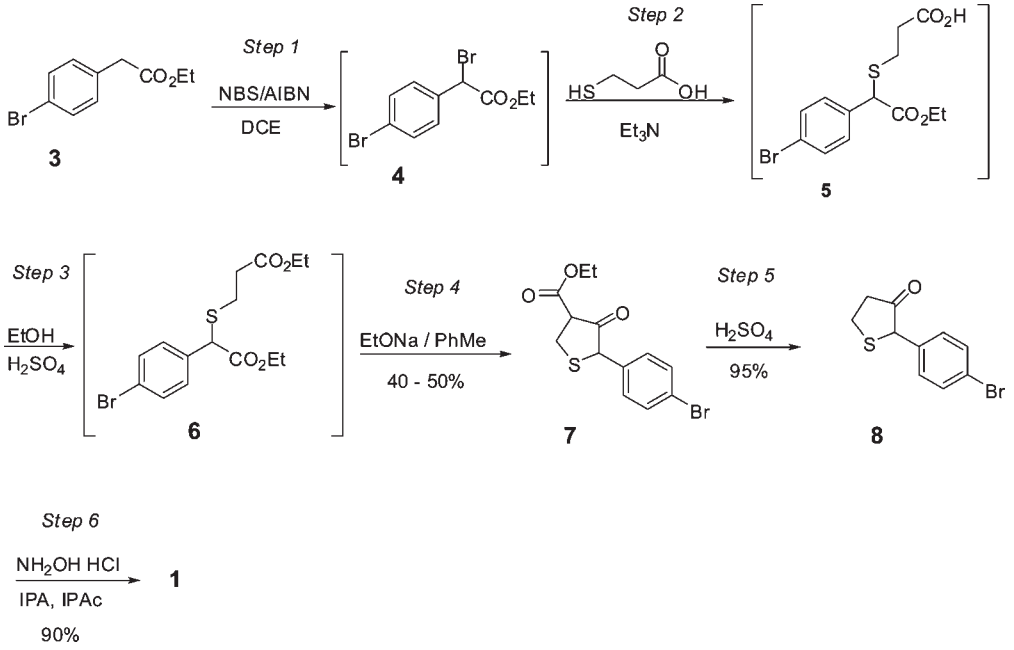
Scheme 1. First-generation synthesis of a highly functional intermediate, 1



for development because the single step operation would reduce overall cycle time. In addition, the requisite starting material, methyl 3-amino-2-thiophene carboxylate (precursor for **9**), was readily available. Also, utilizing the methodology in this alternate synthesis design provided an opportunity to quickly incorporate either the aryl bromide or aryl chloride as part of the molecular architecture. However, the decarboxylative cross-coupling methodology that was required for the transformation was not well understood in our hands and an extensive study was undertaken in order to optimize the process. The investigation was initiated after systematic automated catalyst screening gave ambiguous results. However, certain results from the screen were promising. Utilizing the automated catalyst screen as a starting point, the type of carboxylate substrate as the free acid or carboxylate salt and the reaction solvent system along with the catalyst system that was promising from the initial screens were investigated in an attempt to find a robust transformation. Our choice for the aryl coupling partner was 1-bromo-4-chlorobenzene. Lower yields were observed when 1,4-dibromobenzene was used because of the competing bis addition reaction. Herein, we report the optimization of conditions for the cross-coupling of our reaction.

RESULTS AND DISCUSSION

Variation of Carboxylate Salts. The catalyst screening process had indicated that $PdCl_2$dppf or the preformed $PdCl_2$/dppf ligand along with TBAB as an additive in DMF as solvent were the best conditions for the transformation. Potassium carboxylate salts had been used in previous studies; therefore, we wanted to compare the performance of the other salts with potassium. Li, Na, Cs, NH_4 and Ca salts of compound **9** were prepared and tested in the study. It was considered that formation of a carboxylate salt might increase the rate of decarboxylation due to carboxylate ion pair interaction. We also compared the free carboxylic acid because the reaction's operation would be less complicated if salt formation was unnecessary. For each reaction, 1.2 equiv of a thiophene carboxylate was heated in DMF at 100 °C for up to 18 h with one equivalent of 1-bromo-4-chlorobenzene, 10 mol % of the catalyst, and 15 mol % of TBAB. The results are outlined in Table 1 in which a comparison is made between aryl bromide **10** remaining, product **2** and decarboxylation of the starting material **9** to produce **11**, a byproduct of the reaction. The potassium salt provided superior yield (98%), followed by Cs at 91% and Na at 70%. The *in situ* preparation of the Li, Na, Cs, NH_4, and Ca salts was explored as a measure to avoid an isolation step; lower yields of the product **2** were achieved. Having determined that the potassium carboxylate was the superior partner in the cross-coupling, and that preforming the potassium carboxylate salt was more favorable, we next focused on solvent effects with the hope of exploring the reaction's robustness.

Solvent Screen. At this stage of development, our goal was to have a mild, but robust system which led us to examine solvent and temperature effects on the reaction performance. Due to the solubility of the reactants, aprotic highly dipolar solvents were selected. These solvents, MeCN, DMSO, 1,4-dioxane, DMAc, and NMP were compared with our trials with DMF at temperatures ranging from 70 to 100 °C for up to 18 h. In addition to the cross-coupled product **2**, byproduct **11** was also monitored as this would provide an indication of the reaction's selectivity. Low yields ranging from 10 to 64% were obtained with MeCN, DMSO, and 1,4-dioxane. Therefore, these solvents were not evaluated further. Table 2 summarizes the solvents or mixed-solvent systems and temperatures that performed comparably to the original DMF process. In DMF and NMP, cross-coupled product **2** decreased with decreasing temperatures; however, levels of byproduct **11** increased. When DMAc was utilized as solvent, the opposite trend was observed. A DMF−NMP solvent mixture proved very successful (entries 10−12). On using a 9:1 DMF−NMP mixture, the reaction temperature could be reduced further to 80 °C (entry 11). At 70 °C, the DMF−NMP

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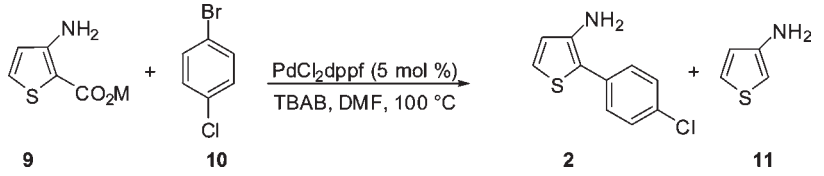
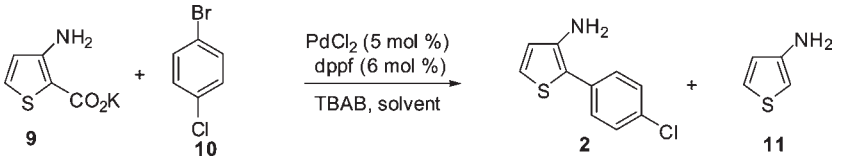
Table 1. Cross-couplings with carboxylate substrate



entry	M	**10** (%)	**2** (%)	**11** (%)
1	Li	76	14	14
2	Na	8	70	22
3	K	0	98	2
4	Cs	0	91	9
5	NH_4	60	0	40
6	Ca	92	0	8

Table 2. Solvent evaluation of the process



entry	solvent	*T* (°C)	**10** (%)	**2** (%)	**11** (%)
1	DMF	100	ND	93	7
2	DMF	90	16	63	21
3	DMF	80	32	25	43
4	DMAc	100	0	85	15
5	DMAc	90	0	87–92	8–13
6	DMAc	80	67	0	33
7	NMP	100	0	100	0
8	NMP	90	0	94–95	5–6
9	NMP	80	14	74	12
10	NMP–DMF	90	0	88	12
11	NMP–DMF	80	0	96	4
12	NMP–DMF	70	0	92	8

Table 3. Scale-up (at 5 mmol) of the process

entry	conditions	**10** (%)	**2** (%)	**11** (%)
1	DMF, 90 °C	0	86	14
2	DMF–NMP, 90 °C	0	85	15
3	DMF–NMP, 80 °C	2	93	5
4	DMF–NMP, 70 °C	39	35	26

solvent mixture had a lower yield than at 80 °C. As a result of this solvent screen, the DMF–NMP solvent mixture was selected as the solvent system for optimization around 80 °C.

Scale-Up Of Optimum Conditions. The cross-coupling was scaled up to a 5 mmol scale using the DMF–NMP mixed-solvent system and temperatures ranging from 70 to 90 °C. The results of this study are summarised in Table 3. The low temperature of 70 °C, which previously gave excellent conversion to **2** on a 1 mmol scale (Table 2, entry 12), led to much poorer conversion on scale-up, with 39% starting material detected at the end of the reaction (Table 3, entry 4). All other conditions identified above scaled up very effectively. Significantly, the excellent conversions obtained at 80 °C were maintained on scale-up (Table 3, entries 1–3). The catalyst loading was also reduced to just 3% using commercial preformed $PdCl_2$dppf, and again the high conversions were preserved. Thus, scaling up the reaction to a 5 mmol scale indicated that the optimum conditions for the cross-coupling of **9** and the potassium salt **10** to produce **2** are 1 equiv of **9**, 1.05 equiv of aryl halide **10**, 15 mol % TBAB, 5 mol % $PdCl_2$, 6 mol % dppf in DMF–NMP (95:5 to 9:1) at 80 °C. The optimized cross-coupling reaction was scaled up to 100 mmol of **9** and **10**. The HCl salt of **2** was isolated in 96% yield following precipitation in MTBE by addition of a 2 M solution of HCl in ether. At the 500 mmol scale, EtOAc replaced MTBE as the extraction solvent, and the HCl solution was generated by adding acetyl chloride to ethanol in ethyl acetate to avoid the use of HCl solution in Et_2O. A yield of 77% was achieved upon precipitating the HCl salt of **2** from EtOAc.

Since carbon dioxide gas was a byproduct of the reaction, an understanding of its formation as a function of the decarboxylative

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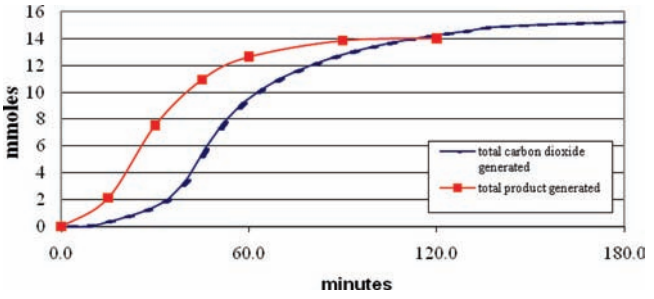

Figure 2. Total CO_2 evolution vs formation of product 2. CO_2 and product 2 formation profile in real-time monitoring. The top plot indicates CO_2 evolution while the bottom plot is a profile of the production of product 2.

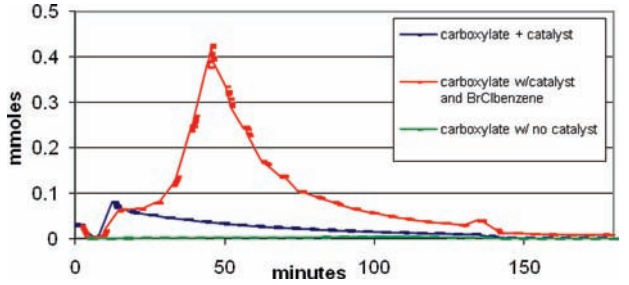

Figure 3. Comparison of CO_2 evolution with three screening parameters for the decarboxylative cross-coupling reaction.

cross-coupling reaction was necessary in order to perform a safety assessment of gas evolution during pilot-plant processing.[20,21] The experimental details for measurement of carbon dioxide can be found in the Experimental Section.

Initially, we measured the amount of carbon dioxide liberation as a function of the reaction progress in real time. Measuring carbon dioxide liberation in conjunction with moles of product (**2**) formation during the reaction indicated a "parallel" process was occurring (Figure 2). The data indicated that carbon dioxide formation was concomitant with formation of product **2**. This fact is consistent with a decarboxylative cross-coupling. From a processing safety viewpoint, no dosing of reagent to control off-gassing would be necessary because carbon dioxide is released in a controlled manner during the coupling/catalytic cycle process.

As the catalytic decarboxylative cross-coupling was a process involving the controlled release of carbon dioxide, we wanted to investigate which substrate was responsible for the gas evolution. Therefore three independent reactions were performed: (1) The first reaction involved heating the carboxylate salt **9** in a solution of DMF in the absence of any catalyst or coupling partner **10**. This experiment would determine whether carbon dioxide generation was a simple thermal process. (2) Experiment number 2 involved carboxylate **9** and coupling partner **10** with no catalyst. (3) The third reaction was a verification of our previous reaction with all reaction substrates present. Figure 3 is a summary plot of the three independent reactions. The reaction with only carboxylate salt **9** indicated no release of carbon dioxide. When the catalyst was reacted with the carboxylate salt in the absence of **10**, a minor release of carbon dioxide was detected. This amount of gas was not significant enough to account for the expected stoichiometric quantity of carbon dioxide released although this may depend on solvent effects. Significant carbon dioxide release was observed only when both coupling partners and catalyst were present in the reaction. Although additional investigation into the release of carbon dioxide during the decarboxylative cross-coupling reactions are ongoing, the three independent reactions we conducted provided information that is consistent with a catalytic process for carbon dioxide release. The information also indicated that carbon dioxide formation is not a simple thermal process but is influenced by the catalyst.

CONCLUSION

A practical decarboxylative cross-coupling to produce **2** has been achieved, using catalytic amounts of Pd(0) and TBAB under a relatively low temperature of 80 °C and avoiding the use of a metal cocatalyst. On a 500 mmol scale, a 77% isolated yield was achieved. Also, although our carbon dioxide measurements were intended to determine a practical control for off-gassing, the observation that very little gas evolved in the absence of the substrate halide has mechanistic implications. In this case, the aryl halide is required for full carbon dioxide liberation.

EXPERIMENTAL SECTION

General. All solvents were distilled prior to use as follows: toluene was distilled over sodium benzophenone ketal, ethanol was distilled from magnesium ethoxide and stored over activated 3 Å molecular sieves, ethyl acetate was distilled over potassium carbonate, and dimethylformamide was distilled over calcium hydride. All reactions were carried out under an inert atmosphere. ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in proton-coupled mode. ^{13}C NMR (100 MHz) spectra and ^{1}H NMR (75.5 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in proton-decoupled mode at 20 °C in deuterated chloroform, using tetramethysilane as internal standard. Infrared spectra were measured as pressed potassium bromide (KBr) on a Perkin-Elmer FT-IR spectrometer. Melting point measurements were carried out on a unimelt Thomas-Hoover Capillary melting point apparatus and are uncorrected. The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Low-resolution mass spectra were recorded on a Waters Quattro Micro triple quadropole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High-resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier ToF LC−MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High performance liquid chromatography analysis was performed on a Waters alliance 2690 separations module with a waters 486 tunable absorbance detector using an ACE 3 phenyl (75 mm × 3.0 mm) column using a flow rate of 1.5 mL/min, a wavelength of 260 nm, and a temperature of 45 °C under a gradient. Mobile phases (A and B) were 0.01% TFA in H_2O and acetonitrile, respectively.

Potassium 3-Aminothiophene-2-carboxylate, 9. IPA (500 mL) was added to a 1 L flask containing methyl 3-aminothiophene-2-carboxylate (66.1 g, 0.4 mol). KOH (28.3 g, 0.5 mol) was added, followed by IPA (150 mL), and the mixture was heated to reflux

for 2 h under a nitrogen atmosphere. Following cooling on an ice bath for 30 min, the reaction mixture was filtered, and the residue was rinsed with IPA (2 × 20 mL). The residue was dried under vacuum at 90 °C for 16 h to give **9** as a pale-brown solid (64.5 g, 85%); ν_{max}/cm^{-1} 3402, 3333, 1563, 1516, 1454, 1361; δ_H (300 MHz, DMSO-d_6) 5.83 (2H, br s, N*H*$_2$), 6.45 (1H, d, *J* 5.4, Ar*H*), 6.98 (1H, d, *J* 5.4, Ar*H*); δ_C (75.5 MHz, DMSO-d_6) 114.2 (*C*), 120.6, 124.1 (2 × *C*H), 148.0, 168.3 (2 × *C*); HRMS (ES$^+$): Exact mass calculated for $C_5H_6NO_2S$ [(M + H)$^+$ − HCl], 144.0119. Found 144.0112; *m*/*z* (ES$^+$) 143.9 {[(M + H)$^+$ − HCl], 28%}.

2-(4-Chlorophenyl)thiophen-3-amine Hydrochloride, 2 HCl. A 3-necked 3 L round bottomed flask was evacuated and backfilled with nitrogen three times. DMF (1.8 L) and NMP (0.2 L) were added under a flow of nitrogen, and the system was then evacuated and backfilled with nitrogen three times. Potassium 3-aminothiophene-2-carboxylate, **9** (95.18 g, 0.525 mol), **2** (96.70 g, 0.5 mol), tetra-*n*-butylammonium bromide (24.67 g, 0.075 mol), 1,1̀-bis(diphenylphosphino)ferrocene (16.63 g, 0.03 mol), and palladium(II) chloride (4.48 g, 0.025 mol) were added under a flow of nitrogen. The vessel was then evacuated and backfilled three times. The resulting mixture was heated at 80 °C for 16 h. The reaction mixture was allowed to cool to room temperature. Celite (150 g) and water (1.5 L) were added to the reaction mixture and stirred for 10 min. The mixture was filtered through a bed of Celite (80 g) into a 5 L Buchner flask. The reaction vessel was rinsed with EtOAc (1.5 L), and the Celite cake was then washed with this EtOAc rinse. The layers were separated, and the aqueous layer was washed with EtOAc (1.5 L). The combined EtOAc layers were washed with water (4 × 1.5 L) and brine (2 × 1.5 L). After drying with magnesium sulfate (600 g), the EtOAc layer was concentrated on a rotary evaporator to approximately 1 L. An HCl solution in EtOAc (2.2 M, 450 mL) was added dropwise over 20 min at 0 °C. A brown solid precipitated out of solution almost immediately. The mixture was stirred at 0 °C for 30 min. The brown solid was filtered through a sintered glass funnel and the solid washed with EtOAc (500 mL) and then dried under vacuum for 1 h. The crude product was then slurried in acetone (450 mL) at reflux for 30 min and filtered to give **2·HCl** as a brown solid (95.2 g, 77%). (Found C, 48.69; H, 4.16; N, 5.15. $C_{10}H_9NSCl_2$ requires C, 48.79; H, 3.69; N, 5.69%); ν_{max}/cm^{-1} 3419, 1670, 1488; δ_H (300 MHz, DMSO-d_6) 7.19 (1H, d, *J* 5.4, Ar*H*), 7.57 (2H, d, *J* 8.7, Ar*H*), 7.67−7.71 (3H, 2 × overlapping d, *J* 8.7, 5.4, Ar*H*); δ_C (150 MHz, DMSO-d_6) 124.8, 126.3 (2 × CH, ArCH), 127.1, 128.3 (2 × C, ArC), 129.1, 130.0 (2 × CH, ArCH), 130.5, 133.0 (2 × C, ArC); HRMS (ES$^+$): Exact mass calculated for $C_{10}H_9NSCl$ [(M + H)$^+$ − HCl], 210.0144. Found 210.0135; *m*/*z* (ES$^+$) 210.0 {[(M + H)$^+$ − HCl], 18%}.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data for the HCl salt of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Goossen, L. J.; Zimmermann, B.; Linder, C.; Rodriguez, N.; Lange, P. P.; Hartung, J. *Adv. Synth. Catal.* **2009**, *351*, 2667–2674.
(2) Wang, Z.; Ding, Q.; He, X.; Wu, J. *Tetrahedron* **2009**, *65*, 4635–4638.
(3) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664.
(4) Forgione, P.; Brochu, M. C.; St Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351.
(5) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745–4747.
(6) Goossen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906–3909.
(7) Goossen, L. J.; Linder, C.; Rodriguez, N.; Lange, P. P. *Chem.—Eur. J.* **2009**, *15*, 9336–9349.
(8) Becht, J. M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161–3164.
(9) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249.
(10) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373–1375.
(11) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833.
(12) Becht, J. M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781–1783.
(13) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251.
(14) Yoshikawa, Y.; Tomitani, K.; Katsuta, H.; Kawashima, H.; Takahashi, T.; Inami, S.; Yanase, Y.; Takashi, A.; Shimotori, H.; Tomura, N. JP Pat. Appl. 1996/121387 A, 1997.
(15) Yoshikawa, Y.; Tomiya, K.; Katsuta, H.; Kawashima, H.; Takahashi, O.; Inami, S.; Yanase, Y.; Kishi, J.; Shimotori, H.; Tomura, N. U.S. Pat. Appl. 1996/627929 A, 1996.
(16) Castano Mansanet, A. M.; Cordier, F. L.; Dominguez-Manzanares, E.; Hong, J. E.; Hornback, W. J.; Jiang, D. WO Pat. Appl. 2006/U.S. 20204 A2, 2006.
(17) Dominguez-Manzanares, E. U.S. Pat. Appl. 2006/422473 A1, 2006.
(18) Castano Mansanet, A. M.; Dominguez-Manzanares, E.; Escribano, A. M.; Fernandez, M. C.; Hornback, W. J.; Jimenez-Aguado, A. M.; Tromiczak, E. G.; Wu, Z.; Zarrinmayeh, H.; Zimmerman, D. M. WO Pat. Appl. 2005/U.S. 4 A1, 2005.
(19) Albaugh, P. A.; Dominguez-Manzanares, E.; Hong, J. E.; Hornback, W. J.; Jiang, D.; Ornstein, P. L.; Thompson, M. L.; Tromiczak, E. G.; Wu, Z.; Zarrinmayeh, H.; Zimmerman, D. M.; Castano, M. A. M.; Huffman, L. G.; Miller, W. D. U.S. 28815, 2005. WO Pat. Appl., 2004.
(20) Hoon Lee, J.; Seung Choi, B.; Hyok Chang, J.; Sik Kim, S.; Shin, H. *Org. Process Res. Dev.* **2007**, *11*, 1062–1064.
(21) Leonhardt, J.; Nau, M.; Wolter, M.; Rau, C. *J. Loss Prev. Process Ind.* **2008**, *21*, 400–406.