DOI: 10.1002/adsc.200800705

Copper(II)-Catalyzed Aminooxygenation and Carboamination of *N*-Aryl-2-allylanilines

Eric S. Sherman[a] and Sherry R. Chemler[a,*]

[a] The University at Buffalo, The State University of New York, Buffalo, New York 14260, USA
Fax: (+1)-716-645-6963; e-mail: schemler@buffalo.edu

Received: November 14, 2008; Published online: February 2, 2009

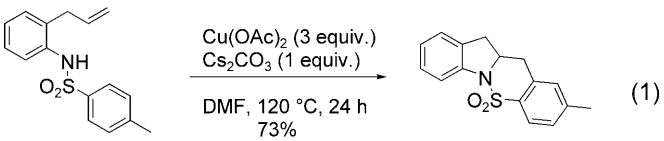
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800705.

Abstract: The scope of the intramolecular copper(II)-catalyzed carboamination and aminooxygenation reactions of olefins has been extended to include *N*-aryl-2-allylanilines. These substrates exhibit divergent reactivity under catalytic *vs.* stoichiometric conditions.

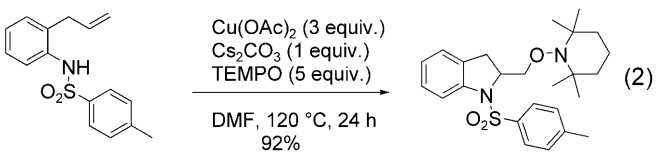
Keywords: alkenes; copper; heterocycles; TEMPO

Nitrogen heterocycles make up an abundant and important class of biologically active molecules. As such, new synthetic transformations that allow for the rapid assembly of these molecules are of great importance in organic chemistry.[1] Recently we have developed a number of copper-catalyzed and -promoted reactions that involve the intermolecular addition of amines to olefins: carboamination[2a–d] (addition of a nitrogen and a carbon across an olefin), diamination[3] (addition of two amines across an olefin), and aminooxygenation (addition of a nitrogen and an oxygen across an olefin).[2b,4]

Both the carboamination and aminooxygenation reactions have proved to be efficient for the reaction of *N*-arylsulfonamides, providing dihydroindoline products [Eq. (1) and Eq. (2)]. The carboamination reaction has also been reported on amides.[2c]

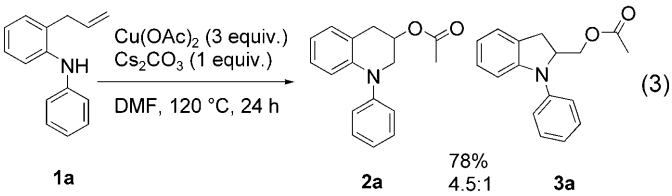


(1)



(2)

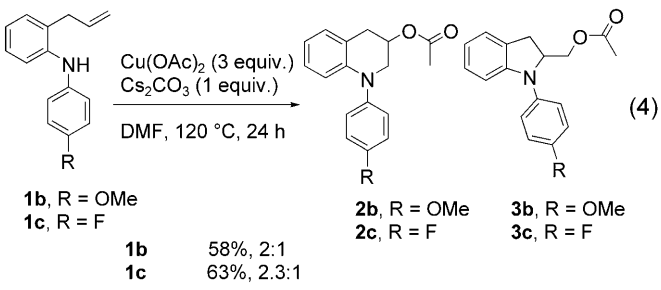
To widen the scope of effective carboamination and aminooxygenation reactions, we initiated a study involving *N*-arylanilines. Some *N*-arylindolines have demonstrated α2 adrenergic receptor and ORL1 antagonist activities, which are linked to the treatment of anxiety and depression.[5] We first attempted the reaction with *N*-phenyl-2-allylaniline (**1a**). To our surprise, treating this substrate with a stoichiometric amount of copper(II) acetate and heating in DMF resulted in the formation of aminoacetoxylation products (**2a** and **3a**) in a 4.5:1 ratio favoring the 6-membered ring [Eq. (3)]. With all of our previous substrates (*vide supra*) the products obtained result from 5-*exo*-trig cyclization of the amine onto the olefin. The structure of the major regioisomer (**2a**) was determined by hydrolysis to the known alcohol.[6]



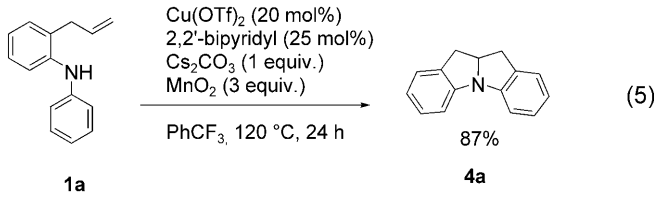
(3)

The aminoacetoxylation reaction also proceeded with good yield for the fluoro- and methoxy-substituted *N*-aryl-2-allylaniline substrates (**1b** and **1c)** [Eq. (4)], and in both cases favored the formation of the 6-membered tetrahydroquinoline products (**2**). The reaction of **1a** with copper(II) acetate in the less polar solvent, α,α,α,-trifluorotoluene, provided a 4.6:1 ratio of **2a**:**2b**, albeit in a lower yield. The reaction of **1a** with stoichiometric copper(II) triflate gave the tetrahydroquinoline product predominatly, but with only 30% conversion (see Supporting Information).

When the reaction conditions were changed to catalytic conditions,[2d] using manganese dioxide as a stoichiometric oxidant, we did obtain our expected intra-



molecular carboamination product [**4a**, Eq. (5)]. Under these conditions, a variety of substituted arylanilines underwent cyclization, providing 10a,11-dihydro-10*H*-indolo[1,2-a]indoles (**4a–h)** in good yield (Table 1).



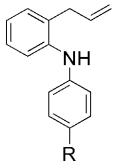
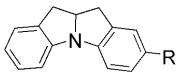
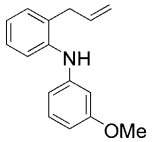
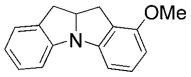
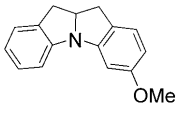
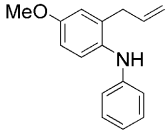
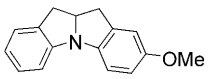
The functional group range of this reaction is broad, as both electron-rich and electron-deficient *N*-arylanilines underwent effective carboamination. The methylthio group was well tolerated, as were the fluoro and nitro groups.

This reaction utilizes a copper(II) triflate-bipyridine complex as the catalyst, and manganese dioxide as a stoichiometric oxidant, presumably turning over the copper catalyst by oxidation from copper(I) to copper(II). Without the bipyridine ligand the carboamination reaction proceeded with only 25% conversion. When the catalytic carboamination was performed on a *meta*-methoxy-substituted aniline (**1g**) the carboamination products were obtained in good yield, but as a 1.5:1 mixture of regioisomers, with the major product having the new carbon-carbon bond formed *ortho* to the methoxy group, which is similar to what was obtained with the arylsulfonamide substrates (Entry 7).[2a] Substitution can be tolerated on either ring system, as *N*-phenyl-4-methoxy-2-allylaniline (**1h**) also performed well in our study (Entry 8).[7]

These substrates also performed well in our copper-catalyzed aminooxygenation reaction.[2b,4] In this reaction, tetramethylpiperidinoxyl radical (TEMPO) is added to the reaction mixture to intercept the primary carbon radical formed during the course of the reaction (*vide infra*).[8] This methodology was tested on several substrates, all of which gave the aminooxygenation products (**5)** in good yield (Table 2).

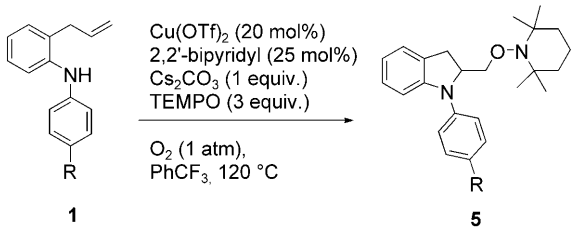
In this reaction oxygen (1 atm) is a better oxidant than manganese dioxide. Unlike the aminoacetoxyla-

Table 1. Copper-catalyzed carboamination of *N*-aryl-2-allylanilines.[a]

	Substrate	Product	Yield [%][b]
1	 **1a**, R = H	 **4a**, R = H	87
2	**1b**, R = OMe	**4b**, R = OMe	69
3	**1c**, R = F	**4c**, R = F	64
4	**1d**, R = Me	**4d**, R = Me	59
5	**1e**, R = SMe	**4e**, R = SMe	81
6	**1f**, R = NO_2	**4f**, R = NO_2	53
7	 **1g**	 **4g**  **4h**	63 (1.5:1 mixture of **4g**:**4h**)[c]
8	 **1h**	 **4b**	67

[a] *Conditions:* $Cu(OTf)_2$ (20 mol%), and 2,2′-bipyridyl (25 mol%) were precomplexed for 2 h at 60 °C, followed by the addition of Cs_2CO_3 (1 equiv.), and MnO_2 (3 equiv.) in $PhCF_3$ for 24 h at 120 °C.
[b] Isolated yield after chromatography.
[c] Product ratio was determined by analysis of the ^1H NMR spectrum of the product

Table 2. Copper-catalyzed aminooxygenation.



1 5

Entry	R	Yield [%][a]
1	**5a**, R = H	64
2	**5b**, R = OMe	59
3	**5c**, R = F	84
4	**5d**, R = Me	64
5	**5e**, R = SMe	88

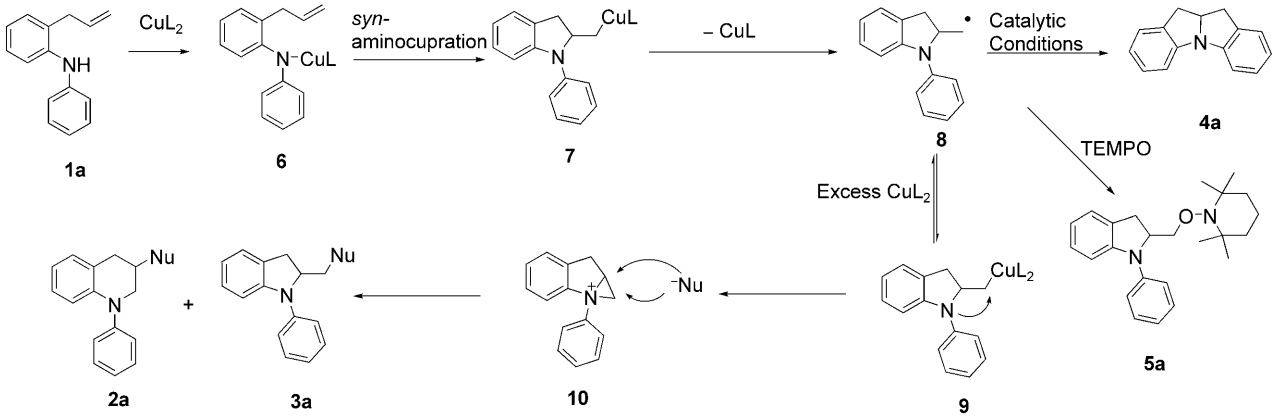
[a] Isolated yield after chromatography.

tion [Eqs. (3) and (4)], the products from these reactions are exclusively the dihydroindoline aminooxygenation products. Methods for converting TEMPO adducts to the corresponding amino alcohols[9] or amino aldehydes[10] have been reported.

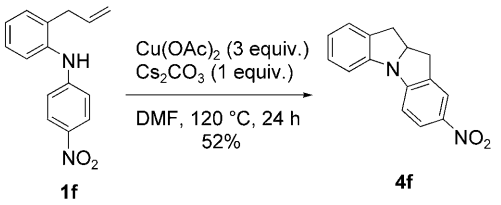
In addition to being a synthetically useful reaction, the aminooxygenation provides mechanistic insight towards the reaction.[2b] TEMPO is a radical trap but does not promote product formation in the absence of copper(II). The formation of the TEMPO adduct shows that a carbon radical is formed during the reaction.[2b,8] The TEMPO product is formed under both the stoichiometric and catalytic conditions (see Supporting Information). This provides evidence for the same radical being a viable intermediate in both the catalytic carboamination reaction and the stoichiometric aminoacetoxylation reaction. This led us to propose a mechanism that takes into account the differential product formation (Scheme 1).

We have provided evidence that copper(II) will react with our amines to add across the olefin *via syn*-aminocupration.[2b] We believe that the *syn*-aminocupration is the rate determining step. This generates an unstable alkyl-copper(II) species (**7**) that undergoes homolysis of the copper-carbon bond to give a primary carbon radical (**8**), expelling Cu(I). With arylamides or arylsulfonamides this radical adds to the aromatic ring to give the carboamination product [Eq. (1)]. This is the likely mechanism in the catalytic carboamination reaction as well (the conversion of **1** to **4**). The divergence to give **2** and **3** can be explained as follows. Copper(II) has been shown to react with carbon radicals to give alkyl-copper(III) intermediates.[11] This occurs in a rapid equilibrium with the alkyl radical. In the case of sulfonamides and amides, this equilibrium is driven to product formation by trapping the radical with π-systems. However, in the case of biarylamines, **1**, the nitrogen atom is sufficiently nucleophilic to intercept this copper(III) intermediate (**9**) and form the aziridinium ion (**10**), which can be opened by nucleophilic attack at either position, with attack at the electronically favored internal carbon predominating. The mechanism of these reactions is mediated by the amount of copper(II) present, and is not an effect of the counter-ion, as efficient carboamination was achieved using catalytic copper(II) acetate as well as copper(II) triflate (see Supporting Information). In the catalytic case, presumably, the concentration of copper(II) in solution is not high enough for it to intercept the radical prior to addition to the aromatic ring. Further evidence for this mechanism was obtained when the aminoacetoxylation was attempted with a substrate bearing a nitro group in the *para*-position on the aromatic ring. This less nucleophilic amine was unable to undergo nucleophilic substitution with the copper(III) intermediate, resulting in carboamination as the only observed product [Eq. (6)].

The substrates used to test this reaction are synthesized by the copper(II) acetate catalyzed coupling of arylboronic acids with arylamines.[12] Because cop-

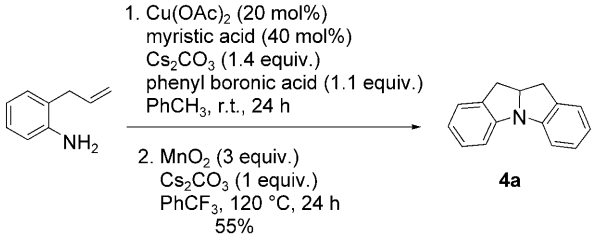


Scheme 1. Proposed mechanism.



1f 4f (6)

per(II) acetate is also an effective catalyst for the carboamination reaction, we believed that it would be possible to perform both the coupling and carboamination in a single pot. Towards that end, 2-allylaniline was treated with 20 mol% copper(II) acetate, 40 mol% myristic acid, 1.1 equiv. of phenylboronic acid, and 1 equiv. of cesium carbonate at room temperature for 24 h in toluene.[12] The toluene was then removed under vacuum and replaced with α,α,α-trifluorotoluene. Manganese dioxide (3 equiv.) and cesium carbonate (1 equiv.) were added, and the mixture was stirred at 120 °C for 24 h, resulting in good overall yield (55%) for the two-step process [Eq (7)]. The solvent had to be changed because the carboamination reaction does not proceed efficiently in toluene, while the coupling does not proceed efficiently in



4a (7)

α,α,α-trifluorotoluene.

In conclusion, we have developed methods for the aminoacetoxylation, aminooxygenation and carboamination of *N*-aryl-2-allylanilines. The aminoacetoxylation, promoted by stoichiometric copper(II) gives predominately tetrahydroquinoline products, whereas the copper(II)-catalyzed aminooxygenation reaction with TEMPO gives solely the dihydroindoline products. In this study the scope of the copper(II)-catalyzed carboamination and aminooxygenation reactions have been increased to include *N*-arylaniline substrates and more mechanistic possibilities for this class of copper-facilitated reactions have been observed.

Experimental Section

For experimental details and spectral data for all new compounds, see the Supporting Information.

Representative Method for Aminoacetoxylation Reactions

1-Phenyl-1,2,3,4-tetrahydroquinolin-3-yl acetate (2a) and 1-phenyl-2,3-dihydro-1*H*-indol-2-ylmethyl acetate (3a): *N*-Phenyl-2-allylaniline (**1a**) (42.0 mg, 0.200 mmol, 1 equiv.) was dissolved in 1.7 mL DMF in a pressure tube equipped with a magnetic stir bar. $Cu(OAc)_2$ (109 mg, 0.600 mmol, 3 equiv.) and Cs_2CO_3 (65.2 mg, 0.200 mmol, 1 equiv.) were added. The tube was sealed and heated to 120 °C for 24 h. After cooling, the mixture was diluted with Et_2O and filtered through a pad of silica gel with additional Et_2O. The filtrate was concentrated under vacuum to give the crude oil. This oil was purified by flash chromatography on silica gel (13% Et_2O in hexanes) to provide the aminoacetoxylation products as a 4.5:1 mixture of regioisomers favoring the 6-member ring product; yield: 41.6 mg (0.156 mmol, 78%). The regioisomers were separated by HPLC (5% EtOAc in hexanes) to give the pure products with the major isomer eluting first, both products as yellow oils.

Data for 1-phenyl-1,2,3,4-tetrahydroquinolin-3-yl acetate (2a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30–7.35$ (m, 2H), 7.20 (d, $J = 7.6$ Hz, 2H), 7.06–7.10 (m, 2H), 6.97 (m, 1H), 6.75–6.80 (m, 2H), 5.30 (m, 1H), 3.72–3.76 (m, 2H), 3.17 (dd, $J = 6.0$, 21 Hz, 1H), 2.96 (dd, $J = 6.5$, 22 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.7$, 147.9, 143.6, 129.9, 129.4, 126.7, 124.2, 123.7, 121.3, 119.2, 116.2, 67.1, 52.9, 32.8, 21.1; IR (neat, thin film): $\nu = 2924$, 2856, 1738, 1652, 1565, 1481, 1455, 1375 cm^{-1}; HR-MS: $m/z = 268.1339$, calcd. for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1332.

Data for 1-phenyl-2,3-dihydro-1*H*-indol-2-ylmethyl acetate (3a) from a 1.2:1 mixture of 3a:2a: ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.70–7.24$ (m, 9H), 4.23 (dd, $J = 4.6$, 11.2 Hz, 1H), 4.11 (m, 1H), 3.88 (dd, $J = 6.4$, 11.6 Hz, 1H), 2.58–2.91 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.9$, 148.3, 143.8, 129.9, 129.0, 127.3, 125.0, 123.2, 121.3, 119.3, 109.5, 65.2, 62.6, 32.6, 20.7; IR (neat, thin film): $\nu = 2921$, 2851, 1736, 1676, 1513, 1456, 1247 cm^{-1}.

Representative Method for Carboamination

10a,11-Dihydro-10*H*-indolo[1,2-*a*]indole (4a): $Cu(OTf)_2$ (13.8 mg, 0.038 mmol, 0.20 equiv.) was added to 1 mL $PhCF_3$ in a pressure tube equipped with a magnetic stirrer. To this was added 2,2′-bipyridyl (7.4 mg, 0.049 mmol, 0.25 equiv.). The resulting mixture was heated to 60 °C for 2 h. *N*-phenyl-2-allylaniline (**1a**) (40.0 mg, 0.191 mmol, 1 equiv.) was dissolved in 0.9 mL $PhCF_3$ and added. Cs_2CO_3 (62.2 mg, 0.191 mmol, 1 equiv.) and MnO_2 (49.5 mg, 0.573 mmol, 3 equiv.) were added. The tube was sealed and the mixture was heated to 120 °C for 24 h. After cooling, the mixture was diluted with Et_2O and filtered through a pad of silica gel. The filtrate was concentrated under vacuum to provide the crude oil. Purification by flash chromatography on silica gel (2% Et_2O in hexanes) provided the product as a red oil; yield: 34.4 mg (0.166 mmol, 87%).

Data for (4a): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.15–7.17$ (m, 6H), 6.88–6.93 (m, 3H), 4.88 (m, 1H), 3.35 (dd, $J = 9.5$, 16.0 Hz, 2H), 3.08 (dd, $J = 7.5$, 16.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.8$, 132.3, 127.5, 125.0, 121.6, 112.9, 65.2, 36.6; IR (neat, thin film): $\nu = 3023$, 2907, 1599, 1489, 1200, 1169, 1073, 810, 746 cm^{-1}; HR-MS: $m/z = 207.1040$, calcd. for $C_{15}H_{13}N$ $[M]^+$: 207.1043.

Representative Method for Aminooxygenation

***N*-Phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxymethyl)-2,3-dihydro-1*H*-indole (5a):** $Cu(OTf)_2$ (15.6 mg, 0.043 mmol, 0.20 equiv.) was added to 1.1 mL $PhCF_3$ in a 100-mL round bottom flask equipped with a stir bar. To this was added 2,2′-bipyridyl (8.1 mg, 0.054 mmol, 0.25 equiv). The resulting mixture was heated to 60 °C for 2 h. *N*-Phenyl-2-allylaniline (**1a**) (45.0 mg, 0.215 mmol, 1 equiv.) was dissolved in 1.0 mL $PhCF_3$ and added. Cs_2CO_3 (70.0 mg, 0.215 mmol, 1 equiv.) and TEMPO (100.8 mg, 0.645 mmol, 3 equiv.) were added. An O_2 balloon was fitted on the flask, and the mixture was heated to 120 °C for 24 h. After cooling, the mixture was diluted with Et_2O and filtered through a pad of silica gel. The filtrate was concentrated under vacuum to provide the crude oil. Purification by flash chromatography on silica gel (2% Et_2O in hexanes) provided the product as a colorless oil; yield: 50.2 mg (0.138 mmol, 64%).

Data for (5a): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.30$–7.33 (m, 4H), 7.15 (d, $J = 7.5$ Hz, 1H), 7.00–7.04 (m, 2H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.74 (m, 1H), 4.43 (m, 1H), 3.98 (dd, $J = 5.5$, 9.0 Hz, 1H), 3.90 (dd, $J = 6.0$, 9.0 Hz, 1H), 3.38 (dd, $J = 9.5$, 15.5 Hz, 1H), 3.00 (dd, $J = 6.0$, 15.5 Hz, 1H), 1.38–1.50 (m, 4H), 1.20–1.30 (m, 2H), 0.96–1.10 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 148.1$, 144.1, 130.0, 129.0, 126.9, 124.8, 122.2, 120.5, 118.9, 109.2, 78.3, 65.8, 62.7, 59.8, 39.6, 33.0, 32.8, 20.1, 17.0, 15.3; IR (neat, thin film): $\nu = 2971$, 2929, 1593, 1496, 1463, 1373, 1261, 1048 cm^{-1}; HR-MS: $m/z = 364.2504$, calcd. for $C_{24}H_{32}N_2O$ $[M]^+$: 364.2509.

Acknowledgements

The authors gratefully acknowledge the financial support of the NIH (NIGMS RO1-GM078383).

References

[1] a) T. E. Muller, M. Beller. *Chem. Rev.* **1998**, 98, 675; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; c) S. R. Chemler, P. H. Fuller, *Chem. Soc. Rev.* **2007**, *367*, 1153; d) J. P. Wolfe *Eur. J. Org. Chem.* **2007**, 571.

[2] a) E. S. Sherman, S. R. Chemler, T. B. Tan, O. Gerlits, *Org. Lett.* **2004**, *6*, 1573; b) E. S. Sherman, P. H. Fuller, D. Kasi, S. R. Chemler, *J. Org. Chem.* **2007**, *72*, 3896; c) P. H. Fuller, S. R. Chemler, *Org. Lett.* **2007**, *9*, 5477; d) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948.

[3] a) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; b) T. P. Zabawa, S. R. Chemler, *Org. Lett.* **2007**, *9*, 2035.

[4] P. H Fuller, J. W. Kim, S. R Chemler, *J. Am. Chem. Soc.* **2008**, *130*, 17638.

[5] a) G. P. Fagan, C. B. Chapleo, A. C. Lane, M. Myers, A. G. Roach, C. F. C. Smith, M. R. Stillings, A. P. Welbourn, *J. Med. Chem.* **1988**, *31*, 944; b) Y. Goto, S. Arai-Otsuki, Y. Tachibana, D. Ichikawa, S. Ozaki, H. Takahashi, Y. Iwasawa, O. Okamoto, S. Okuda, H. Ohta, T. Sagara, *J. Med. Chem.* **2006**, *49*, 847.

[6] B. Barvainiene, A. Stanisauskaite, V. Getautis, *Chem. Heterocycl. Comp.* **2006**, *42*, 123.

[7] Attempts to render the reaction enantioselective using the (*R*,*R*)-Ph-Box ligand with substrate **1b** failed.

[8] K. S. Root, C. L. Hill, L. M. Lawrence, G. M. Whitesides, *J. Am. Chem. Soc.* **1989**, *111*, 5405.

[9] H. M. Sheldrake, T. M. Wallace, *Tetrahedron Lett.* **2007**, *48*, 4407.

[10] T. Inokuchi, H. Wawafuchi, *Tetrahedron* **2004**, *60*, 11969.

[11] J. K. Kochi, *Acc. Chem. Res.* **1974**, *7*, 351.

[12] J. C. Antilla, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 2077.

