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# Catalytic Asymmetric Rearrangement of Allylic *N*-Aryl Trifluoroacetimidates. A Useful Method for Transforming Prochiral Allylic Alcohols to Chiral Allylic Amines

**Larry E. Overman,* Carolyn E. Owen, and Mary M. Pavan**

*Department of Chemistry, University of California, Irvine, 516 Rowland Hall, Irvine, California 92697-2025*

**Christopher J. Richards***

*Department of Chemistry, Queen Mary, University of London, Mile End Road, London E1 4NS, U.K.*

*leoverma@uci.edu*

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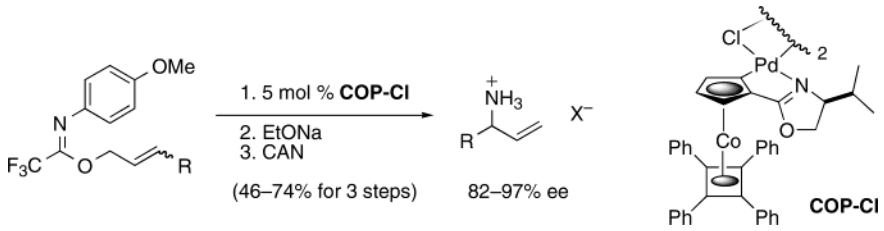
## ABSTRACT




**A useful method for the conversion of prochiral allylic alcohols to chiral allylic amines of high enantiopurity is reported. *N*-(4-Methoxyphenyl)-trifluoroacetimidates are excellent substrates for the palladium(II)-catalyzed allylic imidate rearrangement as the allylic trifluoroacetamide products can be deprotected in two steps to provide chiral nonracemic allylic amines. Di-$\mu$-chlorobis[($\eta^5$-(*S*)-(p*R*)-2-(2′-(4′-isopropyl))oxazolinylcyclopentadienyl,1-*C*,3′-*N*))($\eta^4$-tetraphenylcyclobutadiene)cobalt]dipalladium (6a, COP-Cl) is a superior catalyst because it does not require activation with silver salts and provides rearranged allylic trifluoroacetamides in good yields and high enantiomeric purities.**

Developing the potentially rich catalytic asymmetric chemistry of palladium(II) has been one focus of recent exploratory investigations at Irvine.[1] In 1997, the first catalytic asymmetric rearrangements of prochiral allylic imidates to chiral allylic amides, in this case realized with palladium(II) diamine complexes, were described.[2] Two years thereafter, Donde and Overman reported that ferrocenyloxazoline palladacycles (FOP catalysts, e.g., **5b** depicted in Figure 1) catalyze the asymmetric rearrangement of various prochiral allylic *N*-arylbenzimidates **1** to give chiral allylic *N*-arylbenzamides **2** in high yields and excellent enantiopurity (Scheme 1).[3−5] However, this rearrangement does not constitute a practical method for preparing enantioenriched

(1) For the first reported asymmetric reaction catalyzed by a $Pd^{II}$ complex, see: Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Chem. Soc., Chem. Commun.* **1978**, 687−688.

(2) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456.

(3) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933−2934.

(4) For a review of early studies in this area from Irvine, see: Hollis, T. K.; Overman, L. E. *J. Organomet. Chem.* **1999**, *576*, 290−299.

(5) For a recent report of asymmetric aminocyclizations catalyzed by FOP catalysts, see: Overman, L. E.; Remarchuk, T. *J. Am. Chem. Soc.* **2002**, *124*, 12−13.

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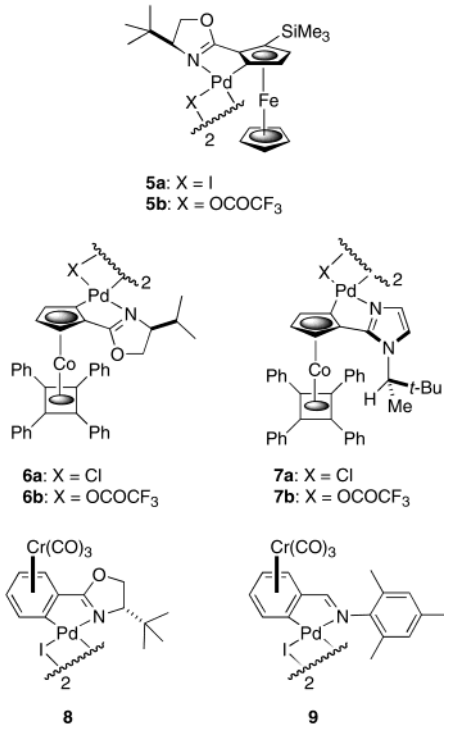
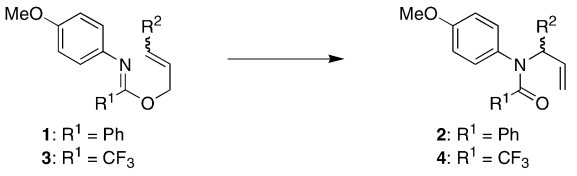



**Figure 1.** Palladacycle catalysts containing various planar chiral fragments.

chiral allylic amines as removal of the benzoyl and 4-methoxyphenyl groups of **2** is problematic, proceeding in less than 40% yield under a variety of conditions.[3,6]

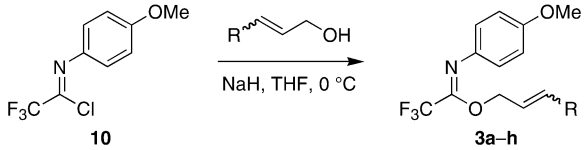
**Scheme 1.** Rearrangement of Prochiral Allylic Imidates




In this paper, we report that *N*-aryltrifluoroacetimidates **3** are excellent substrates for the catalytic asymmetric imidate rearrangement as the *N*-(4-methoxyphenyl)trifluoroacetamide products **4** can be deprotected in good yield to provide chiral allylic amines of high enantiopurity. We describe the evaluation of palladacyclic catalysts containing a variety of planar chiral elements (Figure 1) and identify di-$\mu$-chlorobis-[($\eta^5$-(*S*)-(p*R*)-2-(2′-(4′-isopropyl)oxazolinylcyclopentadienyl,1-*C*,3′-*N*))-($\eta^4$-tetraphenylcyclobutadiene)cobalt]dipalladium (**6a**, COP-Cl)[7] as an optimal catalyst that does not require preactivation with a silver or thallium salt.[8,9]

Allylic *N*-(4-methoxyphenyl)trifluoroacetimidates **3a**−**h** were available in one step from readily available imidoyl chloride **10**[10] by reaction with 1 equiv of the preformed allylic sodium alkoxide in THF at 0 °C (Scheme 2). Allylic imidates

**Scheme 2.** Synthesis of *N*-Aryltrifluoroacetimidates




**3** containing double bonds of both *E* and *Z* geometry were prepared in this way in yields ranging from 70 to 96% (Table 1).

**Table 1.** Synthesis of Allylic *N*-(4-Methoxyphenyl)trifluoroacetimidates **3**

| entry | compd | alkene | R | yield (%) |
|---|---|---|---|---|
| 1 | **3a** | *E* | *n*-Pr | 88 |
| 2 | **3b** | *Z* | n-Pr | 78 |
| 3 | **3c** | *E* | Me | 70 |
| 4 | **3d** | *Z* | Me | 83 |
| 5 | **3e** | *E* | $CH_2CH_2Ph$ | 88 |
| 6 | **3f** | *Z* | $CH_2CH_2Ph$ | 96 |
| 7 | **3g** | *E* | *i*-Bu | 71 |
| 8 | **3h** | *Z* | *i*-Bu | 84 |

Five palladacyclic catalysts containing various planar chiral elements and nitrogen ligands were selected for our initial studies. The FOP trifluoroacetate catalyst **5b** was generated in $CH_2Cl_2$ from iodide-bridged dimer **5a** by reaction with 4 equiv of $AgOCOCF_3$ at room temperature as described previously.[3,11] The congeneric oxazoline trifluoroacetate catalyst **6b** and imidazole catalyst **7b**, both having a ($\eta^5$-cyclopentadienyl)($\eta^4$-tetraphenylcyclobutadiene)cobalt substituent, were prepared in identical fashion from chloride-bridged dimer precursors **6a**[7] and **7a**.[12] ($\eta^6$-Arene)tricarbonylchromium(0) oxazoline complex **8**[13] and analogous imine complex **9**[13] were activated prior to use by reaction with 4 equiv of TlOTf at room temperature in 99:1 $CH_2Cl_2$/$CH_3CN$.[8c,14]

(6) Unpublished studies of C.E.O., UC Irvine.

(7) Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346−1348.

(8) For catalytic asymmetric allylic imidate rearrangements with other catalysts, see: (a) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837−8840. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1065−1072. (c) Cohen, F.; Overman, L. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3213−3222. (d) Jiang, Y.; Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 1449−1450. (e) Leung, P.-H.; Ng, K.-H.; Li, Y.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1999**, 2435−2436. (f) Kang, J.; Yew, K. H.; Kim, T. H.; Choi, D. H. *Tetrahedron Lett.* **2002**, *43*, 9509−9512.

(9) The rearrangement of several prochiral allylic *N*-(4-methoxyphenyl)-benzimidates with the silver-activated COP catalyst **6b** was recently described; see: Kang, J.; Kim, T. H.; Yew, K. H.; Lee, W. K. *Tetrahedron: Asymmetry* **2003**, *14*, 415−418.

(10) Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32−35.

(11) Catalyst **5a** is not a kinetically competent catalyst for the allylic imidate rearrangement of *N*-aryltrfluoroacetimidates **3** or *N*-arylbenzimidates **1**.

(12) Jones, G.; Richards, C. J. *Organometallics* **2001**, *20*, 1251−1254.

(13) (a) Zipp, G. G. Ph.D. Dissertation, University of California, Irvine, CA, 2001. (b) Overman, L. E.; Owen, C. E.; Zipp, G. G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3884−3887.

We initially examined the rearrangement of (*E*)- and (*Z*)-2-hexenyl-*N*-(4-methoxyphenyl)trifluoroacetimidates **3a** and **3b** in the presence of 5 mol % of the aforementioned catalysts and 20 mol % of 1,8-bis(dimethylamino)naphthalene.[15] Reactions were carried out in $CH_2Cl_2$ at room temperature for 36 h (Table 2). With all catalysts, *E* stereoisomer **3a** rearranged faster, providing allylic amide **4** (R = *n*-Pr) in higher yield than *Z* stereoisomer **3b**. In addition, rearrangements were generally faster with catalysts containing an oxazoline fragment rather than an imidazole or imine ligand. The highest yields were realized with FOP trifluoroacetate complex **5b** and ($\eta^5$-cyclopentadienyl)($\eta^4$-tetraphenylcyclobutadiene)cobalt oxazoline complex **6b**; however, only **6b** promoted the rearrangement of both stereoisomeric trifluoroacetimidates in good yield (entries 1−4). With all catalysts surveyed, opposite enantiomers of the allylic amide product were produced from imidate geometrical isomers. Complexes **6b** and **7b** containing a ($\eta^5$-cyclopentadienyl)-($\eta^4$-tetraphenylcyclobutadiene)cobalt substituent provided the highest enantioselection in the rearrangement of **3a** and **3b**. As the best combination of rate and enantioselection was realized with COP (cobalt oxazolidine palladacycle) complex **6b**, this complex and its chloride-bridged dimer precursor **6a** were chosen for further study.

**Table 2.** Enantioselective Formation of Allylic Amide **4** (R = *n*-Pr) from Stereoisomeric Allylic Imidates **3a** and **3b**

| entry | catalyst | imidate | yield[a] (%) | % ee[b,c]/conf |
|---|---|---|---|---|
| 1 | **5b**[d] | **3a** | 88 | 76/*S* |
| 2 | **5b**[d] | **3b** | 21 | 87/*R* |
| 3 | **6b**[d] | **3a** | 84 | 84/*S* |
| 4 | **6b**[d] | **3b** | 71[g] | 94/*R* |
| 5 | **7b**[d] | **3a** | 43 | 86/*S* |
| 6 | **7b**[d] | **3b** | 19 | 88/*R* |
| 7 | **8**/TlOTf[e] | **3a** | 49[f] | 82/*S* |
| 8 | **8**/TlOTf[e] | **3b** | 15[f] | 67/*R* |
| 9 | **9**/TlOTf[e] | **3a** | 66[f,g] | 48/*S* |
| 10 | **9**/TlOTf[e] | **3b** | 13[f] | 42/*R* |

[a] Mean values from duplicate experiments (±3%); the remaining mass is largely starting material. [b] Mean values from duplicate experiments (±2%). [c] Determined by HPLC analysis after cleavage of the trifluoroacetate group (see the Supporting Information). [d] Conditions: 5 mol % catalyst, 20 mol % 1,8-bis(dimethylamino)naphthalene, 0.2 M in $CH_2Cl_2$, 36 h. [e] Conditions: 5 mol % catalyst, 0.2 M in $CH_2Cl_2$, 23 °C, 36 h. [f] The remaining mass is largely starting material and *N*-(4-methoxyphenyl)trifluoroacetamide. [g] Mean values from duplicate experiments (±6%).

As a primary goal of this work was the development of more practical catalysts for asymmetric allylic imidate rearrangements, we examined the use of stoichiometric amounts of silver trifluoroacetate for generating **6b** and the most attractive possibility that the chloride-bridged dimer **6a** itself might be a competent catalyst (Table 3). The rearrangement of *E* allylic imidate **3g** (R = *i*-Bu) in the presence of **6b** took place in comparable yield and enantioselectivity whether 2 or 4 equiv of silver trifluoroacetate were employed to generate the COP trifluoroacetate catalyst (entries 1 and 2). Of greater significance, chloride-bridged dimer **6a** (COP-Cl) provided (*S*)-**4g** in comparably high enantiopurity (93−96% ee), although the reaction rate was somewhat less than that achieved with **6b** (entries 3−7). When the substrate concentration was increased to 0.6 M and the reaction time to 60 h, the COP-Cl-catalyzed reaction gave allylic amide (*S*)-**4g** in 93% yield.

**Table 3.** Rearrangement of Imidate **3g** to Amide **4g** (R = *i*-Bu) with Catalysts **6a** (COP-Cl) and **6b**[a]

| entry | $AgOCOCF_3$ (equiv) | time (h) | concn (M) | yield[b] (%) | % ee[c,d]/conf |
|---|---|---|---|---|---|
| 1 | 4 | 38 | 0.2 | 93 | 93/*S* |
| 2 | 2 | 38 | 0.2 | 94 | 94/*S* |
| 3 | 0 | 38 | 0.2 | 50 | 96/*S* |
| 4 | 0 | 38 | 0.4 | 56 | 96/*S* |
| 5 | 0 | 24 | 0.6 | 64 | 93/*S* |
| 6 | 0 | 48 | 0.6 | 83 | 93/*S* |
| 7 | 0 | 60 | 0.6 | 93 | 93/*S* |

[a] Conditions: 5 mol % **6a**, 23 °C, $CH_2Cl_2$. [b] Mean values from duplicate experiments (±3%); the remaining mass is largely starting material. [c] Mean values from duplicate experiments (±2%). [d] Determined by HPLC analysis after cleavage of the trifluoroacetate group (see the Supporting Information).

Table 4 summarizes the rearrangement of six additional allylic *N*-(4-methoxyphenyl)trifluoroacetimidates with both COP-Cl (**6a**) and COP trifluoroacetate catalyst **6b**. Reactions were again conducted at room temperature for a set time

**Table 4.** Enantioselective Formation of Allylic Amides **4** from Allylic Imidates **3** with COP Catalysts **6a** (COP-Cl) and **6b**

| | | imidate | | | | |
|---|---|---|---|---|---|---|
| entry | catalyst | | *E*/*Z* | R | yield[a] (%) | % ee/conf[b,c] |
| 1 | **6a**[d] | **3a** | *E* | *n*-Pr | 92 | 92/*S* |
| 2 | **6b**[e] | **3a** | *E* | *n*-Pr | 79 | 89/*S* |
| 3 | **6a**[d] | **3b** | *Z* | *n*-Pr | 78 | 89/*R* |
| 4 | **6b**[e] | **3b** | *Z* | *n*-Pr | 70 | 95/*R* |
| 5 | **6a**[d] | **3c** | *E* | Me | 85 | 82/*S* |
| 6 | **6b**[e] | **3c** | *E* | Me | 90 | 73/*S* |
| 7 | **6a**[d] | **3d** | *Z* | Me | 87 | 86/*R* |
| 8 | **6a**[d] | **3e** | *E* | $(CH_2)_2Ph$ | 86 | 93/*S* |
| 9 | **6b**[e] | **3e** | *E* | $(CH_2)_2Ph$ | 80 | 88/*S* |
| 10 | **6a**[d] | **3f** | *Z* | $(CH_2)_2Ph$ | 77[g] | 97/*R* |
| 11 | **6a**[f] | **3f** | *Z* | $(CH_2)_2Ph$ | 99 | 96/*R* |
| 12 | **6b**[e] | **3f** | *Z* | $(CH_2)_2Ph$ | 76 | 96/*R* |
| 13 | **6a**[d] | **3g** | *E* | *i*-Bu | 88 | 94/*S* |
| 14 | **6b**[e] | **3g** | *E* | *i*-Bu | 80 | 92/*S* |
| 15 | **6a**[d] | **3h** | *Z* | *i*-Bu | 58 | 90/*R* |
| 16 | **6b**[e] | **3h** | *Z* | *i*-Bu | 67 | 97/*R* |

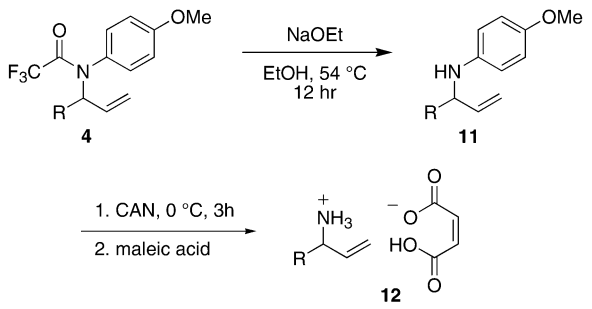
[a] Mean values from duplicate experiments (±3%); the remaining mass is largely starting material. [b] Mean values from duplicate experiments (±2%). [c] Determined by HPLC analysis after cleavage of the trifluoroacetate group (see the Supporting Information). [d] Conditions: 5 mol % **6a**, 0.6 M in $CH_2Cl_2$, 23 °C, 60 h. [e] Conditions: 5 mol % **6b**, 20 mol % $iPr_2NEt$, 0.2 M in $CH_2Cl_2$, 23 °C, 30 h. [f] Conditions: 5 mol % **6a**, 0.6 M in $CH_2Cl_2$, 38 °C, 60 h. [g] Mean values from duplicate experiments (±4%).

(14) In these cases, preliminary scouting experiments indicated that triflate was superior to trifluoroacetate with regard to both catalysis rate and enantioselectivity.

period, in this case 60 h; as a result, product yields largely reflect the rates at which various allylic imidates undergo rearrangement with the two COP catalysts. In general, enantioselection for rearrangements of *E* allylic imidates was higher using COP-Cl, whereas higher enantioselection in the rearrangement of *Z* allylic imidates was realized with COP trifluoroacetate catalyst **6b**. With the proper choice of COP catalyst, allylic amide products were formed with enantiomeric excesses >92% from *E* and *Z* imidates containing both branched and unbranched alkyl chains at the $\gamma$ position (entries 1−4 and 8−16). Even crotyl trifluoroacetimidates **3c** and **3d**, notoriously problematic substrates,[3] rearranged to provide the corresponding amides **4c** in 82−86% ee. Yields of amide **4** from rearrangements of *Z* imidates with COP-Cl (**6a**) were improved with little to no loss in enantioselectivity by carrying out the reactions at 38 °C (entry 11).[16]

The *N*-(4-methoxyphenyl)trifluoroacetamide products **4** can be deprotected in useful yields to give the corresponding enantioenriched allylic primary amines by a two-step sequence (Scheme 3). Initial reaction of amides **4** with freshly

**Scheme 3.** Deprotection of Allylic Amides **4**




prepared sodium ethoxide in ethanol at 54 °C for 12 h generates amines **11** in excellent yield (Table 5). Oxidative dearylation of these products with ceric ammonium nitrate (CAN),[17] followed by treatment with maleic acid, provided the corresponding primary amine maleic acid salts **12** in good yields (Table 5).[18]

**Table 5.** Deprotection of Allylic Amides **4**

| entry | amide | R | yield of **11** (%) | yield of **12** (%) |
|---|---|---|---|---|
| 1 | **4a** | *n*-Pr | 98 | 74 |
| 2 | **4c** | Me | 97 | ~30[a] |
| 3 | **4e** | $CH_2CH_2Ph$ | 93 | 80 |
| 4 | **4g** | *i*-Bu | 99 | 70 |

[a] Low isolated yield due to volatility of product.

The absolute configuration of allylic amides **4a** and **4c** was rigorously established as follows. Amine salt **12a** (R = *n*-Pr) was *N*-benzylated by reaction with benzaldehyde in methanol in the presence of sodium cyanoborohydride to provide (*S*)-*N*-benzyl-3-amino-1-hexene.[19] *N*-(4-Methoxyphenyl)trifluoroacetamide **4c** was chemically correlated[20] with *N*-(4-methoxyphenyl)benzamide **2** (R = Me), whose absolute configuration had been established earlier.[3] Absolute configurations of the other products reported in Table 4 are assigned at this point by analogy.

In conclusion, [3,3]-sigmatropic rearrangement of *N*-(4-methoxyphenyl)trifluoroacetimidates to *N*-(4-methoxyphenyl)trifluoroacetamides in the presence of di-$\mu$-chlorobis-[($\eta^5$-(*S*)-(p*R*)-2-(2′-(4′-isopropyl)oxazolinylcyclopentadienyl,1-*C*,3'-*N*))($\eta^4$-tetraphenylcyclobutadiene)cobalt]dipalladium (COP-Cl, **6a**) is the central step in the best method reported to date for the conversion of prochiral allylic alcohols to enantioenriched chiral allylic amines. These catalytic allylic imidate rearrangements occur at convenient temperatures (23−38 °C), and silver or thallium salts are not required to activate the COP-Cl catalyst.

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**Supporting Information Available:** Representative experimental procedures and characterization data for new compounds; copies of HPLC chromatograms used to establish the enantiopurity of allylic amides **4** formed with catalysts **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) 1,8-Bis(dimethylamino)naphthalene was added to minimize decomposition of the imidate by acid-promoted ionization to form the allyl cation and *N*-(4-methoxyphenyl)trifluoroacetamide. In the case of arenetricarbonyl chromium(0) catalysts **8**/TlOTf and **9**/OTf, added base suppresses catalysis (<10% conversion to **4a** after 36 h); consequently, rearrangements with these catalysts were conducted in the absence of 1,8-bis-(dimethylamino)-naphthalene.

(16) Purification of the trifluoroacetimidate **3** immediately prior to rearrangement with COP-Cl (**6a**) was necessary to ensure reproducible yields of the trifluroracetamide products **4**.

(17) (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765−2768. (b) Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett.* **2000**, *2*, 1891−1984.

(18) It was crucial to add **11** to a rapidly stirred aqueous solution of CAN for high yields to be realized. In addition, although complete consumption of amine **11** occurred immediately upon addition to CAN, yields increased at longer reaction times, with the optimal yield being achieved after 3 h.

(19) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. *Tetrahedron Lett.* **2001**, *42*, 6385−6388.

(20) Deacylation of **4** with sodium ethoxide in ethanol followed by treatment with benzoyl chloride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine provided amide **2**.