ORGANIC LETTERS

2008
Vol. 10, No. 22
5281−5284

Syntheses of Substituted 3-Methyleneisoindolin-1-ones By a Palladium-Catalyzed Sonogashira Coupling−Carbonylation−Hydroamination Sequence in Phosphonium Salt-Based Ionic liquids

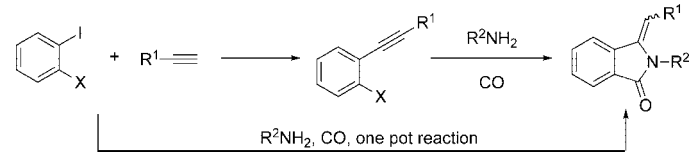
Hong Cao, Laura McNamee, and Howard Alper*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario K1N 6N5, Canada

howard.alper@uottawa.cas

Received September 15, 2008

ABSTRACT



Two efficient approaches for the synthesis of isoindolin-1-one derivatives in phosphonium salt ionic liquids are described. The palladium-catalyzed carbonylation−hydroamination reaction of 1-halo-2-alkynylbenzene with amines afforded the substituted 3-methyleneisoindolin-1-ones in good yields and high selectivities in favor of the *Z*-isomers. The target molecules could also be synthesized by the Sonogashira coupling−carbonylation−hydroamination one-pot reaction of dihalides, alkynes, and amines. Both processes can be conducted under mild conditions and tolerate a wide array of functionalized substrates.

Substituted 3-methyleneisoindolin-1-ones constitute an important part of a number of naturally occurring compounds, such as, magallanesine,[1] an isoindolobenzazocine that has been isolated from various Berberis species, enterocarpam II,[2] a member of the aristolactam alkaloids family, and the secophthalide−isoquinoline ene-lactam fumaridine.[3] They are also found as the key structural feature of biologically active compounds such as AKS186, which displays vasorelaxant properties,[4] and the 4-acetoxyphenylmethyleneisoindolin-1-one derivative whose hydrochloride was claimed to exhibit local anesthetic activity superior to that of procaine.[5] Therefore, the synthesis of substituted 3-methyleneisoindolin-1-ones has generated considerable interest over the past several decades.[6−9]

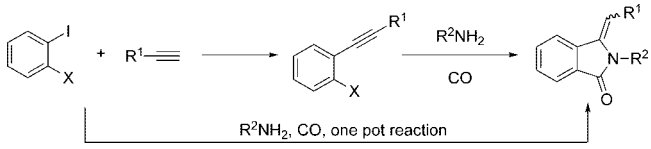
Recently, the combination of task-specific ionic liquids (TSILs) as versatile and novel reaction media, with transition metal complexes as catalysts, has resulted in some effective and easily separable catalytic systems that were successfully used for carbonylation reactions.[10,11] Most ionic liquids research has been conducted in nitrogen-based solvents.[12] Although beneficial in many cases, ammonium ionic liquids have been shown to degrade under strong base and sonication conditions.[13] Aromatic rings, part of many N-based ionic liquids, are also susceptible to aromatic substitution reactions, which can limit their scope of application.[14] For these reasons, researchers began to focus on developing processes in phosphonium salt-based ionic liquids (PSILs). When compared to their ammonium counterparts, PSILs display increased stability toward thermal and chemical degradation, making them ideal for use at high temperatures, or in processes in which the products can be removed by distillation.[15] PSILs are also nonvolatile, economical, and avail-

10.1021/ol8021403 CCC: $40.75
Published on Web 10/25/2008

able on an industrial scale. In the past several years, McNulty and other groups investigated the application of PSILs in general, and specifically for palladium-catalyzed processes.[16] Our own group has recently reported an efficient application of PSILs for palladium-catalyzed thiocarbonylation reactions.[17]

Inspired by our previous research about palladium-catalyzed carbonylation reactions to synthesize heterocyclic compounds,[18] and aiming to explore the unique capabilities of PSILs, we designed a simple route to synthesize the substituted 3-methyleneisoindolin-1-ones. This route includes carbonylation and intramolecular hydroamination reactions of an amine and 1-halo-2-alkynylbenzenes in phosphonium salt ionic liquids. Herein, we report the results obtained from this investigation and also an alternative synthesis of 3-methyleneisoindolin-1-ones through a Sonogashira coupling −carbonylation−hydroamination one-pot approach (Scheme 1).

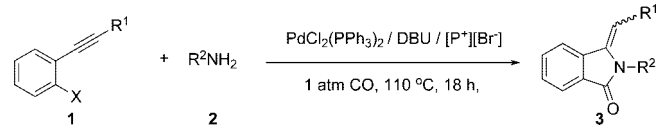
Scheme 1. Multistep and One-Pot Synthesis for the Substituted 3-Methyleneisoindolin-1-one



In the initial screening, a range of PSILs consisting of the trihexyl(tetradecyl)phosphonium cation with a range of common anions were screened for the carbonylation and intramolecular hydroamination reaction of 1-bromo-2-(phenylethynyl)benzene **1a** and benzylamine **2a**. The reactions were conducted under 200 psi of CO, 110 °C, with $Pd(OAc)_2$/dppb as the catalyst system and Cs_2CO_3 as the base. The results reveal that bromide-containing media shows the greatest efficiency for the reaction, and furnished the target product 2-benzyl-3-benzylideneisoindolin-1-one **3a** in 46% isolated yield, while the chloride analogue gave the product in 30% yield. Both reactions provided *Z*-isomers as the main products (*Z*/*E* = 96:4). The ionic liquids with $[NTf_2^-]$ and $[PF_6^-]$ as anions were not effective. The superiority of the bromide-containing media shown in this reaction is consistent with the research reported on carbonylation of arene halides and nucleophiles in PSILs.[16]

Further optimization of the reaction conditions is shown in Table 1. We found that in the ionic liquid $[P^+][Br^-]$, the Pd(0) catalysis systems such as Pd(OAc)/dppb and $Pd_2(dba)_3{\cdot}CHCl_3$ were both useful in catalyzing the reaction and provided the product in 46% and 73% yields, respectively (Table 1, entries 1 and 5). Surprisingly, without any ligand, both $Pd(OAc)_2$ and $PdCl_2$ could also catalyze the reaction and provide the desired products in 62% and 43% yields, respectively (Table 1, entries 2 and 4). Without addition of any extra ligand, $PdCl_2(PPh_3)_2$ was found to be the best catalyst for the reaction by furnishing **3a** in 84% yield, under 1 atm of CO, with DBU as base. In this study, the ionic liquid also showed better efficiency in the reaction when compared to THF. By using $Pd(OAc)_2$ as the catalyst but no added ligand, there was no reaction in THF (Table 1, entry 3), and with $PdCl_2(PPh_3)_2$ in THF, the reaction did occur, but the yield here is lower than those obtained with ionic liquids (Table 1, entry 11). These results demonstrated that ionic liquids may not only play the role of reaction media, but also participate in the reaction as a promoter ligand.

Table 1. Optimization of Palladium-Catalyzed Carbonylation−Hydroamination Reaction between 1-Bromo-2-(phenylethynyl)benzene and Benzylamine[a]



entry	catalyst	solvent[b]	base	temp (°C)	CO (psi)	yield[c] (%)
1	$Pd(OAc)_2$/dppb	$[P^+][Br^-]$	Cs_2CO_3	110	200	46
2	$Pd(OAc)_2$	$[P^+][Br^-]$	Cs_2CO_3	110	200	62
3	$Pd(OAc)_2$	THF	Cs_2CO_3	110	200	NR
4	$PdCl_2$	$[P^+][Br^-]$	Cs_2CO_3	110	200	43
5	$Pd_2(dba)_3$, $CHCl_3$	$[P^+][Br^-]$	Cs_2CO_3	110	200	73
6	$PdCl_2(PPh_3)_2$	$[P^+][Br^-]$	Cs_2CO_3	110	200	82
7	$PdCl_2(PPh_3)_2$	$[P^+][Br^-]$	Cs_2CO_3	60	200	NR
8	$PdCl_2(PPh_3)_2$	$[P^+][Br^-]$	DBU	110	200	84
9	$PdCl_2(PPh_3)_2$	$[P^+][Br^-]$	TEA	110	200	NT
10	$PdCl_2(PPh_3)_2$	$[P^+][Br^-]$	DBU	110	1 atm	84
11	$PdCl_2(PPh_3)_2$	THF	DBU	110	200	42

[a] Reaction conditions: **1** (1 mmol), **2** (3 mmol), bases (2 mmol), Pd catalyst (0.05 mmol), PSIL (2.0 g), 18 h, 110 °C.

The study of the scope of this palladium-catalyzed carbonylation−hydroamination reaction in the PSIL was extended to a series of amines and 1-halo-2-alkynylbenzene (Figure 1). Most of the amines employed in the reaction showed good reactivities, and consistently provided the *Z*-isomer as the main product. Both of the aromatic and the aliphatic amines were active in the reactions, with $4\text{-MeOC}_6H_4CH_2NH_2$ providing the best product yield (92%). Under the same conditions, *tert*-butylamine afforded lower yields of the target products (41%), possibly because of the bulkiness of the *tert*-butyl group. Regarding the 1-halo-2-alkynylbenzene, when the triple bond was substituted with an aromatic ring, the reaction afforded better yields than substrates without such substitution. Interestingly, with the 4-methoxylphenyl group as a substituent of the triple bond, the substrate was reactive and the desired product was isolated in 82% yield. As expected, 1-iodo-2-(phenylethynyl)benzene also gave the product in high yield (88%).

Since similar catalyst systems were employed for the preparation of the starting material, 1-halo-2-alkynylbenzene, and for the synthesis of the substituted 3-methyleneisoindolin-1-ones, we wondered whether one could directly access the products in a one-pot fashion. Therefore, we attempted the reaction of 1-bromo-2-iodobenzene, phenylacetylene, and

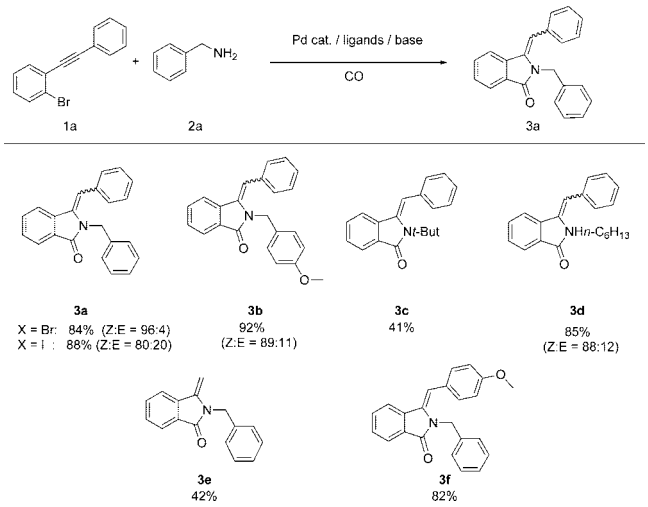
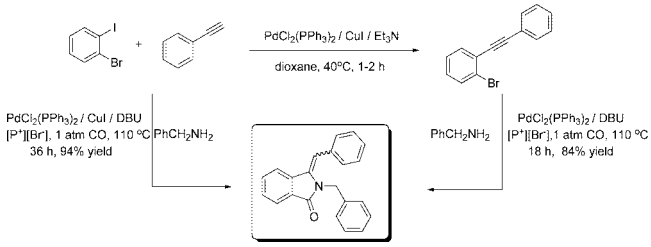


Figure 1. Substrates scope of the palladium-catalyzed hydroamination−carbonylation reaction. Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), bases (2 mmol), Pd catalyst (0.05 mmol), PSIL (2.0 g) or THF (5 mL), 18 h, 110 °C. [b] $[P^+] = (C_6H_{13})_3P^+(CH_2)_{13}CH_3$. [c] Isolated yields.

benzylamine with $PdCl_2(PPh_3)_2$/CuI as the catalyst, DBU as the base, and [P+][Br−] as solvent, under 1 atm of CO, at 110 °C. We were delighted to obtain the heterocycle in 94% yield (Scheme 2).

Scheme 2. One-Pot Sonogashira Coupling−Carbonylation−Intramolecular Hydroamination Reaction



We explored this one-pot protocol by reacting various amines with alkynes and arene dihalides. The results are presented in Figure 2. The results indicate that the $PdCl_2(PPh_3)_2$/CuI/DBU catalyst system could be successfully employed for the one-pot synthesis of a range of 3-methyleneisolindolin-1-ones. All processes were highly stereoselective, and gave the *Z*-isomer as the main product. When different arene dihalides were employed, the 1,2-diiodobenzene efficiently provided the isoindolin-1-one derivative in 85% yield, whereas with the 1-chloro-2-iodobenzene the reaction stopped at the first step and gave the Sonogashira coupling product as the only isolated product.

Two pathways can be considered as possible mechanisms for this reaction (Scheme 3). The first step is likely to be

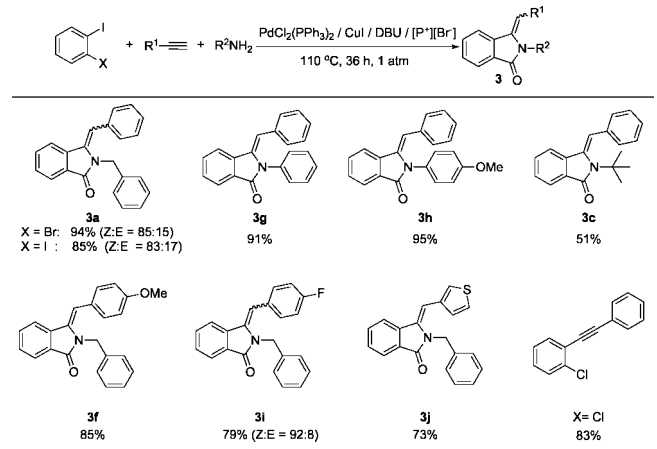
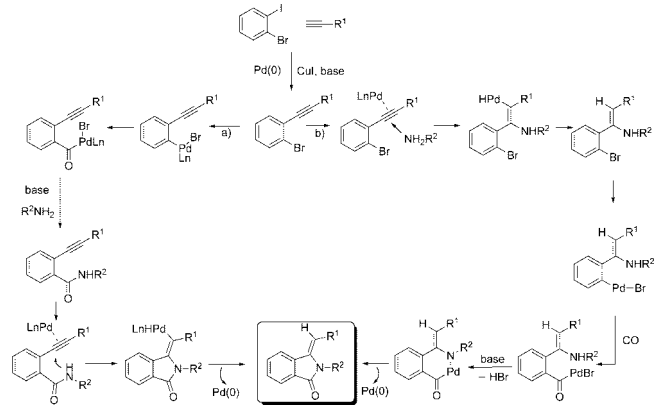


Figure 2. Substrates scope of the one-pot protocol of amine, arene dihalides, and alkynes. Reaction conditions: arene dihalides (1 mmol), alkyne (1.2 mmol), amine (3 mmol), bases (2 mmol), Pd catalyst (0.05 mmol), PSIL (2.0 g), 1 atm of CO, 36 h, 110 °C.

the Sonogashira coupling reaction, then the 1-halo-2-alkynylbenzenes may go through either path a or b. Path a involves oxidative addition of PdLn to the C−Br bond, followed by carbonyl insertion into the Pd−C bond. Attack of the amine followed by reductive elimination of Pd(0) would give rise to the amide. Intramolecular hydroamination of the triple bond, followed by reductive elimination of Pd(0) results in the formation of the substituted 3-methyleneisoindolin-1-one. The reaction may alternatively proceed via path b, i.e., Pd(0) coordination to the triple bond, followed by hydroamination, then carbonyl insertion of the latter, followed by intramolecular attack of the NH group, and reductive elimination of Pd(0) would lead to the desired products. On the basis of the result of the reaction of 1-chloro-2-iodobenzene, which gave the Sonogashira coupling product as the only product, we think it is more likely that the reaction would go through path a, as we would

Scheme 3. Possible Mechanisms for the Sonogashira Coupling−Carbonylation−Intramolecular Hydroamination One-Pot Reactions of Amine, Arene Dihalides, and Alkynes



otherwise anticipate the isolation of the hydroamination product after the Sonogashira coupling reaction.

In conclusion, we have developed two effective methods for the synthesis of substituted 3-methyleneisoindoline-1-one derivatives under mild conditions. This protocol is based on a sequential use of Sonogashira coupling, carbonylation, and hydroamination chemistry. This one-pot protocol gave the target products in high stereoselectivity and good yields. The application of this reaction for the synthesis of natural and bioactive compounds is under investigation currently in our laboratory.

Acknowledgment. We are indebted to Cytec Canada Inc. and NSERC for financial support of this work.

Supporting Information Available: Full experiment details, characterization for all compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8021403

(1) (a) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39. (b) Valencia, E.; Freyer, J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599. (c) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron* **1984**, *40*, 3957. (d) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993.

(2) Chang, Z.-L.; Zhu, D. Y. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1978; Vol. 31, p 29.

(3) Blasko, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105.

(4) (a) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003. (b) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060.

(5) Laboratori Baldacci, S. p. A. (Italy) Jpn. Patent 59046268, 1984; *Chem. Abstr.* **1984**, *101*, 54922.

(6) Addition of organolithium or Grignard reagents, see: (a) Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707. (b) Daıch, A.; Marchalin, S.; Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1998**, *39*, 9187. (c) Chihab-Eddine, A.; Daıch, A.; Jilale, A.; Decroix, B. *Heterocycles* **2002**, *58*, 449. (d) Islam, A. M.; El-Sharief, A. M. S.; Bedair, A. H.; Hammad, N. E. *Egypt. J. Chem.* **1983**, *25*, 251. (e) Islam, A. M.; El-Sharief, A. M. S.; El-Maghraby, A. A.; Bedear, A. H. *Indian J. Chem., Sect. B* **1978**, *16*, 3014. (f) Marsili, A.; Scartoni, V. *Gazz. Chim. Ital.* **1972**, *102*, 806. (g) Hitchings, G. J.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1757. Organosamarium reagents can also be used, see: (h) Li, Z.; Zhang, Y. *Tetrahedron Lett.* **2001**, *42*, 8507. (i) Ha, D. C.; Yun, C. S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577. For other approaches, see: (j) Griesbeck, A. G.; Warzecha, K. D.; Neudörfl, J. M.; Görner, H. *Synlett* **2004**, 2347. (k) Katritzky, A. R.; He, H. Y.; Jiang, R. *Tetrahedron Lett.* **2002**, *43*, 2831. (l) Hendi, M. S.; Natalie, K. J., Jr.; Hendi, S. B.; Campbell, J. A.; Greenwood, T. D.; Wolfe, J. F. *Tetrahedron Lett.* **1989**, *30*, 275. (m) Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. (n) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2004**, *69*, 4527. (o) Sanchez-Sanchez, C.; Perez-Inestrosa, E.; Garcıa-Segura, R.; Suau, R. *Tetrahedron* **2002**, *58*, 7267.

(7) (a) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (b) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (c) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777, and references cited therein. (d) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2000**, *59*, 1571. A related approach involves the anionic cylization of 2-alkynylbenzonitriles initiated by treatment with sodium methoxide, see: (e) Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, *55*, 13193. (f) Lu, W. D.; Lin, C. F.; Wang, C. J.; Wang, S. J.; Wu, M. J. *Tetrahedron* **2002**, *58*, 7315. Electrophilic cyclizations of 2-alkynylbenzamides have also been reported, see: (g) Kundu, N. G.; Khan, M. W. *Tetrahedron Lett.* **1997**, *38*, 6937. (h) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, *55*, 12361. (i) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432.

(8) Cho, C. S.; Shim, H. S.; Choi, H. J.; Kim, T.-J.; Shim, S. C. *Synth. Commun.* **2002**, *32*, 1821.

(9) For some representative examples, see: (a) Garcıa, A.; Rodrıguez, D.; Castedo, L.; Saa, C.; Domınguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903. (b) Comins, D. L.; Joseph, S. P.; Zhang, Y. M. *Tetrahedron Lett.* **1996**, *37*, 793. (c) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511.

(10) (a) Davis, J. H. Task-specific ionic liquids. *Chem. Lett.* **2004**, *33*, 1072. (b) Xue, H.; Verma, R.; Shreeve, J. M. *J. Fluorine Chem.* **2006**, *127*, 159. (c) Shi, F.; Gu, Y.; Zhang, Y.; Deng, Y. *Catal. Surv. Asia* **2004**, *8*, 179. (d) Wasserscheid, P.; Welton, T. *Ionic Liquid in Synthesis*; Wiley-VCH & CoKGaA: Weinheim, Germany, 2002.

(11) (a) Mizushima, E.; Hayashi, T.; Tanaka, M. *Green Chem.* **2001**, *3*, 76. (b) Calo, V.; Giannoccaro, P.; Nacci, A.; Monopoli, A. *J. Organomet. Chem.* **2002**, *645*, 152. (c) Li, Y.; Alper, H.; Yu, Z. K. *Org. Lett.* **2006**, *8*, 5199. (d) Ye, F.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1855. (e) Calo, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* **2006**, 3791. (f) Zhao, X.; Alper, H.; Yu, Z. *J. Org. Chem.* **2006**, *71*, 3988. (g) Li, Y.; Yu, Z.; Alper, H. *Org. Lett.* **2007**, *9*, 1647. (h) Ye, F.; Alper, H. *J. Org. Chem.* **2007**, *72*, 3219. (i) Fukuyama, T.; Inouye, T.; Ryu, I. *J. Organomet. Chem.* **2007**, *692*, 685. (j) Cao, H.; Xiao, W. J.; Alper, H. *J. Org. Chem.* **2007**, *72*, 8562.

(12) (a) For a recent example, see: Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. *Chem. Commun.* **2006**, 3591. (b) For a comprehensive review, see: Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, Germany, 2003.

(13) (a) Oxley, J. D.; Prozorov, T.; Suslick, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 11138. (b) Dupont, J.; Spencer, J. *Angew. Chem.* **2004**, *116*, 5408. (c) Dupont, J.; Spencer, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5296.

(14) Lancaster, N. L.; Llopis-Mestre, V. *Chem. Commun.* **2003**, *n/a*, 2812.

(15) (a) Bradaric, C. J.; Downard, A.; Kennedy, C.; Robertson, A. J.; Zhou, Y. *Green Chem.* **2003**, *5*, 143. (b) Kim, Y. J.; Varma, R. S. *J. Org. Chem.* **2005**, *70*, 7882.

(16) (a) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. J. *Chem. Commun.* **2002**, 1986. (b) Gerritsma, D. A.; Robertson, A. J.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 7629. (c) McNulty, J.; Capretta, A.; Cheekoori, S.; Clyburne, J. A. C.; Robertson, A. J. *Chem. Oggi* **2004**, *22*, 13. (d) McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrahedron Lett.* **2005**, *46*, 3641. (e) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. *Chem. Eur. J.* **2006**, *12*, 9314. (f) McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A. *Eur. J. Org. Chem.* **2007**, *9*, 1423. (g) McNulty, J.; Nair, J. J.; Robertson, A. J. *Org. Lett.* **2007**, *9*, 4575.

(17) Cao, H.; Alper, H. *J. Org. Chem.* **2008**, *73*, 3530.

(18) (a) Dong, C.; Alper, H. *Tetrahedron: Asymmetry.* **2004**, *15*, 35. (b) Dong, C.; Alper, H. *J. Org. Chem.* **2004**, *69*, 5011. (c) Lu, S. M.; Alper, H. *J. Am. Chem. Soc.* **2005**, *127*, 14776. (d) Cao, H.; Xiao, W. J.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1807. (e) Lu, S. M.; Alper, H. *Chem. Eur. J.* **2007**, *13*, 5908. (f) Zheng, Z. Y.; Alper, H. *Org. Lett.* **2008**, *10*, 829. (g) Lu, S. M; Alper, H. *J. Am. Chem. Soc.* **2008**, *130*, 6451.