ORGANIC LETTERS

2012
Vol. 14, No. 12
3116–3119

Copper-Catalyzed Arylation of *o*-Bromoanilides: Highly Flexible Synthesis of Hexahydropyrroloindole Alkaloids

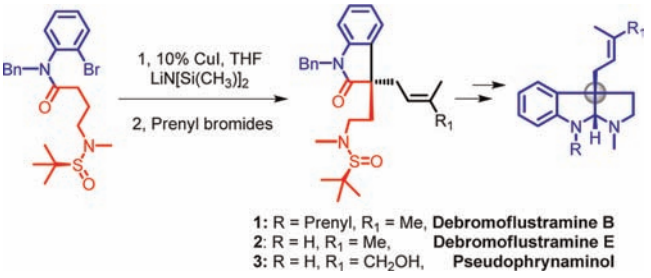
Yongyun Zhou, Yongkai Xi, Jingfeng Zhao, Xianfu Sheng, Shuqin Zhang, and Hongbin Zhang*

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. China

zhanghb@ynu.edu.cn; zhang_hongbin@hotmail.com

Received May 2, 2012

ABSTRACT



In the presence of catalytic amount of copper iodide, a remote amide-assisted intramolecular arylation followed by alkylation leads to a general and flexible synthetic method toward the synthesis of medicinally interesting hexahydropyrroloindole alkaloids.

The hexahydropyrrolo[2,3-*b*]indole ring system appears in a wide selection of natural alkaloids and a number of marketed drugs and drug candidates.[2] Among them, the C_{3a} all-carbon quaternary center containing members are especially attractive because of their important biological activities.[1e,f] As a unique family of the hexahydropyrrolo-[2,3-*b*]indole alkaloids, natural products shown in Figure 1 are characterized by a sterically congested all-carbon quaternary center containing prenyl substitutent.[2] The efficient and enantioselective construction of the prenyl substituted quaternary carbon center at the C_{3a} position offers an interesting synthetic problem.[3] Recently, we disclosed a new synthesis of esermothole and its analogues through a palladium-mediated sequential arylation–alkylation.[4] We envisioned that a metal mediated "one-pot" arylation–alkylation of the *o*-bromoanilide bearing a certain chiral auxiliary might lead to the required C_{3a} all-carbon quaternary center in a diastereoselective manner. Herein we report the first stereocontrolled copper-catalyzed arylation-alkylation of *o*-bromoanilides and the flexible synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids based on this new methodology.

The retrosynthetic analysis is outlined in Scheme 1. The metal-mediated arylation of *o*-bromoanilide **7** bearing a chiral sulfinyl amide unit followed by alkylation would

(1) For selected reviews and books, see:(a) Hino, T.; Nakagawa, M. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 34, pp 1–75. (b) Anthoni, U.; Christophersen, C.; Nielsen, P. H. in *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: London, 1999; Vol. 13, pp 163–236. (c) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (d) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem.—Eur. J.* **2011**, *17*, 1388 and references cited therein. (d) Santos, P. E.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Heterocycles* **2001**, *55*, 1029. (e) Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3. (f) Sorbera, L. A.; Castaner, J. *Drugs Future* **2003**, *28*, 18.

(2) For alkaloids in Figure 1, see: (a) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H. *J. Nat. Prod.* **1994**, *57*, 997. (b) Badio, B.; Garraffo, H. M.; Padgett, W. L.; Greig, N. H.; Daly, J. W. *Biochem. Pharmacol.* **1997**, *53*, 671. (c) Smith, B. P.; Tyler, M. J.; Kaneko, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **2002**, *65*, 439. (d) Raju, R.; Piggott, A. M.; Huang, X.-C.; Capon, R. J. *Org. Lett.* **2011**, *13*, 2770.

(3) (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (d) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488.

(4) Zhou, Y.; Zhao, Y.; Dai, X.; Liu, J.; Li, L.; Zhang, H. *Org. Biomol. Chem.* **2011**, *9*, 4091.

10.1021/ol3012056
Published on Web 06/05/2012

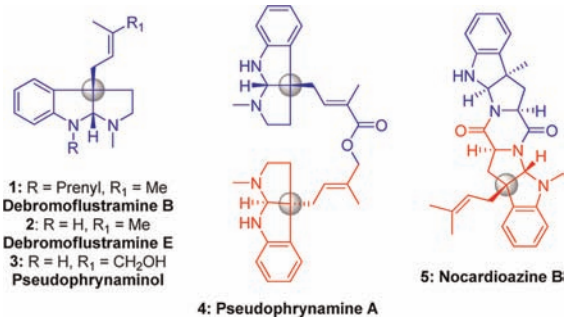
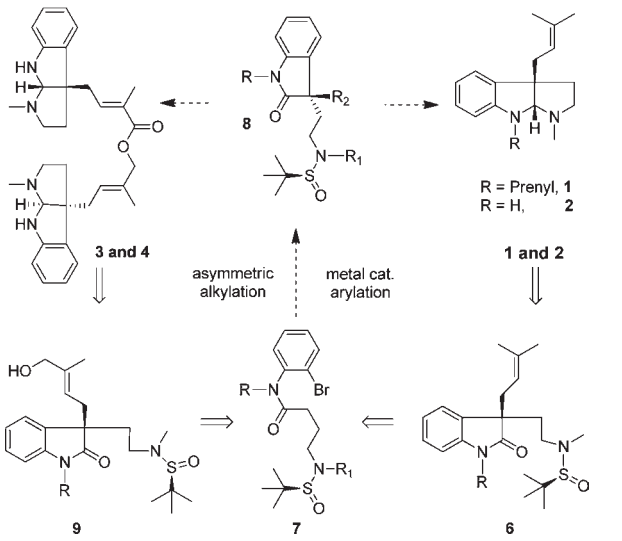


Figure 1. Representative hexahydropyrroloindole alkaloids.

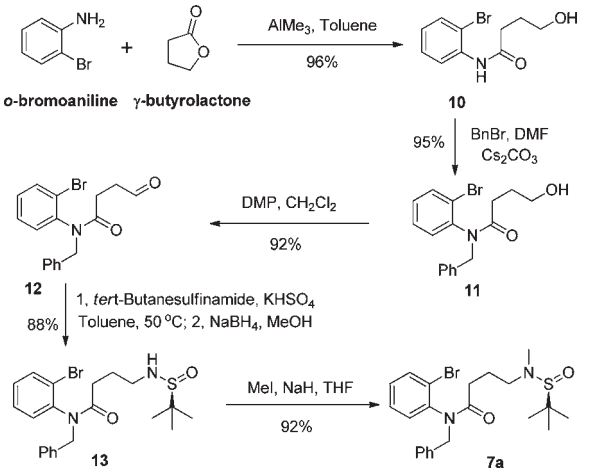
give precursors (**8**) for the synthesis of debromoflustramines B and E and pseudophrynamine alkaloids (see Scheme 1).

We began our research by preparing amide **7a** bearing a chiral sulfinyl amide unit. Treatment of 2-bromoaniline with butenolide in the presence of trimethylaluminum in toluene afforded amide **10** in 96% yield. Protection of amide **10** followed by oxidation afforded aldehyde **12** (87%, two steps). Heating aldehyde **12** with (*S*)-(−)-*tert*-butanesulfinamide[5] in toluene, followed by reduction with sodium borohydride, led to amide **13** in 88% yields in two steps. The amide (**7a**, 95% ee, Scheme 2) was finally obtained by treatment of compound **13** with methyl iodide in the presence of sodium hydride.

Scheme 1. Retrosynthetic Analysis of HPI Alkaloids **1**−**4**

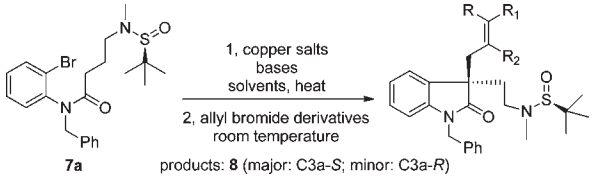


Scheme 2. Synthesis of *o*-Bromoanilide Bearing a Chiral *tert*-Butanesulfinamide Unit



Next, we came to the key stage of our research, the metal-mediated arylation of *o*-bromoanilide and the subsequent asymmetric alkylation. Inspired by recent reports that copper salts could mediate the formation of oxindoles,[6] we decided to explore the copper-mediated arylation of *o*-bromoanilides in the hope that an efficient and asymmetric "one-pot" process could be developed for the synthesis of oxindoles bearing a C_{3a} all-carbon quaternary center.

Table 1. Studies on the Copper-Catalyzed Arylation−Alkylation of *o*-Bromoanilide Bearing a *tert*-Butanesulfinamide Unit[a]



entry	metal salts	R, R_1 and R_2	ee[b] (%)	yield[a] (%)
1	$CuCl_2$	**8a**: R = R_1 = R_2 = H		0[c]
2	$Cu(OAc)_2 \cdot H_2O$	**8a**: R = R_1 = R_2 = H		0[d]
3	$CuCl_2$	**8a**: R = R_1 = R_2 = H		0[d]
4	CuI	**8a**: R = R_1 = R_2 = H		0[e]
5	CuI	**8a**: R = R_1 = R_2 = H	71	,72[f,g]
6	CuI	**8b**: R = R_1 = H, R_2 = Me	71	71[g]
7	CuI	**8c**: R = R_1 = Me, R_2 = H	66	84[g]
8	CuI	**8d**: R = Me, R_2 = H R_1 = CH_2OTBS	72	74[g]
9	CuI	**8e**: R = R_1 = H, R_2 = CO_2Me		80[g]
10	CuI	**8f**: R = R_1 = H, R_2 = Br	80	57[g]

[a] Yields represent isolated yields; see the Supporting Information for detailed reaction conditions. [b] The ee values were determined after removal of the *tert*-butanesulfinamide. [c] $CuCl_2$ (2.0 equiv), *t*-BuONa (5.0 equiv), and DMF, 110 °C. [d] Copper salts (1.0 equiv), *t*-BuOK (2.0 equiv), DMF, 110 °C. [e] CuI (1.0 equiv), *t*-BuOK (2.0 equiv), THF (80 °C oil bath). [f] CuI (1.0 equiv), $LiN(SiMe_3)_2$ (2.0 equiv), THF (80 °C). [g] CuI (0.1 equiv), $LiN(SiMe_3)_2$ (2.0 equiv), THF (80 °C).

(5) Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, 1334.

(6) For the synthesis of racemic C3a all-carbon oxindoles by copper-mediated intramolecular coupling of anilides, substrates are limited to phenylacetanilide derivatives or β-keto acetanilides; see: (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (b) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (c) Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010**, 934. (d) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446.

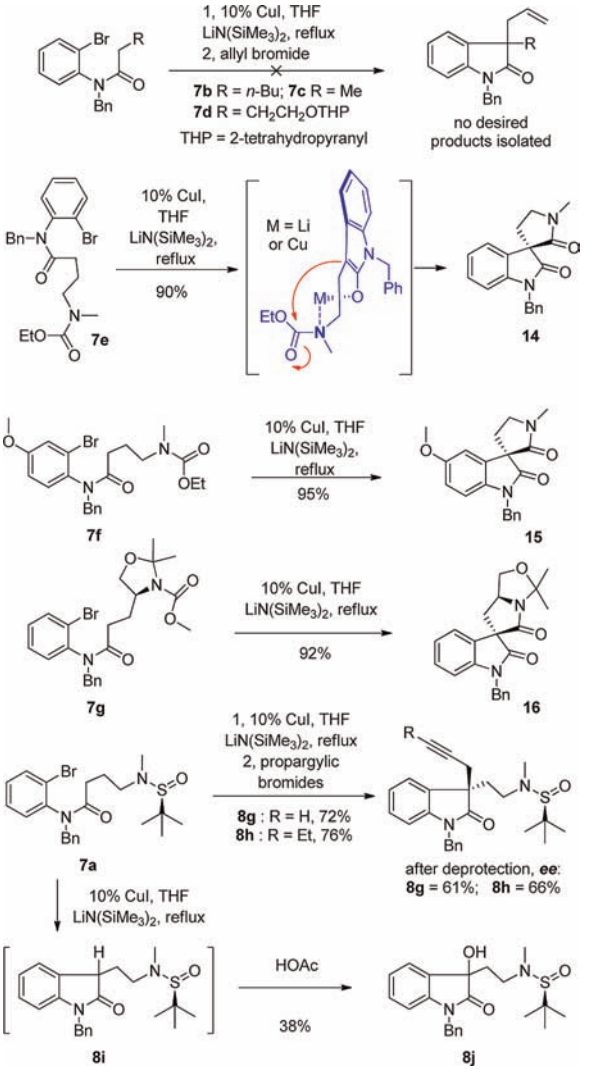
The proposed arylation of compound **7a** was initially attempted with copper chloride and copper acetate in the presence of sodium *tert*-butoxide in DMF at 110 °C under argon[6a] or under air[6b] as reported in the literature (Table 1, entries 1−4). Unfortunately, these reaction conditions afforded no desired product, with starting material being recovered. We next attempted copper(I) iodide in combination with a number of bases. To our delight, copper(I) iodide was found to effect the transformation in the presence of lithium bis(trimethylsilyl)amide. After some experimentation, the optimal reaction conditions were established, and this transformation could be effected in only a catalytic amount (10%) of CuI (Table 1, entry 6) to afford the C3a-*S* and C3a-*R* products as an inseparable mixture of diastereoisomers. To the best of our knowledge, this is the first example of copper-catalyzed intramolecular arylation−alkylation of an *o*-bromoanilide, a cost-effective process for the asymmetric synthesis of oxindoles bearing a C_{3a} all-carbon quaternary center.[7]

In order to get some insight toward this copper-catalyzed process, we carried out the reaction with a number of *o*-bromoanilides (**7b**−**g**, Scheme 3). Arylation of *o*-bromoanilides (**7b**−**d**) without the neighboring *tert*-butanesulfinamide unit did not yield the desired arylation−alkylation products. It was noteworthy that substrates **7e** and **7f** bearing a carbamate group underwent the arylation efficiently in the presence of copper(I) iodide and unprecedentedly led to spiro-oxindoles **14** and **15** in excellent yields. The remote aza-assistance of a *tert*-butanesulfinamide or a carbamate unit was critical to this copper-catalyzed arylation. Arylation of the optically active substrate **7g** (derived from L-glutamic acid) provided spirooxindole **16** in high yield with excellent diastereoselectivity (Scheme 3, 16, dr >99:1, based on NMR). Attempts made to isolate the arylation intermediate, namely oxindole **8i**, were fruitless, and a complex mixture was formed after workup, with the major product being identified as oxindole **8j**, an air oxidized product (similar results see ref 10b).

Although the mechanism for this copper-catalyzed arylation needs further elaboration,[8] we favor the concerted single-electron-transfer pathway.[6] We conducted the reaction in the presence of a radical inhibitor, 2,2-diphenyl-1-picrylhydrazyl (DPPH, 3.0 equiv),[9] as well as *p*-dinitrobenzene (5.0 equiv)[10] and found that the arylation process was totally inhibited with starting material being recovered.

To demonstrate the usefulness of our new method, we next turned to the synthesis of selective butyrylcholinesterase

Scheme 3. Further Experiments for Copper-Catalyzed Arylation of *o*-Bromoanilide



inhibitor debromoflustramine B[11] and antibacterial agent debromoflustramine E.[12] Amide **7a** was subjected to the sequential arylation−alkylation reaction on a gram scale under our optimized conditions, and compound **8c** was obtained in 84% yield. Treatment of the key intermediate **8c** with HCl in methanol and 1,4-dioxane provided amine **17** ($C_{3a}S/C_{3a}R$ = 6:1). Formation of the HPI ring with a reductive amination and deprotection of the benzyl group with a Birch reduction afforded debromoflustramine E

(7) The C3a absolute configurations for **8c** and **8d** were established by the total synthesis of (−)-debromoflustramine B and (−)-pseudophrynaminol. (*S*)-(−)-*tert*-butanesulfinamide results in C3a-*S* configuration, while (*R*)-(+)-*tert*-butanesulfinamide leads to C3a-*R* configuration. The C3a absolute configurations (might require further experiments to confirm its absolute configurations) for compounds **8a**, **8b**, and **8e**−**h** were deduced by comparing with the sign of the specific rotations of **8c** and **8d**.

(8) We proposed a working hypotheses in the Supporting Information.

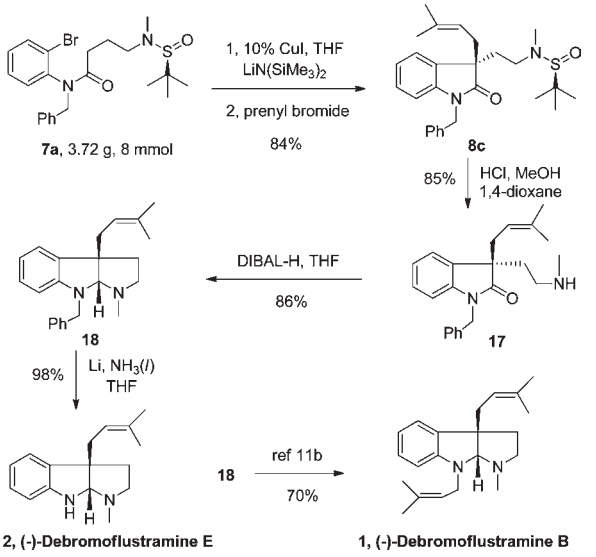
(9) Hristea, E. N.; Caproiu, M. T.; Pencu, G.; Hillebrand, M.; Constantinescu, T.; Balaban, A. T. *Int. J. Mol. Sci.* **2006**, *7*, 130.

(10) (a) Kornblum, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 734. (b) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480.

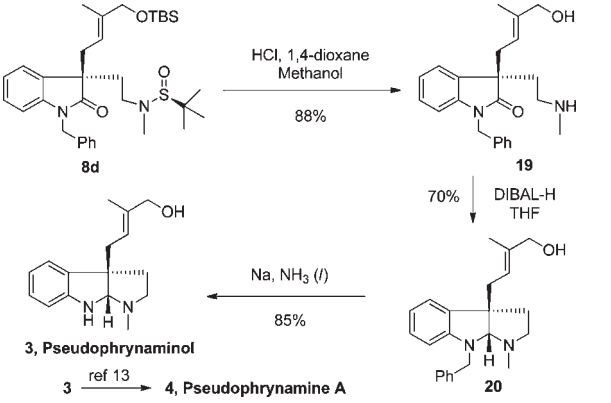
(11) For enantioselective syntheses of debromoflustramine B, see: (a) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543. (b) Cardoso, A. S.; Srinivasan, N.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2001**, *42*, 6663. (c) Morales-Ríos, M. S.; Rivera-Becerril, E.; Joseph-Nathan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2493. (d) Cardoso, A. S. P.; Marques, M. M. B.; Srinivasan, N.; Prabhakara, S.; Lobo, A. M. *Tetrahedron* **2007**, *63*, 10211. (e) Rivera-Becerril, E.; Joseph-Nathan, P.; Pérez-Álvarez, V. M.; Morales-Ríos, M. S. *J. Med. Chem.* **2008**, *51*, 5271. (f) Trost, B. M.; Zhang, Y. *Chem.—Eur. J.* **2011**, *17*, 2916.

(12) (a) Dix, A. V.; Meseck, C. M.; Lowe, A. J.; Mitchell, M. O. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2522. (b) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2007**, *48*, 1805.

Scheme 4. Total Synthesis of Debromoflustramine B and E



Scheme 5. Synthesis of Pseudophrynamine Alkaloids



(**2**, nine steps, 41% overall yield). Debromoflustramine B (**1**) was obtained by Birch reduction of compound **18** followed by *N*-alkylation with prenyl bromide[11b] (Scheme 4, nine steps, 29% overall yield).

Finally, the enantiomerically enriched pseudophrynamine alkaloid, namely pseudophrynaminol (**3**),[13] was synthesized from **8d** in 52% yield in three steps, and the pseudophrynamine (**4**) was thus synthesized in a formal sense (Scheme 5).[14]

In conclusion, we have developed a highly useful copper catalyzed intramolecular arylation-alkylation of *o*-bromoanilides.[15] On the basis of this method, a general synthetic strategy has been established for the synthesis of (−)-debromoflustramines B and E and pseudophrynamine alkaloids. We have also developed a ligand-free copper-catalyzed process for the synthesis of spirocyclic oxindoles and revealed a remote aza-assisted effect. These sequential reactions lead to the medicinally interesting oxindoles bearing a C_{3a} full quaternary carbon center in a flexible and practical way.[16] Currently, we are investigating the synthesis of other HPI alkaloids based on this new process and the utilization of other substrates (such as δ-amino *o*-bromoanilide and other less-activated alkylating reagents) in this copper-catalyzed reaction; the results will be reported in due course.

Acknowledgment. This work was supported by grants from the Natural Science Foundation of China (20925205, 20832005), National Basic Research Program of China (973 Program 2009CB522300), and Yunnan Provincial Science & Technology Department (2010GA014).

Supporting Information Available. Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) For syntheses and biological activity of pseudophrynaminol, see: (a) Mitchell, M. O.; Le Quesne, P. W. *Tetrahedron Lett.* **1990**, *31*, 2681. (b) Sun, W. Y.; Sun, Y.; Tang, Y. C.; Hu, J. Q. *Synlett* **1993**, 337. (c) Crich, D.; Pavlovic, A. B.; Samy, R. *Tetrahedron* **1995**, *51*, 6379. (d) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951. (e) Kawasaki, T.; Ogawa, A.; Takashima, Y.; Sakamoto, M. *Tetrahedron Lett.* **2003**, *44*, 1591.

(14) Cozzi, P. G.; Palazzi, C.; Potenza, D.; Scolastico, C.; Sun, W. Y. *Tetrahedron Lett.* **1990**, *31*, 5661.

(15) For reviews on metal-catalyzed α-arylation of carbonyl derivatives, see: (a) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (d) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821. For palladium catalyzed α-arylation-alkylation sequential reactions leading to racemic 3,3-disubstituted oxindoles, see ref 4 and (e) Li, P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 6396.

(16) For recent palladium-catalyzed enantioselective intramolecular α-arylation of *o*-bromoanilides, substrates are limited to *N*-(2-bromophenyl)-2-phenylacetamide derivatives. Only two examples without additional aromatic groups at the newly formed C3a full quaternary carbon centers were reported, with 40% (see ref 15d) and 70% (see ref 15e) ee values being observed, respectively; see: (a) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743. (b) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484. (c) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569. (d) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344. (e) Jia, Y.-X.; Katayev, D.; Bernardinelli, G.; Seidel, T. M.; Kündig, E. P. *Chem.—Eur. J.* **2010**, *16*, 6300. (f) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912. (g) Liu, L.; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666.

The authors declare no competing financial interest.