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Stereoselective Oxidative Rearrangement of 2-Aryl Tryptamine Derivatives

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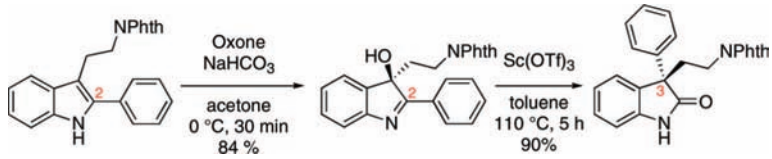
ABSTRACT



The oxidation of 2-aryl tryptamines followed by a stereoselective rearrangement provides a versatile strategy for the synthesis of C3-quaternary oxindoles bearing a C3-aryl group. Treatment of optically active 2-aryl hydroxyindolenines with scandium trifluoromethanesulfonate in toluene at 110 °C leads to complete and stereoselective isomerization to the corresponding C3-aryl oxindoles which represent versatile intermediates for the synthesis of C3a-aryl hexahydropyrroloindoles.

Hexahydropyrroloindole alkaloids constitute a large family of natural products.[1] They are isolated from a wide range of organisms and display an extensive array of biological activities, including anticancer and analgesic properties. Many of these alkaloids contain at least one diaryl quaternary stereogenic center at the junction of two tryptamine-derived fragments (Figure 1). Alkaloids exhibiting this substructure present fascinating molecular architectures and significant challenges for stereoselective total synthesis.[2] Herein we describe the stereoselective oxidative rearrangement of readily available 2-aryl tryptamines for the synthesis of 3-aryl-3-alkyl oxindoles, offering a versatile entry to the desired C3a-aryl-substituted hexahydropyrroloindole substructure found in many natural alkaloids.

Overman and co-workers have developed and successfully applied an elegant Pd-catalyzed intramolecular Heck cyclization reaction in their synthesis of 3-aryl-3-alkyl oxindoles en route to a number of complex hexahydropyrroloindole alkaloids.[2] We described a strategy for the simultaneous stereocontrolled introduction of vicinal quaternary (Csp^3−Csp^3) stereocenters via a Co-mediated reductive dimerization of C3a-halo hexahydropyrroloindoles.[3] As an outgrowth of these studies, we sought a general strategy for a late-stage stereocontrolled introduction

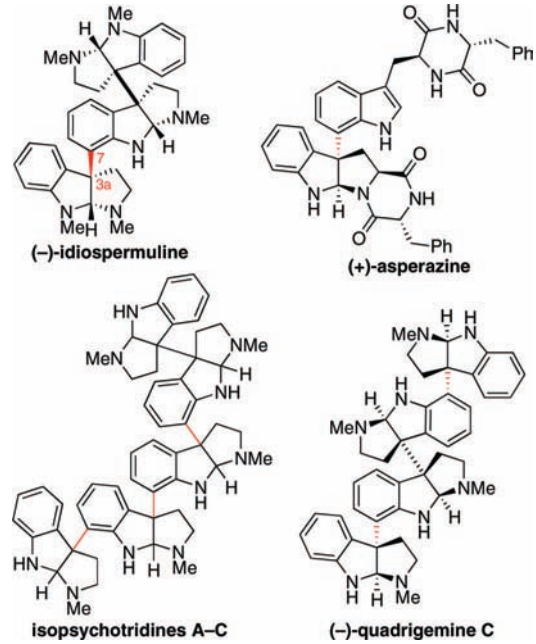


Figure 1. Representative hexahydropyrroloindole alkaloids.

(1) (a) Hino, T.; Nakagawa, M. *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. *Alkaloids Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: London, 1999; Vol. 13, pp 163−236.

(2) Steven, A.; Overman, L E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488.

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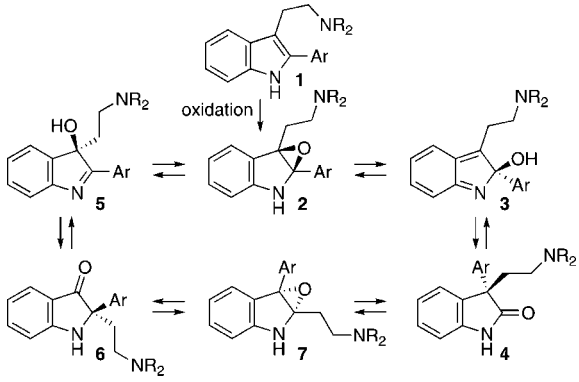
of the Csp^3-Csp^2 quaternary stereocenters found in related hexahydropyrroloindole alkaloids (Figure 1).[4] The oxidative rearrangement of 2,3-disubstituted indoles to the corresponding 3,3-disubstituted oxindoles enjoys a rich history.[5,6] However, only a few reported examples involve the migration of an aryl group.[5]

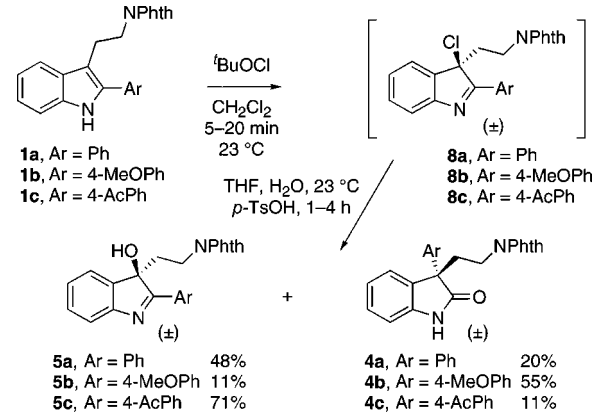
We envisioned that the oxidation of the 2-aryl tryptamine **1** would result in the desired oxindole **4** via the isomerization of intermediate **3** (Scheme 1). However, the involvement and

Scheme 1. Stereoselective Rearrangement of 2-Aryl Tryptamines

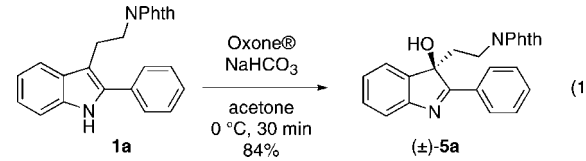


rearrangement of intermediate **5** would give the isomeric indoxyl **6**. For an effective application of this strategy in stereoselective hexahydropyrroloindole alkaloid synthesis, the selective formation of **4** over **6** upon oxidation of **1** would be required in addition to a high level of stereochemical control in the rearrangement of oxidized intermediates. The considerable literature precedent[6,7] for the efficient halogenative oxidation of 2,3-disubstituted indoles prompted our initial studies to rely on chlorination of 2-aryltryptamines. Oxidation of *N*-phthaloyl-2-phenyl tryptamine (**1a**, Scheme 2) with *t*-butyl hypochloride cleanly afforded the chloroindolenine **8a**. Removal of the volatiles and dissolution of a crude sample of **8a** in THF−water (9:1) followed by the addition of *p*-toluenesulfonic acid (15 equiv)[7] afforded the desired oxindole **4a** in 20% yield along with 48% of the hydroxylindolenine **5a** upon complete consumption of **8a**. Interestingly, formation of the oxindole derivative was favored (5:1, **4b**:**5b**) in the case of an electron-rich migrating C2-aryl group, while the hydroxyindolenine was favored (>6:1, **5c**:**4c**) when an electron-deficient C2-aryl group was involved (Scheme 2). Notably, the mass balance in these

Scheme 2. Oxidative Rearrangement of 2-Aryl Tryptamines



reactions was predominantly the corresponding indoxyl derivative (i.e., **6**, Scheme 1). Early observations led to the hypothesis that oxindoles **4a**−**c** were formed, at least in part, upon hydrolysis of **8a**−**c** followed by the rearrangement of hydroxyindolenines **5a**−**c**. Thus, we explored the direct conversion of 2-aryl tryptamines to the corresponding hydroxyindolenines. Under optimal conditions, substrate **1a** was oxidized with in situ generated dimethyldioxirane to afford **5a** in 84% yield (eq 1).



With efficient access to hydroxyindolenine **5a**, we focused on the development of optimal conditions for its isomerization to the desired oxindole **4a**. Treatment of **5a** with protic acid led to almost exclusive conversion to indoxyl **6a**, albeit with poor efficiency (Table 1, entry 1). Use of Lewis acids such as titanium tetrabutoxide and lithium perchlorate also promoted the rearrangement of **5a** to the indoxyl **6a** (Table 1, entries 2 and 3). Use of ytterbium, copper, zinc, and scandium trifluoromethanesulfonate all led to isomerization of **5a** to the desired indoxyl **4a** but with varying levels of efficiency. Notably, treatment of **5a** with copper or scandium trifluoromethanesulfonate in toluene at 110 °C led to exclusive isolation of **4a** upon complete consumption of starting material (Table 1, entries 5 and 9). Under optimal

(3) (a) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725. (b) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485.

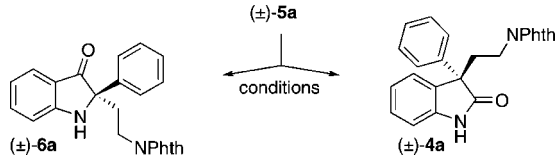
(4) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, *3*, 313.

(5) For examples of aryl migration, see: (a) Witkop, B.; Ek, A. *J. Am. Chem. Soc.* **1951**, *73*, 5664. (b) Evans, F. J.; Lyle, G. G.; Watkins, J.; Lyle, R. E. *J. Org. Chem.* **1962**, *27*, 1553. (c) Hishmat, O. H.; Abd-El Rahman, A. H.; El-Ebrashi, N. M. A.; Ishmail, M. M. F. *Chem. Ind. Med.* **1986**, *4*, 142.

(6) For elegant examples, please see: (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127, and references cited therein. (b) Lindel, T.; Bräuchle, L.; Golz, G.; Böhrer, P. *Org. Lett.* **2007**, *9*, 283. (c) Poriel, C.; Lachia, M.; Wilson, C.; Davies, J. R.; Moody, C. J. *J. Org. Chem.* **2007**, *72*, 2978. (d) Lachia, M.; Poriel, C.; Slawin, A. M. Z.; Moody, C. J. *Chem. Commun.* **2007**, 286. (e) Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623. (f) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (g) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (h) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867. (i) Awang, D. V. C.; Vincent, A.; Kindack, D. *Can. J. Chem.* **1984**, *62*, 2667. (j) Walser, A.; Blount, J. F.; Fryer, R. I. *J. Org. Chem.* **1973**, *38*, 3077. (k) Acheson, R. M.; Snaith, R. W.; Vernon, J. M. *J. Chem. Soc.* **1964**, 3229. (l) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871.

(7) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557.

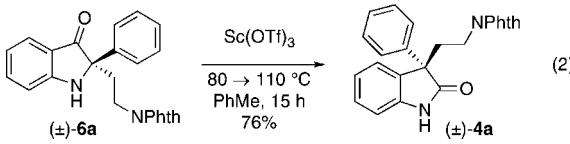
Table 1. Rearrangement of Hydroxyindolenine **5a**



entry	conditions	mol % (**5a**:**6a**:**4a**)[a]
1	HCl (1 equiv), THF−H_2O (9:1), 70 °C, 22 h	~90:10:0
2	Ti(O^tBu)$_4$ (1 equiv), PhMe, 110 °C, 12 h	85:15:0
3	$LiClO_4$ (3 equiv), THF, 70 °C, 24 h	89:11:0
4	Yb(OTf)$_3$ (1 equiv), PhMe, 110 °C, 24 h	0:17:83
5	Cu(OTf)$_2$ (1 equiv), PhMe, 110 °C, 3 h	0:0:100 (35%)[b]
6	Zn(OTf)$_2$ (1 equiv), PhMe, 110 °C, 24 h	0:31:69
7	Sc(OTf)$_3$ (1 equiv), PhMe, 23 °C, 4.3 h	(18:56:18)[c]
8	Sc(OTf)$_3$ (0.25 equiv), PhMe, 110 °C, 19 h	0:15:85
9	*Sc(OTf)$_3$ (1 equiv), PhMe, 110 °C, 5 h*	*0:0:100 (90%)*[b]
10	Sc(OTf)$_3$ (1 equiv), MeCN, 82 °C, 5 h	0:60:40
11	Sc(OTf)$_3$ (1 equiv), DMF, 120 °C, 5 h	36:64:0

[a] Ratios determined by ^{1}H NMR. [b] Isolated yield of (±)-**4a**. [c] Ratio of isolated compounds (instead of mol %).

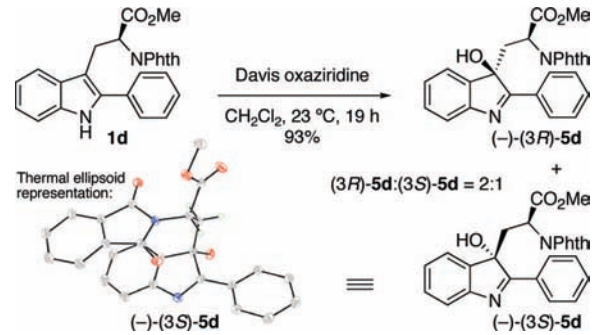
conditions, the use of stoichiometric quantities of scandium trifluoromethanesulfonate afforded the desired product in 90% isolated yield (Table 1, entry 9).[8] Using a substoichiometric amount of scandium trifluoromethanesulfonate or lower reaction temperatures led to slower conversion to **4a**. Interestingly, treatment of **5a** with stoichiometric quantities of scandium trifluoromethanesulfonate at 23 °C predominantly afforded the indoxyl **6a** after 4.3 h (Table 1, entry 7). Similarly, replacement of toluene with acetonitrile or dimethylformamide as the solvent principally gave indoxyl **6a** after 5 h. Significantly, heating the indoxyl **6a** with scandium trifluoromethanesulfonate in toluene over 15 h cleanly provided the oxindole **4a** in 76% yield (eq 2).[9]



(2)

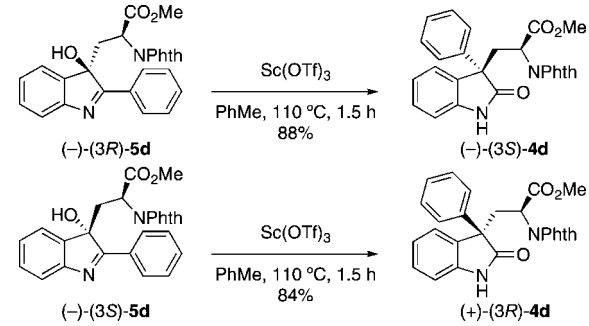
With optimized conditions for the desired rearrangement of hydroxyindolenines to the corresponding oxindoles at hand, we probed the stereochemical course of this interesting transformation. The 2-phenyl L-tryptophan derivative **1d** served as a versatile system to explore this chemistry. The oxidation of 2-phenyl indole **1d** with Davis' oxaziridine[10,11] afforded a 2:1 mixture of diastereomeric hydroxyindolenines (−)-(3*R*)-**5d** and (−)-(3*S*)-**5d**, respectively, in 93% combined yield (Scheme 3). The diastereomers were separated, and the stereochemistry of the minor diastereomer (−)-(3*S*)-**5d** was established by X-ray crystallography (Scheme 3).

Scheme 3. Oxidation of 2-Phenyl L-Tryptophan Derivative **1d**



Treatment of diastereomerically pure samples of hydroxyindolenines (−)-(3*R*)-**5d** and (−)-(3*S*)-**5d** with one equivalent of scandium trifluoromethanesulfonate in refluxing toluene for 1.5 h afforded the corresponding oxindoles (−)-(3*S*)-**4d** and (+)-(3*R*)-**4d**, respectively (Scheme 4). Importantly, this completely stereoselective isomerization occurs efficiently with both diastereomeric hydroxyindolenines and suggests a process without ionization or dehydration of intermediates (e.g., **3** or **5**).

Scheme 4. Completely Stereoselective Rearrangement of 2-Phenyl Hydroxyindolenines (−)-(3*R*)-**5d** and (−)-(3*S*)-**5d**



The relative stereochemistry of oxindole (−)-(3*S*)-**4d** was confirmed by its chemical derivatization to the lactam (+)-**9** (Scheme 5). The treatment of (−)-(3*S*)-**4d** with hydrazine provided the corresponding free amine. Warming of the

(8) While control experiments revealed no product inhibition by either the indoxyl or the oxindole products, we prefer the use of stoichiometric quantities of scandium trifluoromethanesulfonate to accelerate the overall rate of conversion to the desired product (compare entries 8 and 9, Table 1).

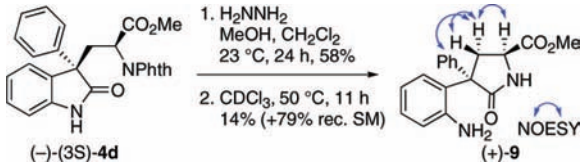
(9) For an important observation with a dialkyl indoxyl, see: (a) Güller, R.; Borscheberg, H. *Tetrahedron: Asymmetry* **1992**, *3*, 1197. (b) Güller, R.; Borscheberg, H. *Tetrahedron Lett.* **1994**, *35*, 865; notably, heating **5a** under these conditions (BF_3•OEt_2) led to decomposition. (c) Sheehan, J. C.; Frankenfeld, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 4792.

(10) For 3-*n*-butyl-1,2-benzisothiazole-1,1-dioxide oxide, see: Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254. Use of this reagent generally resulted in cleaner reaction mixtures than those observed with in situ generated DMDO.

(11) (a) Grubbs, A. W.; Artman, G. D.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2257. (b) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

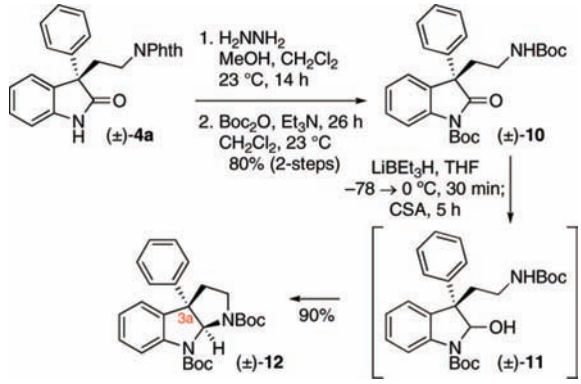
resulting amine in chloroform led to slow intramolecular transamidation to lactam (+)-**9**. The stereochemistry of (+)-**9** was secured using NOESY experiments and was found to be consistent with that originating from the oxindole (−)-(3*S*)-**4d**.

Scheme 5. Derivatization and Stereochemical Assignment of **4d**



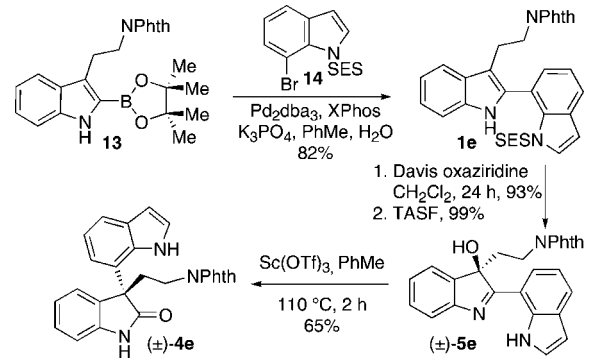
The oxindoles prepared above serve as versatile precursors to the corresponding hexahydropyrroloindole derivatives bearing a C3a-aryl substituent. This is illustrated by the conversion of oxindole **4a** to the corresponding hexahydropyrroloindole **12** (Scheme 6). The desired imide **10** was prepared in two steps from oxindole **4a** in 80% overall yield. Reduction[12] of the oxindole **10** followed by treatment of the resulting hemiaminal **11** with camphorsulfonic acid gave the desired C3a-phenyl hexahydropyrroloindole **12** in 90% yield.

Scheme 6. Synthesis of C3a-Phenyl Hexahydropyrroloindole **12**



The stereoselective rearrangement of optically active hydroxyindolenines (3*R*)-**5d** and (3*S*)-**5d** to the corresponding C3-aryl−C3-alkyl oxindoles (3*S*)-**4d** and (3*R*)-**4d**, respectively (Scheme 4), in addition to the synthesis of C3a-aryl hexahydropyrroloindole **12** from oxindole **4a** (Scheme 6) prompted an investigation into the potential use of this chemistry in the conversion of bisindoles to the desired C3-(7-indolyl)oxindoles of interest. The requisite bisindole **1e** was readily prepared via a Pd-catalyzed cross-coupling reaction as shown in Scheme 7.[13] Oxidation of **1e** followed by unraveling of the indolyl fragment upon treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[14] provided the hydroxyindolenine **5e** and set the stage for the planned isomerization. Treatment of 2-(7-indolyl)-3-hydroxyindolenine **5e** with scandium trifluoromethanesulfonate in toluene at 110 °C for 2 h afforded the desired 3-(7-indolyl)oxindole **4e** in 65% isolated yield.[15] The complete conversion of hydroxyindolenine **5e**, as well as the corresponding indoxyl derivative,[15,16] to the desired oxindole **4e** is noteworthy.

Scheme 7. Synthesis of the C3a-(7-Indolyl)-oxindole (±)-**4e**



The chemistry described here offers a general strategy for the stereocontrolled synthesis of C3a-aryl substituted hexahydropyrroloindoles, a common substructure found in various natural alkaloids. Importantly, the completely stereoselective conversion of optically active hydroxylindolenine to the corresponding oxindoles (Scheme 4) and the facile and complete conversion of indoxyls to the desired oxindoles, combined with advances in catalytic asymmetric oxidation chemistry,[17] offer tremendous potential for application in asymmetric synthesis of complex alkaloids. Further development and application of this chemistry will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for key compounds in addition to crystallographic data for compound (−)-(3*S*)-**5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468. (b) Govek, S. P.; Overman, L. E. *Tetrahedron* **2007**, *63*, 8499.

(13) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.

(14) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

(15) Shortening of the reaction time to 1 h led to isolation of the desired **4e** along with the corresponding 2-(7-indolyl)-2-(2-phthalimido-ethyl)indoxyl (**S6e**) in 97% yield (**4e**:**S6e**, 84:16).

(16) Please see Supporting Information for details.

(17) For representative examples, see: (a) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759, and references therein. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.