

Indole Synthesis Based On A Modified Koser Reagent**

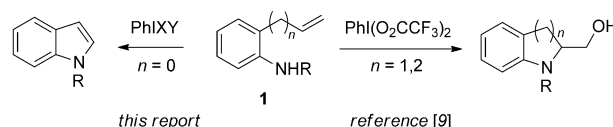
Laura Fra, Alba Millán, José A. Souto, and Kilian Muñiz*

Abstract: A new metal-free method for the rapid and productive preparation of indoles has been developed. This process is based on sterically congested hypervalent iodine compounds of the family of Koser reagents, and iodosobenzene in combination with 2,4,5-tris-isopropylbenzene sulfonic acid provides the highest yields and fastest reaction times. This reagent alone promotes the chemoselective oxidative cyclization of 2-amino styrenes to indoles in high yields under mild conditions.

Indoles constitute privileged structures in natural products, as well as in medicinal and biological chemistry.^[1] Starting with the seminal synthesis by Emil Fischer,^[2] synthetic access to this class of compounds has received huge attention for more than 130 years, and numerous routes to their synthesis have become available.^[1,3] Important contributions from recent years are based on innovative transition-metal-catalyzed transformations.^[4,5] A particularly useful reaction in the area has been the oxidative cyclization of 2-vinyl anilines to indoles. This reaction has been a hallmark in the area of palladium catalysis.^[6]

The development of the corresponding metal-free oxidation reaction would be an important addition to the field of indole synthesis, given the particular purity requirements in the areas of biological and medicinal chemistry. In view that such a reaction is notably absent, we started to explore the synthetic basis for the realization of such a process using hypervalent iodine reagents as sole oxidants.^[7] For example, the corresponding intramolecular cyclization reactions are available for carbazole synthesis from 2-amino biphenyls.^[8] Though conceptually related, the switch from aromatic amination in these cases to the required amination of an alkene represents a significantly more challenging process to pursue.

Important intramolecular amination reactions of alkenes were developed by Domínguez. These reactions are characterized by the use of iodosobenzene bis(trifluoroacetate) (PhI(O₂CCF₃)₂, PIFA) as an efficient oxidant (Scheme 1).^[9] An initial interaction between an amino group and this



Scheme 1. Intramolecular alkene amination with hypervalent iodine(III) reagents.

reagent has been suggested to generate a cationic nitrogen atom, which is subsequently attacked by the alkene to initiate the intramolecular amination. While this concept has proven extremely versatile for the intramolecular synthesis of a large series of nitrogen heterocycles,^[10,11] it is surprising to note that the notable class of indoles has so far precluded this approach. We herein present the successful realization of such an approach of indole synthesis through a hypervalent iodine(III) mediated oxidation of 2-vinyl anilines.^[12]

The reaction was developed exploring the potential of different hypervalent iodine compounds to promote the intramolecular cyclization of various 2-vinyl anilines. In order to introduce a standard substituent at nitrogen, *N*-Cbz-protected 2-vinyl aniline **1a** was employed as standard substrate (Table 1). This compound was found to deliver the desired indole **2a** upon exposure to several hypervalent iodine reagents, although yields remained low. Examples of this initial screening include iodosobenzene diacetate (Table 1, entry 1), PIFA (entry 2), and combinations of the former with Brønsted acids (entries 3 and 4). While these reactions resulted only in low yields of the desired isolated product **2a**, the use of Koser's reagent ([[(hydroxy)-(tosyloxy)iodo]benzene, Table 1, entry 5)^[13] gave the product in 55% yield together with some unidentified side products. The yield could be further increased by using chloroform as the solvent (Table 1, entry 6). An in situ formation^[13a] of the active reagent from iodosobenzene and 4-toluene sulfonic acid gave the same result (Table 1, entry 7). Formation of related Koser reagents with different steric arrangements at the aryl group of the sulfonic acid, as in 2,4,6-tris-isopropylbenzene sulfonic acid (**A**) and 2,4,5-tris-isopropylbenzene sulfonic acid (TIPBSA, **B**) led to the identification of the latter as an efficient promoter (Table 1, entries 8 and 9, respectively). For this optimum combination of PhIO and **B**, the reaction time could be lowered to 1 h without loss of yield (Table 1, entry 10).

This reagent combination also promotes the indole cyclization from related *N*-carbamoyl precursors such as the methyl carbamate **1b** and the Fmoc derivative **1c**. To a certain extent, a benzoyl group is also tolerated (Table 1, entries 11–13). Because of the acidic conditions, the Boc group is beyond the scope of the present transformation (Table 1, entry 14), as

[*] L. Fra, Dr. A. Millán, Dr. J. A. Souto, Prof. Dr. K. Muñiz
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: kmuniz@icq.es

Prof. Dr. K. Muñiz
Catalan Institution for Research and Advanced Studies (ICREA)
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

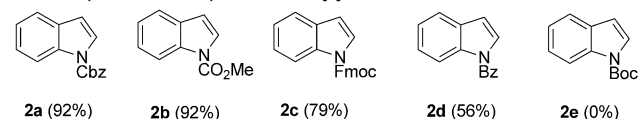
[**] The authors thank the Fundación ICIQ and the Spanish Ministerio de Economía (CTQ2011-25027) for financial support. L.F. and A.M. thank the Ministerio de Economía y Competitividad and Universidad de Granada for respective fellowships.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201402661>.

Table 1: Optimization of reaction conditions.^[a]

Entry	Protecting Group	Iodine(III)	Acid	Solvent	Product	Yield [%] ^[b]
1	Cbz (1a)	PhI(OAc) ₂	—	CH ₂ Cl ₂	2a	22
2	Cbz (1a)	PIFA	—	CH ₂ Cl ₂	2a	14
3	Cbz (1a)	PhI(OAc) ₂	<i>p</i> -TsOH	CH ₂ Cl ₂	2a	31
4	Cbz (1a)	PhI(OAc) ₂	TfOH	CH ₂ Cl ₂	2a	13
5	Cbz (1a)	PhI(OH)(OTs)	—	CH ₂ Cl ₂	2a	55
6	Cbz (1a)	PhI(OH)(OTs)	—	CHCl ₃	2a	64
7	Cbz (1a)	PhIO	<i>p</i> -TsOH	CHCl ₃	2a	64
8	Cbz (1a)	PhIO	A	CHCl ₃	2a	65
9	Cbz (1a)	PhIO	B	CHCl ₃	2a	92
10 ^[c]	Cbz (1a)	PhIO	B	CHCl ₃	2a	92
11 ^[c]	CO ₂ Me (1b)	PhIO	B	CHCl ₃	2b	92
12 ^[c]	Fmoc (1c)	PhIO	B	CHCl ₃	2c	79
13 ^[c]	Bz (1d)	PhIO	B	CHCl ₃	2d	56
14	Boc (1e)	PhIO	B	CHCl ₃	2e	—
15	H (1f)	PhIO	B	CHCl ₃	2f	—

[a] Boc = *tert*-butoxycarbonyl, Bz = benzoyl, Cbz = benzyloxycarbonyl, Fmoc = fluorenylmethoxycarbonyl, PG = protecting group, TfOH = trifluoromethanesulfonic acid, TsOH = *p*-toluenesulfonic acid. [b] Yield of isolated product after purification. [c] Reaction time of 1 h.



it suffers rapid degradation to the free aniline, which does not engage in indole formation (Table 1, entry 15), but rather suffers from unspecific oxidative degradation.^[14]

It is an important observation that under the optimized conditions, the oxidative cyclization of **1a** with the PhIO/TIPBSA reagent combination benefits from an unprecedented high rate. Figure 1 displays the result of an NMR study

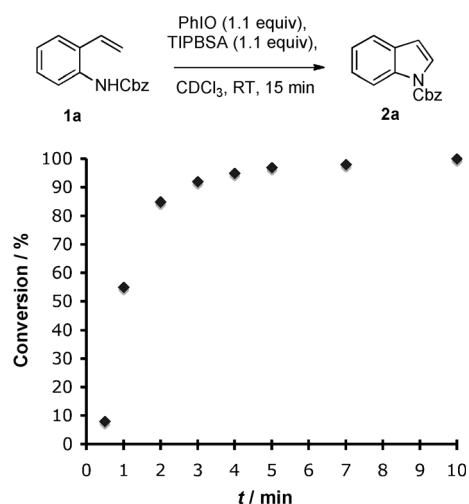
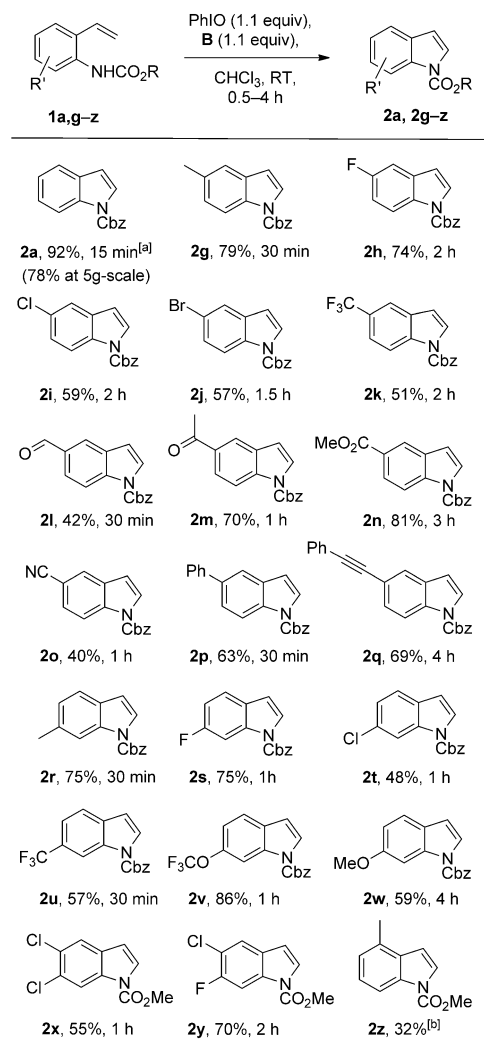


Figure 1. Kinetic profile for formation of indole **2a** from **1a**.

that suggests that for the parent compound **1a**, oxidation to indole **2a** is complete within ten minutes at room temperature.

Under the optimized conditions shown in Table 1, a series of different precursors could be conveniently cyclized to the corresponding indoles. A total of 21 different products are presented in Scheme 2. Examples include the synthesis of

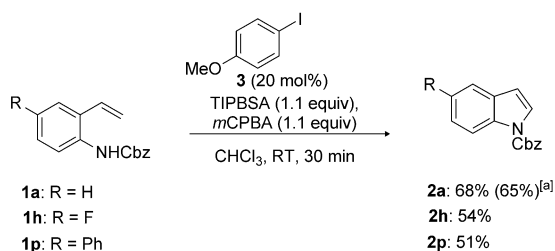


Scheme 2. Substrate scope for the metal-free indole synthesis with PhIO/B (yield of isolated product after purification). [a] Reaction time until consumption of all starting materials (control by TLC). [b] PIFA (1.1 equiv), CHCl₃, 0°C, 24 h.

several five-substituted indoles **2g–k** with alkyl and halide substituents and the related 5-carbonyl substituted products **2l–o**, including a formyl group (**2l**) that proved reasonably stable under the strong oxidation conditions. Other carbon substituents, such as phenyl and phenylacetylenyl, were also found to be fully compatible with the reaction conditions (compounds **2p,q**). Related substitution patterns were also tolerated for the synthesis of 6-functionalized indoles **2r–w**, including again alkyl, halide, and alkoxy substituents. The general reaction conditions were also found to be applicable

to the 5,6-disubstituted derivatives **2x** and **2y**. This demonstrates a rapid and highly productive reaction with a broad substrate scope that surpasses related ones from metal-mediated processes. For **1a**, the reaction could be conveniently conducted at a 5 g scale (78% yield). A certain limitation was found for the synthesis of 4-methyl indole **2z**. The cyclization with the PhIO/TIPBSA reagent combination was slow, probably as a result of steric hindrance; a faster conversion was achieved with the more reactive PIFA as the hypervalent iodine oxidant.

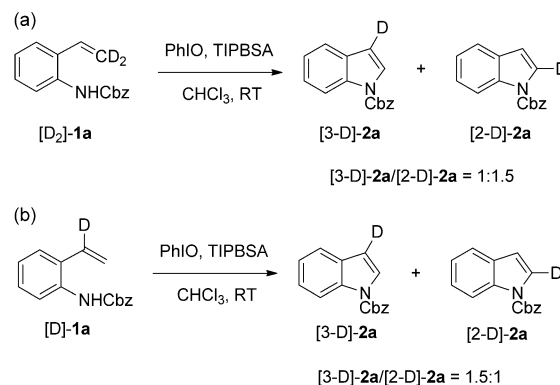
The present oxidative indole cyclization could also be realized using a catalytic amount of an aryl iodine catalyst with a stoichiometric amount of the sulfonic acid TIPBSA and in the presence of *meta*-chloroperbenzoic acid (*m*CPBA) as terminal oxidant (Scheme 3).^[15,16] An extensive screening



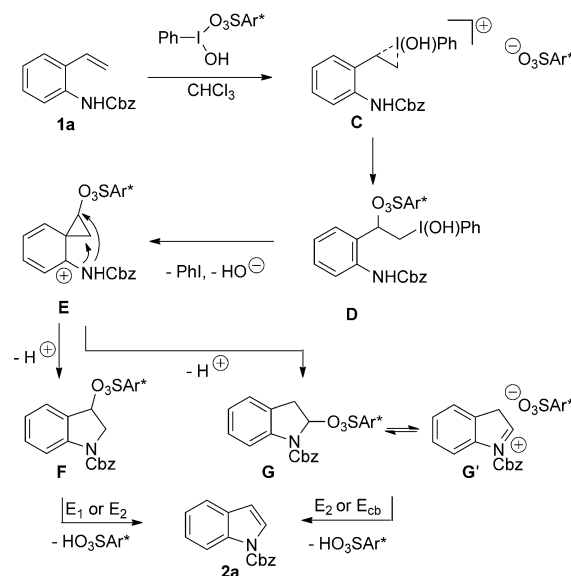
Scheme 3. Indole formation in the presence of a catalytic amount of **3**. [a] Reaction time of 6 h with 0.3 equivalents of TIPBSA.

of the ideal catalyst showed the more electron-rich 4-methoxyiodobenzene to give the best results.^[14] Under optimized conditions, this compound catalyzes the oxidation of **1a** to indole **2a** within 30 min and with a yield of 68% of isolated product. The reaction works equally well in the presence of 30 mol % of TIPBSA, although a longer reaction time of 6 h is required (65% yield of isolated **2a**). Related reactions with **1h** and **1p** gave comparable yields of 54 and 51%, respectively. In view of the extraordinary productivity of the stoichiometric reaction from Scheme 2, the catalytic version is slightly less efficient.^[17]

The reaction mechanism is more complex than expected. Control experiments with selectively deuterated compounds [D₂]-**1a** and [D]-**1a** show partial migration of the deuterium label throughout the course of indole formation (Scheme 4).^[18] Obviously, such a reaction outcome renders an oxidation of the carbamate nitrogen^[10] mediated by hypervalent iodine highly improbable. On the basis of electronic studies^[14] and literature precedence, we propose the following mechanism (Scheme 5): The reaction is initiated through an interaction between the modified Koser reagent and the alkene group of **1a**, leading to an alkene-iodine(III) adduct **C** and then to the 1,2-iodooxygenated intermediate **D**. Such a sequence is known from styrene dioxygenation with related Koser reagents.^[19] The same process had been invoked for related intramolecular oxidation reactions of alkenes that bear a methyl carbamate, although these transformations were only discussed within a review article.^[13c] 1,2-Iodooxygenated products from styrene oxidation can be stabilized by a neighboring phenyl group through the formation of a cyclo-



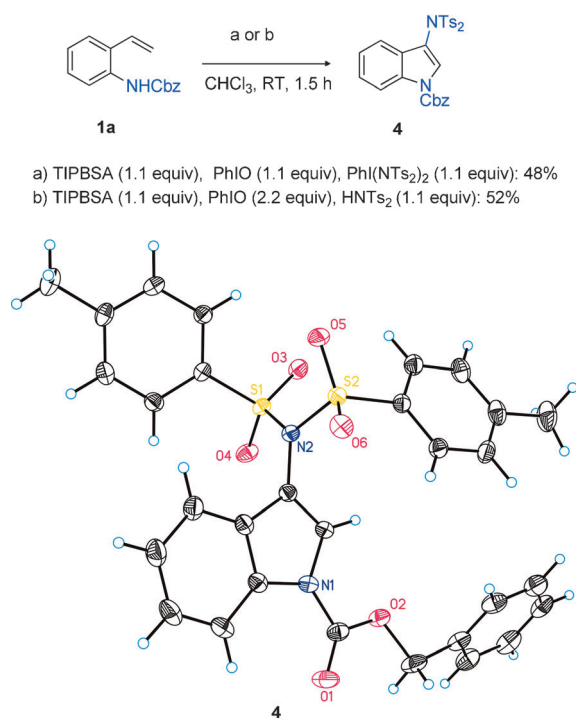
Scheme 4. Control experiments using selectively deuterated derivatives of **1a**.



Scheme 5. Proposal of a mechanism for the formation of **2a** from **1a**.

propyl phenonium ion. Such phenonium ion intermediates in the oxidation of styrene derivatives with hypervalent iodines have ample precedence.^[20] In the present case, the phenonium ion **E** receives stabilization through the amino group. The subsequent opening of the spiro-cyclopropyl ring in **E** should be feasible at two positions: attack at the methylene position will result in the formation of 3-oxygenated indoline **F**, which should undergo a rapid aromatization to form indole product **2a**. Alternatively, ring opening at the oxygenated carbon atom will provide a 2-oxygenated indoline **G** and/or the corresponding iminium derivative **G'**. Again, elimination of the arylsulfonic acid generates the final indole **2a**. This mechanism explains the observed deuterium scrambling as the result of the different pathways at stage **E**. The observed 1.5:1 ratio of the deuterium-labelling experiments suggests some preference for the former pathway through **F**, which potentially is due to steric reasons.^[21]

In view that the cyclization toward the indole core represents an extremely fast process, we explored a possible sequential oxidation process by combining two different



Scheme 6. Sequential metal-free amination reactions using defined iodine(III) oxidants. Crystal structure of **4** (thermal ellipsoids at 50% probability).

iodine(III) oxidants. Indeed, when substrate **1a** was oxidized in the presence of an equimolar amount of the iodosobenzene/TIPBSA reagent and our previously described aminating reagent PhI(NTs₂)₂,^[22] a clean two-fold oxidative aminating event took place.^[14] Apparently, the modified Koser reagent exercised a kinetic dominance over the potentially competing second hypervalent iodine reagent, which in turn engaged in the subsequent position-selective 3-amination of the cyclized indole **2a** to give the final product **4** from two independent metal-free amination reactions in 48% yield (Scheme 6).^[23,24] The reaction could also be conducted with iodosobenzene as the sole oxidant by adding TIPBSA and bistosylimide for the two individual amination reactions (52% yield). This observation demonstrates the robustness of the initial indole cyclization and exemplifies the exciting synthetic possibilities that may result by its combination with other oxidation processes.

In summary, we have extended the family of iodine(III)-mediated intramolecular aminations of alkenes to the corresponding synthesis of indoles from 2-vinyl anilines. The reaction employs a modified Koser reagent that is generated from sterically congested 2,4,5-tris-isopropylbenzene sulfonic acid and an iodosobenzene, either in stoichiometric amounts or as catalyst together with *m*CPBA as terminal oxidant. This reaction complements related transition-metal catalyses and broadens the synthetic possibilities of metal-free amination methodology.

Experimental Section

Iodosobenzene (61 mg, 0.275 mmol) and 2,4,5-tris-isopropylbenzene sulfonic acid (78 mg, 0.275 mmol) were added to a stirred solution of the 2-vinyl aniline **1a** (63 mg, 0.25 mmol) in CHCl₃ (3 mL). After 15 min, the reaction was quenched with pyridine (22 μL, 0.275 mmol) and all volatile material was removed under reduced pressure. The crude reaction product was purified by column chromatography (neutral alumina, *n*-hexane/ethylacetate, 98/2, v/v) to give Cbz-protected indole **2a** (58 mg, 0.23 mmol, 92%).

Received: February 24, 2014

Revised: March 21, 2014

Published online: May 28, 2014

Keywords: amination · catalysis · hypervalent iodine · indole · oxidation

- [1] R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**.
- [2] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241; b) B. Robinson, *Chem. Rev.* **1963**, *63*, 373.
- [3] a) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195; b) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29; c) S. A. Patil, R. Patil, D. D. Miller, *Curr. Med. Chem.* **2011**, *18*, 615; d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *21*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.
- [4] Selected reviews: a) Z. Shi, F. Glorius, *Angew. Chem.* **2012**, *124*, 9354; *Angew. Chem. Int. Ed.* **2012**, *51*, 9220; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215; c) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469; S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641; d) J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem. Asian J.* **2009**, *4*, 1036.
- [5] Selected examples: a) M. Peña-López, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 1818; b) L. Zheng, R. Hua, *Chem. Eur. J.* **2014**, *20*, 2352; c) D. Zhao, Z. Shi, F. Glorius, *Angew. Chem.* **2013**, *125*, 12652; *Angew. Chem. Int. Ed.* **2013**, *52*, 12426; d) C. Wang, Y. Huang, *Org. Lett.* **2013**, *15*, 5294; e) S. Maity, N. Zheng, *Angew. Chem.* **2012**, *124*, 9700; *Angew. Chem. Int. Ed.* **2012**, *51*, 9562; f) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098; g) A. Varela-Fernández, J. A. Varela, C. Saá, *Synthesis* **2012**, 3285; h) T. W. Liwosz, S. R. Chemler, *Chem. Eur. J.* **2013**, *19*, 12771; i) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2010**, *132*, 11416; j) D. Tselikhovsky, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14048; k) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 4642; *Angew. Chem. Int. Ed.* **2009**, *48*, 4572; l) R. Bernini, G. Fabrizi, A. Sferazza, S. Cacchi, *Angew. Chem.* **2009**, *121*, 8222; *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; m) Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2010**, *46*, 2823; n) G. Shore, S. Morin, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 1351; o) M. Shen, B. S. Leslie, T. G. Driver, *Angew. Chem.* **2008**, *120*, 5134; *Angew. Chem. Int. Ed.* **2008**, *47*, 5056; p) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500; q) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 1551; *Angew. Chem. Int. Ed.* **2007**, *46*, 1529; r) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276; s) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610.
- [6] a) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800; b) L. S. Hegedus, P. M. Winton, S. Varaparthi, *J. Org. Chem.* **1981**, *46*, 2215; c) P. J. Harrington, L. S. Hegedus, *J. Org. Chem.* **1984**, *49*, 2657; d) A. Kasahara, T. Izumi, H. Yanai, S. Murakami, A. Yusa, H. Kon, T. Kikuchi, S. Tsuda, N. Kudo, M. Takatori, T. Nikaido, *Bull. Yamagata Univ.* **1986**, *19*, 39; e) P. J. Harrington, L. S. Hegedus, K. F. McDaniel, *J. Am.*

- Chem. Soc.* **1987**, *109*, 4335; R. C. Larock, T. R. Hightower, L. A. Hasvold, K. P. Peterson, *J. Org. Chem.* **1996**, *61*, 3584; See also: T. Izumi, Y. Nishimoto, K. Kohei, A. Kasahara, *J. Heterocycl. Chem.* **1990**, *27*, 1419.
- [7] a) V. V. Zhdankin, *Hypervalent Iodine Chemistry Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester, **2013**; b) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299.
- [8] a) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605; b) S. H. Cho, J. Yoo, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996.
- [9] A. Correa, I. Tellitu, E. Domínguez, R. SanMartin, *J. Org. Chem.* **2006**, *71*, 8316.
- [10] I. Tellitu, E. Domínguez, *Trends Heterocycl. Chem.* **2011**, *15*, 23.
- [11] For the application of this concept in the indole synthesis from 3-aryl enamines: a) Y. Du, R. Liu, G. Linn, K. Zhao, *Org. Lett.* **2006**, *8*, 5919; b) W. Yu, Y. Du, K. Zhao, *Org. Lett.* **2009**, *11*, 2417; c) X. Li, Y. Du, Z. Liang, X. Li, Y. Pan, K. Zhao, *Org. Lett.* **2009**, *11*, 2643.
- [12] For alternative prominent indole syntheses from anilines under metal-free conditions: a) A. Bischler, *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2860; b) R. Möhlau, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 171; c) P. G. Gassman, T. J. van Bergen, G. Gruetzmacher, *J. Am. Chem. Soc.* **1973**, *95*, 6508; d) P. G. Gassman, T. J. van Bergen, D. P. Gilbert, B. W. Cue, Jr., *J. Am. Chem. Soc.* **1974**, *96*, 5495; e) T. Sugawara, M. Adachi, K. Sasakura, A. Kitagawa, *J. Org. Chem.* **1979**, *44*, 578; f) for an approach from nitro arenes: G. Bartoli, G. Palmieri, M. Bosco, R. Dalpozzo, *Tetrahedron Lett.* **1989**, *30*, 2129.
- [13] a) G. F. Koser, R. H. Wettach, J. M. Troup, B. A. Frenz, *J. Org. Chem.* **1976**, *41*, 3609; b) M. S. Yusubov, T. Wirth, *Org. Lett.* **2005**, *7*, 519; c) R. M. Moriarty, R. K. Vaid, G. F. Koser, *Synlett* **1990**, 365.
- [14] Please see Supporting Information for details.
- [15] a) R. D. Richardson, T. Wirth, *Angew. Chem.* **2006**, *118*, 4510; *Angew. Chem. Int. Ed.* **2006**, *45*, 4402; b) M. Ochiai, K. Miyamoto, *Eur. J. Org. Chem.* **2008**, 4229; c) M. Ochiai, *Chem. Rec.* **2007**, *7*, 12; d) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073; e) M. Uyanik, K. Ishihara, *Chem. Commun.* **2009**, 2086.
- [16] a) E. A. Merritt, V. M. T. Carneiro, L. F. Silva Jr., B. Olofsson, *J. Org. Chem.* **2010**, *75*, 7416; b) Y. Yamamoto, H. Togo, *Synlett* **2006**, 798; c) A. Tanaka, K. Moriyama, H. Togo, *Synlett* **2011**, 1853.
- [17] It also bears no environmental advantage, as the stoichiometric amount of iodobenzene from the stoichiometric reaction is replaced by 3-chlorobenzoic acid in the catalytic version.
- [18] While this scrambling of the alkene substituent currently prevents the use of higher-substituted alkenes, the present approach toward 2,3-unsubstituted indoles should be considered synthetically noteworthy. Usually, alternative methodologies^[12] generate the corresponding 2- or 3-substituted indoles, from which the parent indole cores are not accessible any longer.
- [19] a) G. F. Koser, L. Rebrovic, R. H. Wettach, *J. Org. Chem.* **1981**, *46*, 4324; b) N. S. Zefirov, V. V. Zhdankin, Y. V. Dan'kov, V. D. Sorokin, V. N. Semerikov, A. S. Kožmin, R. Caple, B. A. Berglund, *Tetrahedron Lett.* **1986**, *27*, 3971; c) U. H. Hirt, B. Spingler, T. Wirth, *J. Org. Chem.* **1998**, *63*, 7674; d) T. Wirth, U. H. Hirt, *Tetrahedron: Asymmetry* **1997**, *8*, 23; e) U. H. Hirt, M. F. H. Schuster, A. N. French, O. G. Wiest, T. Wirth, *Eur. J. Org. Chem.* **2001**, 1569; f) A. C. Boye, D. Meyer, C. K. Ingison, A. N. French, T. Wirth, *Org. Lett.* **2003**, *5*, 2157; g) Y.-B. Kang, L. H. Gade, *J. Am. Chem. Soc.* **2011**, *133*, 3658; h) G. F. Koser, *Top. Curr. Chem.* **2003**, *208*, 137.
- [20] See ref. [19e] and a) Review: F. V. Singh, T. Wirth, *Synthesis* **2013**, 2499; b) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem.* **2013**, *125*, 7156; *Angew. Chem. Int. Ed.* **2013**, *52*, 7018; c) A. Citterio, M. Gandolfi, C. Giordano, G. Castaldi, *Tetrahedron Lett.* **1985**, *26*, 1665; See also: d) I. Tellitu, E. Domínguez, *Tetrahedron* **2008**, *64*, 2465; e) A. Ahmad, P. Scarassati, N. Jalalian, B. Olofsson, L. F. Silva, Jr., *Tetrahedron Lett.* **2013**, *54*, 5818.
- [21] A less-hindered sulfonic acid leads to formation of a 1:1 mixture.^[14]
- [22] a) J. A. Souto, C. Martínez, I. Velilla, K. Muñiz, *Angew. Chem.* **2013**, *125*, 1363; *Angew. Chem. Int. Ed.* **2013**, *52*, 1324; b) C. Röben, J. A. Souto, Y. González, A. Lishchynskiy, K. Muñiz, *Angew. Chem.* **2011**, *123*, 9650; *Angew. Chem. Int. Ed.* **2011**, *50*, 9478; c) C. Röben, J. A. Souto, E. C. Escudero-Adán, K. Muñiz, *Org. Lett.* **2013**, *15*, 1008.
- [23] CCDC 987831 (4) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [24] For the only other 3-amination of indoles using NFSI (*N*-fluorobenzenesulfonimide) under basic conditions, see: H.-H. Liu, Y. Wang, G. Deng, L. Yang, *Adv. Synth. Catal.* **2013**, *355*, 3369.