Indole Synthesis via Sequential Electrophilic N-H and C-H Bond Activation using Iodine(III) Reactivity

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Dedicated to Professor Ángel R. de Lera on the occasion of his 60th birthday.

Abstract: An intramolecular approach towards the regioselective construction of 2,3-diarylated indoles is reported. The reaction follows an intramolecular approach of an electrophilic N-H and C-H bond functionalization between an aniline and an acetylene. It employs the concept of a traceless tether to provide access to the free 2,2-diarylated indole products comprising a total of 18 examples. Hypervalent iodine reagents were identified as suitable promoters and four different protocols are provided including stoichiometric and catalytic transformations.

Over a century after Emil Fischer´s landmark achievement of the first synthesis of the indole core,[1] new revenues for indole preparation remain an active field of research. The wide-spread occurrence of this heterocycle in molecules of pharmaceutical and biological interest[2] has triggered paramount synthetic efforts towards its construction.[3]
We recently reported a metal-free oxidative approach using a modified Koser reagent for the intramolecular cyclization of 2-vinyl anilines.[4] This approach allows unprecedented access to the 2,3-unsubstituted indole core, while all different kinds of substituents at the arene were tolerated. Generally, the complimentary synthesis of indole derivatives with predictable 2,3-substitution pattern meets with certain restriction. For the case of 2,3-diarylated derivatives, the use of transition metal catalysis has enabled some elegant solutions to this problem (Figure 1, top).[5,6] To establish an alternative approach, we decided to explore this synthetic challenge from the perspective of an intramolecular reaction using a removable tether (Figure 1, bottom). In order to provide suitable conditions for application in the pharmaceutical and biological sciences, we expected an iodine(III) compound to be the reagent of choice, since residual contamination by toxic metals is not an issue with this type of reagents.[7,8] An iodine(III)-based oxidant should be able to promote the required sequential N-H and C-H bond activation at the aniline component for oxidative fusion of the two respective centers with the acetylene to construct the indole core.[9] This overall process can be conceptually understood as a formal oxidative [3+2] cycloaddition.[10] Traceless removal of the tether group would then generate the 2,3-diarylated indole with complete selectivity regarding the individual aryl group positioning.

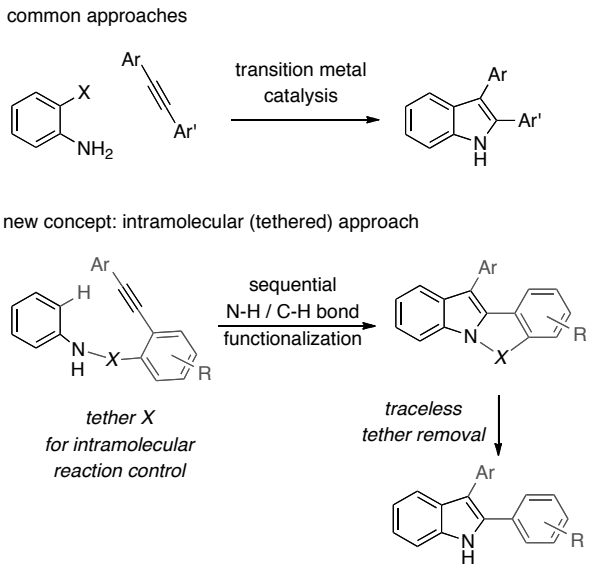

Figure 1. Conceptual approach for tethered 2,3-diaryl indole synthesis.

The viability of this approach was pursued using a sulfonyl group as the tether.[11] Within this approach a modular synthesis of starting materials could be carried out departing from commercially available 2-bromobenzene sulfonylchloride **1**.

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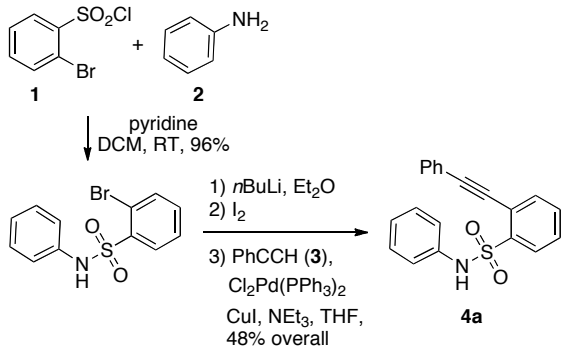
Scheme 2 exemplifies the synthesis of the unsubstituted cyclization precursor **4a**. It starts with the condensation of **1** with aniline **2** followed by bromine for iodine exchange and Sonogashira coupling with phenyl acetylene **3**. In this way, compound **4a** was obtained in a straightforward manner. Higher-functionalized derivatives of **4a** are accessible through incorporation of the corresponding substituted derivatives of **1**, **2** and/or **3**.[12]



Scheme 1. Synthesis of cyclization precursor **4a**.

With the required precursor **4a** in hand, the intramolecular indole synthesis was investigated for standard hypervalent iodine(III) reagents as promoters (Table 1). Initially, bis(trifluoroacetoxy) iodobenzene (PIFA) was tested. Validating our assumption, this reagent readily converted **4a** into **5a** in 57% isolated yield (entry 1). The structure of **5a** was unambiguously assured by X-ray analysis at this stage.[13] Lowering the temperature to 0 ºC led to a significant increase in yield, while a further decrease in temperature had no beneficial effect (entries 2,3). The related reaction with diacetoxy iodobenzene (PIDA) led to almost no conversion (entry 4), however, upon changing the solvent to hexafluoroisopropanol (HFIP),[14] complete conversion within 45 min was observed (85% isolated yield, entry 5).

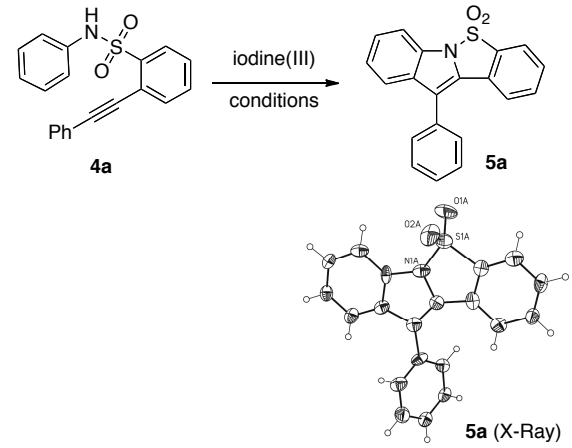


Table 1. Optimization for preformed iodine(III) reagents.

Entry	Reagent	Solvent	T [ºC]	t	Yield [%][a]
1	PIFA	CH_2Cl_2	25	10 min	57
2	PIFA	CH_2Cl_2	0	6 h	78
3	PIFA	CH_2Cl_2	-15	10 h	64
4	PIDA	CH_2Cl_2	25	12 h	< 10[b]
5	PIDA	HFIP	25	45 min	85

[a] Isolated yield after purification. [b] Based on crude reaction mixture (^{1}H NMR).

Having thus established conditions for the formation of indole **5a** under stoichiometric conditions, the possibility of a reaction using catalytic amounts of aryliodine was explored (Table 2).[15] The PIDA/HFIP system was taken as a starting point. To this end, peracetic acid was chosen as a benign terminal oxidant together with iodobenzene as potential catalyst. While some reactivity could indeed be accomplished, isolated yields of **5a** remained low (entries 1,2). Changing the catalyst to 2,2'-diiodobiphenyl **6** resulted in improved yields (64% at 20 mol% loading, entry 3). Lowering the catalyst led to diminished yields (entries 4,5) together with formation of unidentified degradation products. To reduce the latter, the oxidant was employed as limiting agent, which increased the yield to 65% (at 5 mol% catalyst, entry 6). Surprisingly, at increased catalyst loading of 10 mol%, product formation again became less selective (entry 7). The same context was initially observed for Kita's catalyst **7**[16](entries 8,9). However, in this case an increase in oxidant resulted also in improved yields (entries 10, 11). Finally, introduction of dichloroethane as solvent component and two consecutive addition of the oxidant at 0 ºC resulted in a protocol that provided **5a** in 78% isolated yield (entries 12,13).

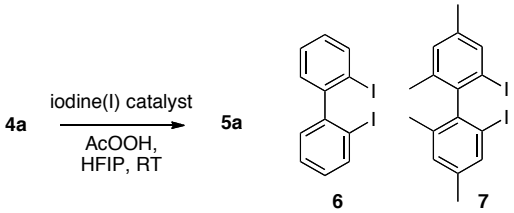
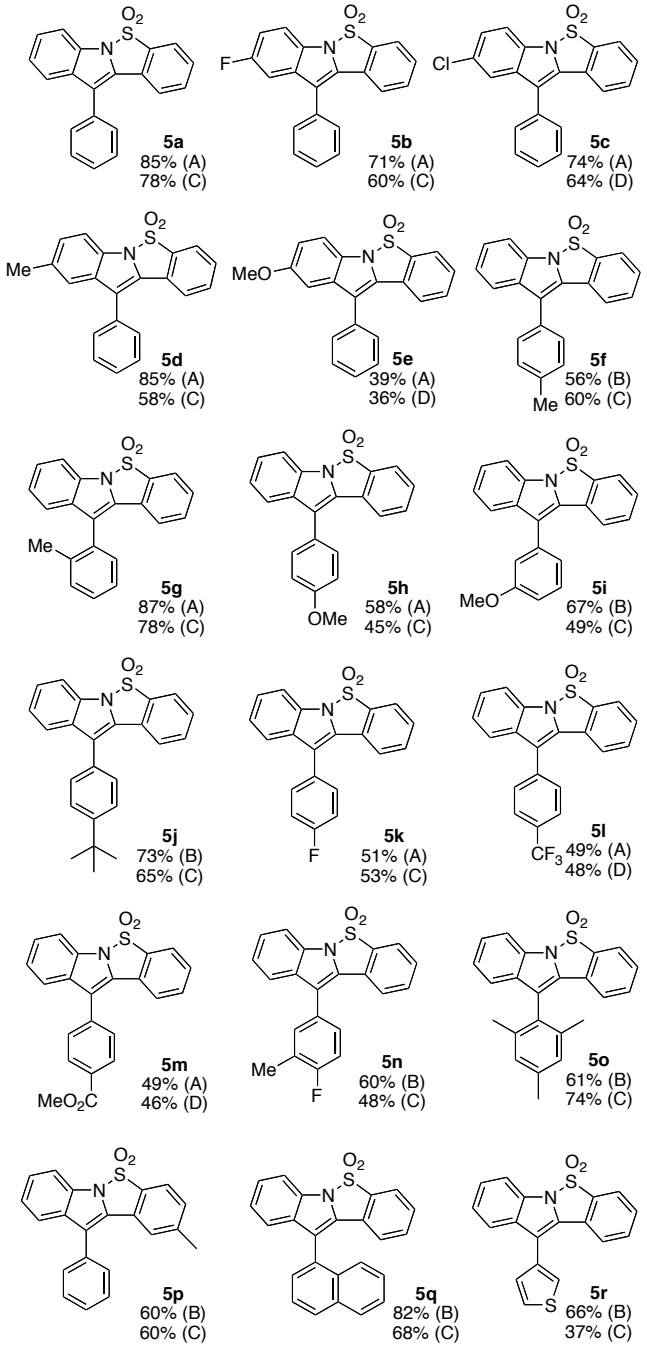


Table 2. Optimization for reactions under iodine(III) catalysis.

Entry	Catalyst (mol%)	Equiv. Oxidant	Yield [%][a]
1	PhI (20)	1.1	33
2[b]	PhI (20)	1.1	38
3	**6** (20)	2.2	64
4	**6** (10)	2.2	47
5	**6** (5)	2.2	35
6	**6** (5)	0.95	65
7	**6** (10)	0.95	55
8	**7** (5)	0.95	44
9	**7** (10)	0.95	35
10	**7** (10)	1.1	57
11	**7** (20)	1.5	61
12[c]	**7** (20)	1.5	69
13[c]	**7** (20)	1.8	78

[a] Isolated yield after purification. [b] With 1 equivalent of acetic acid. [c] In HFIP/$(CH_2Cl)_2$, 1/1 (v/v) and with sequential addition of the oxidant in two portions (second one after 15 min reaction time) at 0 ºC.

Examples demonstrating the general scope of the present reaction are presented in Scheme 2. For each compound, conditions are given for one stoichiometric and one catalytic transformation demonstrating that the cyclization reactions to compounds **5** can be conducted both with equimolar amounts of a preformed iodine(III) reagent (protocols A,B) or under conditions of homogeneous aryliodine(I/III) catalysis (protocols C,D).[12] A total of 18 successful examples with different substitution pattern at all three arene rings exemplifies the capacity of the present transformation to act as a general route towards indole synthesis.



Scheme 2. Substrate scope. Procedures. (A): starting sulfonamide **4** (0.1 mmol), PIDA (0.15 mmol) in HFIP (1 mL) at RT. (B): starting sulfonamide **4** (0.085 mmol), PIFA (0.094 mmol) in DCM (1 mL) at 0 ºC. (C): starting sulfonamide **4** (0.1 mmol), **7** (20 mol%), AcOOH (0.18 mmol) in HFIP/DCE (1/1, v/v, 1 mL) from 0 ºC to RT. (D): starting sulfonamide **4** (0.1 mmol), **6** (5 mol%), AcOOH (0.095 mmol) in HFIP (1 mL) at RT.

A reasonable mechanistic context is depicted in Figure 2. The reaction is initiated by interaction between the hypervalent iodine reagent and substrate **4**, most probably through formation of an I-N bond.[17] Heterolytic cleavage of this bond results in the generation of an electrophilic nitrogen (stage **A**),[18,19] which upon attack by the acetylene moiety triggers a 5-exo-dig cyclization to **B**. This intermediary vinylic cation **B** undergoes further cyclization by nucleophilic attack of the aromatic ring of the aniline[20] followed by re-aromatization of the resulting cationic intermediate **C**. Rearomatization to the final product **5** is accomplished upon loss of a proton. This step is comparably fast as demonstrated by a kinetic competition experiment between **4g** and **4g-d_5**, which gave no observable kinetic isotope effect (k_H/k_D = 1.0). A Hammett correlation using electronic information at the remote aryl group of the tolane core resulted in a ρ-value of -0.35, which indicated that the slow step of the overall reaction belongs to one of the electrophilic cyclization events at stages **A** or **B**.

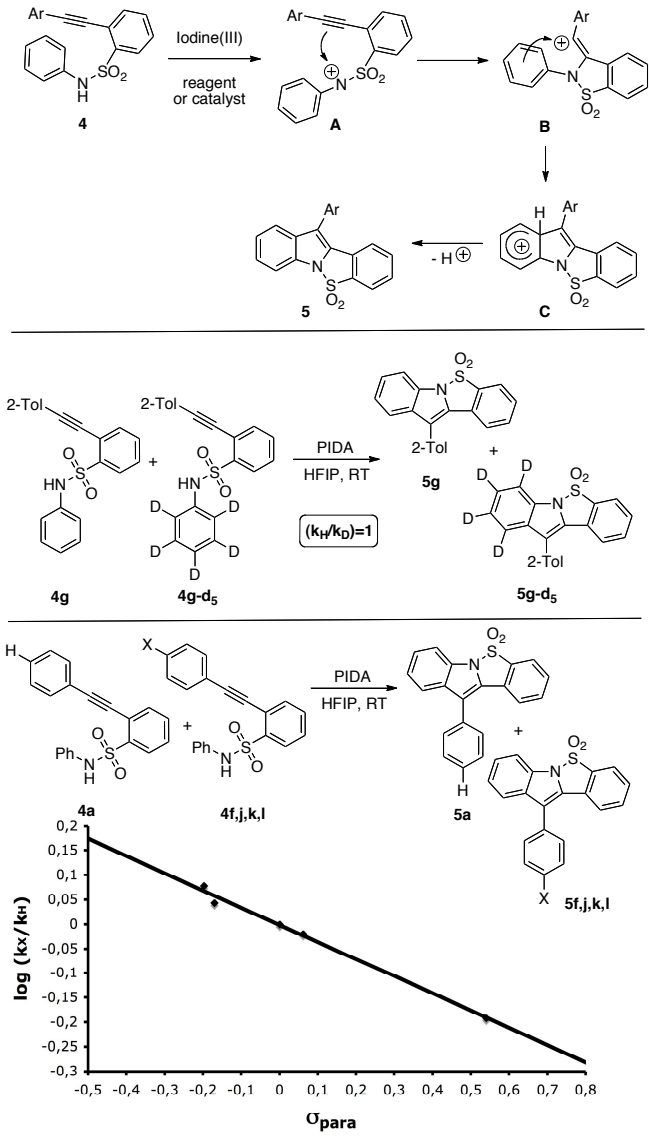
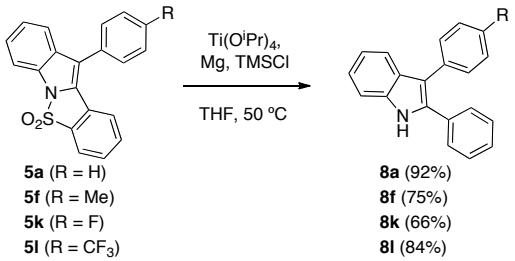


Figure 2. Mechanistc context and control experiments.

In the final step, the sulfonyl tether is tracelessly removed upon treatment of the cyclization products **4** with titanium tetraisopropoxide, magnesium and TMSCl (Scheme 3).[21] Under these conditions the desired free 2,3-diarylated indoles **8** can be generated in good yields as demonstrated for the four derivatives **8a,f,k,l.**



5a (R = H)
5f (R = Me)
5k (R = F)
5l (R = CF_3)

8a (92%)
8f (75%)
8k (66%)
8l (84%)

Scheme 3. Deprotection to free 2,3-diaryl indoles.

In summary, we have developed an environmentally benign variant for the iodine(III)-mediated or catalyzed construction of indoles through a new sequential N-H/C-H oxidation reaction. The reaction is of high scope and is based on the initial presence of a sulfonyl tether, which can be readily removed in a traceless manner to provide regioselective access to 2,3-diarylated indoles.

Acknowledgements

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Keywords: Catalysis • Hypervalent Iodine • Indoles • Oxidation • Tether

[1] a) E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2241-2245; b) B. Robinson, *Chem. Rev.* **1963**, *63*, 373-401.

[2] a) M. Somei, F. Yamada, *Nat. Prod. Rep*. **2005**, *22*, 73; b) J. A. Joule in *Science of Synthesis, Methods of Molecular Transformations* (Ed.: E. J. Thomas) Thieme, Stuttgart, 2000, Vol. 10, p 361; c) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, C. W. Bird) Pergamon Press, Oxford, 1996, Vol. 2, p 119; d) G. W. Gribble in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven, C. W. Bird) Pergamon Press, Oxford, 1996, Vol. 2, p 207.

[3] Reviews: a) T. Guo, F. Huang, L. Yu, Z. Yu, *Tet. Lett.* **2015**, *56*, 296-302; b) M. Inmana, C. J. Moody, *Chem. Sci*. **2013**, *4*, 29-41; c) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195-7210; d) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29-41; e) S. A. Patil, R. Patil, D. D. Miller, *Curr. Med. Chem.* **2011**, *18*, 615-637; f) M. Platon, R. Amardeil, L. Djakovitch, J. C. Hierso, *Chem. Soc. Rev*. **2012**, *41*, 3929-3968.

[4] L. Fra, A. Millán, J. A. Souto, K. Muñiz, *Angew. Chem.* **2014**, *126*, 7477-7481; *Angew. Chem. Int. Ed*. **2014**, *53*, 7349-7353.

[5] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6690-6692; b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998,** *63*, 7652-7662; c) D. Stuart, M. Betrand-Laperle, K.M.N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475; d) D. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339; e) L. Ackermann, A. Althammer, *Synlett*, **2006**, *18*, 3125-3129; f) L. Ackermann, A. V. Lygin, *Org. Lett.* **2012**, *14*, 764-767; g) L. Ackermann, R. Sandmann, A. Villar, L. T. Kaspar, *Tetrahedron*, **2008**, *64*, 769-777; h) W. Song, L. Ackermann, *Chem. Commun*. **2013**, *49*, 6638-6640, i) M. Shen, G. Li, B. Z. Lu, A. Hossain, F. Roschangar, V. Farina, C. H. Senanayake *Org. Lett.* **2004**, *6*, 4129-4132; j) B. Z. Lu, H.-X. Wei, Y. Zhang, W. Zhao, M. Dufour, G. Li, V. Farina, C. H. Senanayake, *J. Org. Chem.* **2013**, *78*, 4558-4562; k) F. Zhou, X. Han, X. Lu, *Tet. Lett*. **2011**, *52*, 4681-4685; l) G. Zhang, H. Yu, G. Qin and H. Huang, *Chem. Commun*. **2014**, *50*, 4331-4334; m) Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, *356*, 1577-1585.

[6] Selected reviews on metal-mediated synthesis: a) Z. Shi, F. Glorius, *Angew. Chem.* **2012**, *124*, 9354-9356; *Angew. Chem. Int. Ed.* **2012**, *51*, 9220-9222; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873-2920; S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215-PR283; c) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469-6480; S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641-652; d) J. Barluenga, F. Rodríguez, F. J. Fañanas, *Chem. Asian J.* **2009**, *4*, 1036-1048.

[7] a) V. V. Zhdankin, *Hypervalent Iodine Chemistry Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester 2013; b) *Hypervalent Iodine Chemistry. Modern Developments in Organic Synthesis* (Ed.: T. Wirth), *Top. Curr. Chem*. 224, Springer, Berlin, 2003; c) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123-1178; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523-2584; e) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299-5358.

[8] 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*, 5919-5922; b) W. Yu, Y. Du, K. Zhao, *Org. Lett.* **2009**, *11*, 2417-2420; c) X. Li, Y. Du, Z. Liang, X. Li, Y. Pan, K. Zhao, *Org. Lett.* **2009**, *11*, 2643-2646.

[9] For reviews on sequential bond activation with hypervalent iodine reagents: a) R. Narayan, S. Manna, A. P. Antonchick, *Synlett* **2015**, *26*, 1785; b) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem.* **2013**, 5769-5804.

[10] For precedence on iodine(III)-promoted oxidative [3+2] cycloadditions: a) S. Wang, B. D. Gates, J. S. Swenton, *J. Org. Chem.* **1991**, *56*, 1979-1981; b) B. D. Gates, P. Dalidowicz, A. Tebben, S. Wang, J. S. Swenton, *J. Org. Chem.* **1992**, *57*, 2135-2143; c) A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem.* **2003**,*115*, 5111–5116; *Angew. Chem. Int. Ed.* **2003**, *42*, 4961-4966; d) C. Chan, C. Li, F. Zhang, S. J. Danishefsky, *Tetrahedron Lett.* **2006**, *47*, 4839-4841; e) D. Berard, A. Jean, S. Canesi, *Tetrahedron Lett.* **2007**, *48*, 8238-8241; f) D. Bérard, L. Racicot, C. Sabot, S. Canesi, *Synlett* **2008**, 1076-1080; g) K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, D. Y. K. Chen, *Angew. Chem.* **2009**, *121*, 7736–7739; *Angew. Chem. Int. Ed.* **2009**, *48*, 7616 - 7620; h) G. Jacquemot, M. A. Ménard, C. L'Homme, S. Canesi, *Chem. Sci.* **2013**, *4*, 1287-1292; i) T. Tomakinian, R. Guillot, C. Kouklovshy, G. Vincent, *Angew. Chem.* **2014**, *126*, 12075-12079; *Angew. Chem. Int. Ed.* **2014**, *53*, 11881-11885.

[11] For pioneering use of such tethers: a) P. Evans, T. McCabe, B. S. Morgan, S. Reau, *Org. Lett.* **2005**, *7*, 43-46; c) P. Evans, *J. Org. Chem.* **2007**, *72*, 1830-1833; c) K. Geoghegan, P. Evans, *J. Org. Chem*. **2013**, *78*, 3410−3415.

[12] See Supporting Information for details.

[13] Details on crystal structure analysis of **5a** were deposited with the Cambridge Crystallographic Data Centre (CCDC). They can be obtained from the CCDC citing the following number: CCDC 1441257.

[14] For a recent review on the use of fluorinated solvents in oxidative reactions, see: T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron* **2010**, *66*, 5775-5785.

[15] For general reviews on iodine(I/III) catalysis in homogeneous oxidation: a) R. D. Richardson, T. Wirth, *Angew. Chem.* **2006**, *118*, 4510-4512; *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404; b) M. Ochiai, K. Miyamoto, *Eur. J. Org. Chem.* **2008**, 4229-4239; c) M. Ochiai, *Chem. Rec.* **2007**, *7*, 12-23; d) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073-2085; e) M. Uyanik, K. Ishihara, *Chem. Commun.* **2009**, 2086-2099; f) M. S. Yusubov, V. V. Zhdankin, *Reef. Tech.* **2015**, *1*, 49-67.

[16] T. Dohi, N. Takenaga, K.-i. Fukushima, T. Uchiyama, D. Kato, S. Motoo, H. Fujioka, Y. Kita, *Chem. Commun*. **2010**, *46*, 7697-7699.

[17] I. Tellitu, E. Domínguez, *Trends Heterocycl. Chem.* **2011**, *15*, 23-32.

[18] A. Correa, I. Tellitu, E. Domínguez, R. SanMartin, *J. Org. Chem.* **2006**, *71*, 8316-8319.

[19] For a comparable step in *N*-arylation catalysis with **7**: A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764-8767; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605-8608.

[20] M. Ito, H. Kubo, I. Itani, K. Morimoto, T. Dohi, Y. Kita, *J. Am. Chem. Soc.* **2013**, *135*, 14078-14081.

[21] N. Shohji, T. Kawaji, S. Okamoto, *Org. Lett.* **2011**, *13*, 2626-2629.

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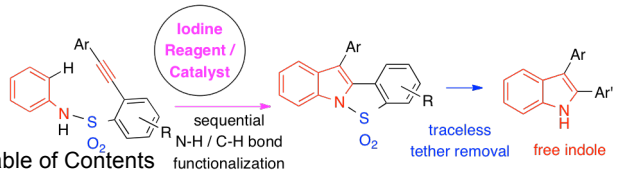

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By use of a preformed iodine(III) reagent or its corresponding catalytic derivative, an oxidative addition of an N-H and a C-H group onto an acetylene provides efficient conditions for the construction of the indole core. Removal of the initial SO_2 tether provides free indoles with selective 2,3-diarylation pattern.