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Reductive Alkylation of Indoles with Alkynes and Hydrosilanes under Indium Catalysis

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ABSTRACT

Under Indium catalysis, diverse alkylindoles were successfully prepared with a flexible combination of indoles and alkynes in the presence of hydrosilanes. In addition to the hydrosilane, carbon nucleophiles are also available. This new method generates alkylindoles in yields over 70% with a broad scope of functional group compatibility.

Indoles having alkyl units at the C2 and/or C3 positions are widely recognized as structural motifs, especially in natural products and pharmaceuticals.[1] Due to this reason, Friedel–Crafts (F.C.) alkylation of indoles, which features easy accessibility, has been broadly studied in organic synthesis, where addition or substitution has been the reaction mode of choice.[2] From atom economical and environmental viewpoints, the addition mode is apparently more useful. However, it is rather surprising that alkenes successfully accepting indoles intermolecularly have been restricted to the following two types:[2−4] highly electrophilic alkenes with electron-withdrawing groups,[5] and aryl- and multi-substituted alkenes with the ability to stabilize intermediary positive charges.[6] These thus appear to have narrowed the applicability of the F.C. alkylation of indoles.

Alkynes also have been well-established as platforms to accept addition of a variety of molecules.[7] We envisaged that achievement of reductive F.C. alkylation of indoles using alkynes with broad substrate generality including

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(1) d'Ischia, M.; Napolitano, A.; Pezzella, A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Jones, G., Eds.; Elsevier: Oxford, 2008; Vol. 3, pp 353−388.

(2) (a) Trofimov, B. A.; Nedolya, N. A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Jones, G., Eds.; Elsevier: Oxford, 2008; Vol. 3, pp 110−133. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644.

(3) Use of simple aliphatic terminal alkenes causes some undesired reactions on the alkene, i.e., isomerization of the C=C bond, formation of regioisomers, and rearrangement of alkyl groups: (a) Zhang, Z.; Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 3717–3719. (b) Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2008**, *14*, 8353–8364.

(4) Although Terada and Sorimachi have reported addition of indoles to enamines as electron-rich alkenes, the mechanistic study indicates that imines produced in situ by isomerization of the enamine are actual acceptors of the indole: Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292–293.

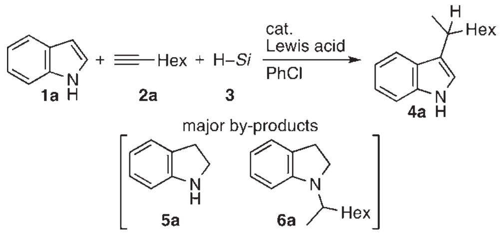
(5) For selected recent examples, see: (a) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016–4018. (b) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464–16465. (c) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654–5657. See also recent reviews: (d) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222. (e) Bandini, M.; Eichholzer, A.; Umani-Ronchi, A. *Mini-Rev. Org. Chem.* **2007**, *4*, 115–124.

(6) For selected recent examples, see: (a) Rozenman, M. M.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 14933–14938. (b) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genet, J.-P.; Michelet, V. *Chem.—Eur. J.* **2009**, *15*, 1319–1323. See also ref 3b.

(7) For selected recent reviews, see: (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725–748. (b) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366–2447. (c) Kondoh, A.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2010**, *5*, 398–409. (d) Wang, X.; Zhou, L.; Lu, W. *Curr. Org. Chem.* **2010**, *14*, 289–307. (e) de Mendoza, P.; Echavarren, A. M. *Pure Appl. Chem.* **2010**, *82*, 801–820.

10.1021/ol1029673

Table 1. Lewis Acid-Catalyzed Reductive Octylation of Indole[a]



entry	Lewis acid (mol %)	Si in 3	temp (°C)	time (h)	conv of **2a** (%)[b]	**4a** (%)[b]
1	$In(OTf)_3$ (20)	$SiEt_3$	100	12	27	8
2	$Cu(OTf)_2$ (20)	$SiEt_3$	100	12	16	<1
3	AgOTf (20)	$SiEt_3$	100	12	7	<1
4	$Zn(OTf)_2$ (20)	$SiEt_3$	100	12	14	<1
5	$Bi(OTf)_3$ (20)	$SiEt_3$	100	12	18	2
6	$In(NTf_2)_3$ (20)	$SiEt_3$	100	12	97	43
7	$In(NTf_2)_3$ (20)	$SiEt_3$	40	12	45	32
8	$In(NTf_2)_3$ (30)	$SiEt_3$	40	24	86	61
9	$In(NTf_2)_3$ (30)	$SiMe_2Ph$	40	24	84	78
10	$In(NTf_2)_3$ (30)	$SiMePh_2$	40	24	94	82
11	$In(NTf_2)_3$ (30)	$SiPh_3$	40	24	89	65
12	$In(NTf_2)_3$ (30)	$SiMePh_2$	45	24	>99	86

[a] Reagents: **1a** (0.6 mmol), **2a** (0.4 mmol), **3** (0.6 mmol), PhCl (0.6 mL for entries 1–11 or 0.4 mL for entry 12). [b] Determined by GC.

high functional group tolerance would open up promising perspectives to construct alkylindoles toward a variety of situations.[8] This study with an indium catalyst, which is the first example of reductive alkylation of indoles with alkynes and hydrosilanes, proves to be the case.[9−11]

We first examined suitable conditions in the reductive alkylation of indole (**1a**) with 1-octyne (**2a**) (Table 1). Thus, treating **1a**, **2a** and $HSiEt_3$ with $In(OTf)_3$ (20 mol %, Tf = SO_2CF_3) in PhCl at 100 °C for 12 h gave 3-(2-octyl)indole (**4a**), albeit in a low yield (entry 1). In contrast to other metal triflates, $In(NTf_2)_3$ greatly improved the reaction rate, while significant amounts of by-products, mainly **5a** and **6a**, were formed (entries 2−6). Lowering the temperature made the reaction sluggish, but favorably affected to suppress the side reaction (entry 7). The higher conversion of **2a** was achieved by the prolonged reaction time with $In(NTf_2)_3$ (30 mol %) (entry 8).[12] Under the conditions, screening of hydrosilanes **3** showed that those having phenyl group(s) are more promising (entries 9−11). With $HSiMePh_2$ (**3a**), the fine-tuning of the solvent volume and temperature finally raised the yield to 86% (entry 12).

Under the suitable conditions, 15−30 mol % of $In(NTf_2)_3$ was found to affect effectively the present reaction with a broad substrate scope on both indoles **1** and alkynes **2** (Table 2). Besides **1a**, substituted indoles **1b**−**1f** were thus alkylated successfully, in the presence of **3a**, by **2a** as well as aliphatic terminal alkynes **2b**−**2e** with a range of functional groups (entries 1−11). Importantly, with alkynol **2e**, oxygen-silylated or -unsilylated alkylindole **4j** [R^6 = $(CH_2)_4OSiMePh_2$] or **4j′** [R^6 = $(CH_2)_4OH$] was obtained exclusively in each case, by performing the reaction without or with H_2O (entries 10 and 11). Worthy of note is that no troublesome reaction was observed in the use of **2f** and **2g**, in contrast to the variants with the corresponding alkenes (entries 12 and 13).[3] Terminal aryl- and heteroarylalkynes **2h**−**2k** with different electronic natures also participated well in this strategy (entries 14−20). In these cases, adding H_2O greatly accelerated the reaction (e.g., entries 14 vs 15, and also see Scheme 2). The source of the alkyl group can be further extended to aliphatic and aromatic internal alkynes (entries 21 and 22). The less nucleophilic C2, compared to C3, also worked well as a reaction site, giving **4u** and **4v** (entries 23 and 24). As shown thus far, the outstanding compatibility of the functional groups, OMe, Br, Cl, CN, phthalimidoyl, OH, *t*-Bu, B(pinacolate), I and NO_2, is noteworthy. Among them, the carbon−OMe,[13] −boron[14] and −halogen[14] bonds should be useful for further elongation of a carbon−carbon bond. The achievement of perfect regioselection on both **1** and **2**[15] and of yields of **4** over 70% in all cases represent high validity and reliability of this strategy. Moreover, a practical advantage can be demonstrated by synthesis on a preparative-scale. For example, **4m** was synthesized on 10 mmol scale using 10 mol % of $In(NTf_2)_3$ at 70 °C for 2 h, and thus obtained in 97% yield (2.48 g).

Instead of hydride nucleophiles, carbon nucleophiles [Nu(*C*)] **3**, such as Me_3SiCN (**3b**) and 2-methoxythiophene (**3c**), can be adopted to install a quaternary carbon center into the product, where the stepwise procedure in one-pot as shown in Scheme 1 is effective. The assembly of indole **1a**, alkyne **2n** and thiophene **3c** for **7c** can be regarded as a substrate-selective double addition of two different heteroarenes to a C≡C bond.

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(8) (a) Tsuchimoto, T.; Wagatsuma, T.; Aoki, K.; Shimotori, J. *Org. Lett.* **2009**, *11*, 2129–2132. See also a Concept article: (b) Tsuchimoto, T. *Chem.*−*Eur. J.* **2011**, accepted.

(9) A part of this research was presented at the 89th annual meeting of the Chemical Society of Japan on March 29, 2009 (presentation #3F2−53). During the course of this research, two research groups reported alkylation of indoles with alkynes. However, their research profiles are different from ours. (a) Barluenga, J.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Chem.*—*Eur. J.* **2009**, *15*, 8121–8123. (b) Cadierno, V.; Francos, J.; Gimeno, J. *Chem. Commun.* **2010**, *46*, 4175–4177.

(10) For variants with carbonyl compounds as alkyl group suppliers, but always requiring more than a stoichiometric amount of acid promoters, see: (a) Appleton, J. E.; Dack, K. N.; Green, A. D.; Steele, J. *Tetrahedron Lett.* **1993**, *34*, 1529–1532. (b) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. *Tetrahedron Lett.* **2003**, *44*, 4589–4591. (c) Campbell, J. A.; Bordunov, V.; Broka, C. A.; Dankwaedt, J.; Hendricks, R. T.; Kress, J. M.; Walker, K. A. M.; Wang, J.-H. *Tetrahedron Lett.* **2004**, *45*, 3793–3796. (d) Rizzo, J. R.; Alt, C. A.; Zhang, T. Y. *Tetrahedron Lett.* **2008**, *49*, 6749–6751.

(11) For our recent reports on indium-catalyzed carbon−carbon bond-forming reaction with indoles as nucleophiles, see: (a) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823–15835. (b) Tsuchimoto, T.; Iwabuchi, M.; Nagase, Y.; Oki, K.; Takahashi, H. *Angew. Chem., Int. Ed.* **2011**, DOI: 10.1002/anie.201005750.

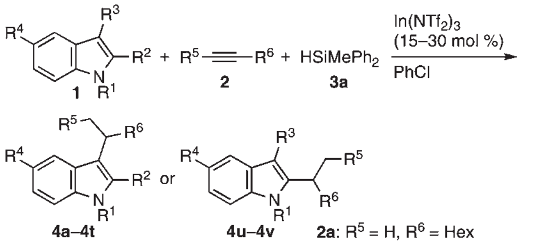
(12) Effect of other solvents also was examined under the conditions shown in entry 8: PhH (55%), PhMe (48%), $ClCH_2CH_2Cl$ (46%), CH_2Cl_2 (35%), $CHCl_3$ (46%), Bu_2O (40%), *n*-decane (9%).

(13) For a leading example, see: Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866–4869 and references therein.

(14) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.

(15) Ratios of **4** and other possible regioisomers were assessed to be >99:<1 by GC and GC−MS analyses.

Table 2. Indium-Catalyzed Reductive Alkylation of Indoles[a]



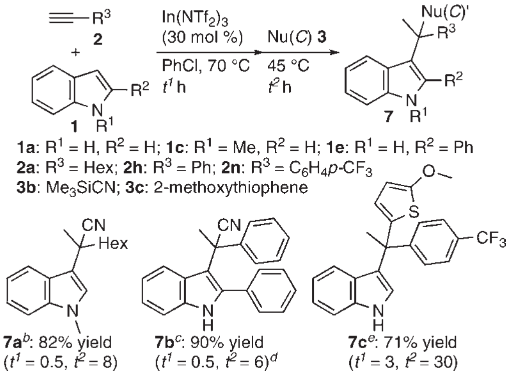
2a: R^5 = H, R^6 = Hex
2b: R^5 = H, R^6 = $(CH_2)_4Cl$
2c: R^5 = H, R^6 = $(CH_2)_3CN$
2d: R^5 = H, R^6 = $(CH_2)_3PI$[c]
2e: R^5 = H, R^6 = $(CH_2)_4OH$
2f: R^5 = H, R^6 = CH_2Ph
2g: R^5 = H, R^6 = t-Bu
2h: R^5 = H, R^6 = Ph
2i: R^5 = H, R^6 = C_6H_4p-OMe
2j: R^5 = H, R^6 = C_6H_4p-NO_2
2k: R^5 = H, R^6 = 3-thienyl
2l: R^5 = Bu, R^6 = Bu
2m: R^5 = Me, R^6 = Ph

1a: $R^1 = R^2 = R^3 = R^4$ = H
1b: $R^1 = R^3 = R^4$ = H, R^2 = Me
1c: R^1 = Me, $R^2 = R^3 = R^4$ = H
1d: $R^1 = R^3$ = H, R^2 = Me, R^4 = OMe
1e: $R^1 = R^3 = R^4$ = H, R^2 = Ph
1f: $R^1 = R^2 = R^3$ = H, R^4 = Br
1g: $R^1 = R^2$ = Me, $R^3 = R^4$ = H
1h: R^1 = Me, $R^2 = R^3$ = H, R^4 = B(pin)[b]
1i: $R^1 = R^2 = R^3$ = H, R^4 = I
1j: $R^1 = R^2 = R^4$ = H, R^3 = Ph

entry	indole **1**	alkyne **2**	$In(NTf_2)_3$ (mol %)	temp (°C)	time (h)	product, yield (%)[d]
1	**1a**	**2a**	30	45	24	**4a**, 84
2	**1b**	**2a**	30	45	24	**4b**, 93
3	**1c**	**2a**	30	45	24	**4c**, 87
4	**1d**	**2a**	30	45	24	**4d**, 82
5	**1e**	**2a**	30	45	24	**4e**, 92
6	**1f**	**2a**	30	45	24	**4f**, 80
7	**1c**	**2b**	30	45	30	**4g**, 70
8	**1c**	**2c**	30	70	5	**4h**, 72
9	**1c**	**2d**	15	85	30	**4i**, 81
10	**1c**	**2e**	30	70	6	**4j**, 85
11[e]	**1c**	**2e**	30	70	1	**4j'**, 86
12	**1g**	**2f**	30	85	9	**4k**, 81
13[f]	**1c**	**2g**	30	85	48	**4l**, 78
14	**1g**	**2h**	30	70	12	**4m**, 98
15[g]	**1g**	**2h**	15	70	1	**4m**, 98
16[g]	**1c**	**2h**	15	70	0.5	**4n**, 97
17[h]	**1h**	**2h**	30	rt	7	**4o**, 80
18[g]	**1i**	**2i**	20	45	4	**4p**, 75
19[g]	**1c**	**2j**	30	70	8	**4q**, 77
20[g]	**1g**	**2k**	20	70	0.7	**4r**, 99
21[i]	**1c**	**2l**	30	–[i]	–[i]	**4s**, 90
22	**1c**	**2m**	30	70	120	**4t**, 98
23	**1j**	**2a**	30	70	7	**4u**, 75
24[g]	**1j**	**2h**	15	70	4	**4v**, 71

[a] Reagents (unless otherwise specified): **1** (0.48−0.60 mmol), **2** (0.40 mmol), **3a** (0.60 mmol), $In(NTf_2)_3$ (0.060−0.12 mmol), PhCl (0.4 mL). See Supporting Information for further details. [b] pin = pinacolate. [c] PI = phthalimidoyl. [d] Isolated yield based on **2**. [e] Performed in the presence of H_2O (0.80 mmol). [f] $HSiPh_3$ instead of **3a** was used. [g] Performed in the presence of H_2O (0.20 mmol). [h] Performed in the presence of $MgSO_4$ (1.2 mmol). [i] Procedure, reagents and conditions: After treatment of **1c** (2.0 mmol) and **2l** (0.40 mmol) with $In(NTf_2)_3$ (0.12 mmol) in o-$Cl_2C_6H_4$ at 135 °C for 24 h, $HSiPh_3$ (0.60 mmol) was added and then the mixture was stirred at 70 °C for 12 h.

Scheme 1. Indium-Catalyzed Alkylation of Indoles with Alkynes and Carbon Nucleophiles[a]



[a] Reagents (unless otherwise specified): **1** (0.48−1.2 mmol), **2** (0.40 mmol), **3** (0.80−2.4 mmol), $In(NTf_2)_3$ (0.12 mmol), PhCl (0.4 mL). Isolated yields of **7** based on **2** are shown here. See Supporting Information for further details. [b] Obtained with **1c**, **2a** and **3b**. [c] Obtained with **1e**, **2h** and **3b**. [d] H_2O (0.40 mmol) was added successively after the addition of **3b**. [e] Obtained with **1a**, **2n** and **3c**.

We next performed some reactions to get insight into the reaction mechanism (Scheme 2). Thus, the indium-catalyzed reaction of **1g** with **2h**, but without **3a**, was completed in only 10 min to give alkenylindole **8a** in 97% yield. Subsequently, the treatment of isolated **8a** with **3a**, H_2O and $In(NTf_2)_3$ (15 mol %) for 30 min provided **4m** in 98% yield, whereas the absence of H_2O resulted in the much slower reaction (30 h), even with the higher loading of $In(NTf_2)_3$ (30 mol %). Interestingly, in contrast to the single addition using C2-substituted indole **1g**, the double addition was exclusive for C2-free indole **1c** to give **9a**, which was then readily converted to alkylindole **4n**. Here again, H_2O actively worked to hasten the hydride reduction. These results suggest that the single and double additions depending on the structure of indoles are crucial as the first steps and that H_2O would act as an activator, enhancing nucleophilicity of **3a** by its coordination.[16] The exclusive double addition should be due mainly to little or no steric congestion in **9a**, compared to steric stress that would arise between the two methyl groups at the C2, in case of further addition of **1g** to **8a**.

Two plausible routes, which are paths A and B for C2-substituted and -unsubstituted indoles, respectively, are depicted in Scheme 3 that exemplify the reaction with $H{-}SiR_3$ as a nucleophile. In path A, the first step is the single addition of indoles **1** ($R^2 \neq H$) to alkynes **2** activated by the indium (*In*),[17] which successively activates the C=C bond of **8** to induce the hydride reduction from $H{-}SiR_3$ coordinated by H_2O. Finally, protonation of the C−*In* bond affords alkylindoles **4** and $HOSiR_3$,[18] and regenerates the *In* catalyst. On the other hand, path B starts with the double addition of **1** (R^2 = H) to **2** via C≡C and C=C

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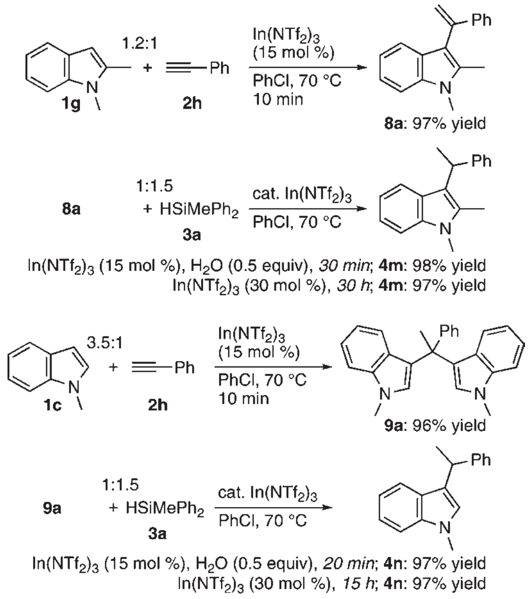
(16) H_2O reportedly coordinates to a silicon center. For example, see: Kobayashi, J.; Kawaguchi, K.; Kawashima, T. *J. Am. Chem. Soc.* **2004**, *126*, 16318–16319.

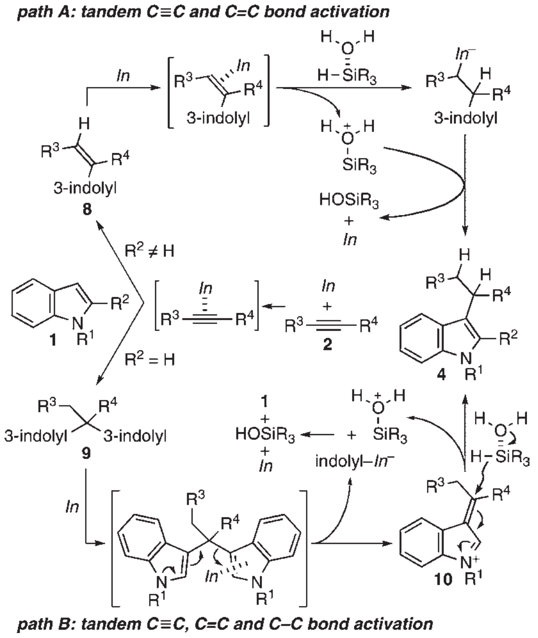
(17) We have also previously observed that indoles with a (hetero)-aryl group at the C2 position add to phenylacetylene under indium catalysis to give alkenylindoles such as **8**. See ref 11a.

(18) All of the reactions shown in Table 2 produced the silanol and/or its self-condensation compounds, disiloxanes, both of which can be confirmed by GC−MS analysis. Since substrates other than solvent PhCl were used without any special care, H_2O that would be present in each substrate should contribute to the activation of hydrosilanes and thus to the formation of the silanol in the reaction carried out without adding external H_2O.

Scheme 2. Indium-Catalyzed Reaction for Mechanistic Studies



Scheme 3. Plausible Reaction Mechanisms[a]



[a] Substituents other than R^1 and R^2 on indoles **1** are omitted for clarity.

bond activations giving diindolylalkanes **9**,[19] one indolyl group of which coordinates to the *In* and then eliminates to provide cationic species **10** by way of the C(sp^3)−C(indolyl) bond cleavage.[8,20] The hydride transfer to **10** gives products **4**. These considerations imply that indium Lewis acids have unique characteristics to activate carbon functional groups, C≡C, C=C and C−C,[21] while typical Lewis acids consisting of B, Ti or a rare earth metal prefer activating heteroatom-containing functional groups, e.g., C=O, C=NR and C−halogens.[22]

In closing, we disclosed the first reductive alkylation of indoles with alkynes and hydrosilanes, where In(NTf$_2$)$_3$ proved to be highly effective at catalyzing this transformation with high levels of reaction efficiency and perfect regioselection on both indoles and alkynes. A further salient feature herein is a wide range of substrate coverages with excellent functional group compatibility. From a mechanistic point of view, the operation of the two different pathways in this single transformation is a unique aspect.

Acknowledgment. We greatly appreciate Dr. Go Hirai as well as Dr. Mikiko Sodeoka at RIKEN, Japan, for their help in HRMS measurements.

Supporting Information Available. Experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For indium-catalyzed double addition of heteroarenes to alkynes, see: Tsuchimoto, T.; Hatanaka, K.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2003**, 2454–2455.

(20) For a precedent with respect to C(sp^3)−C(indolyl) bond cleavage, see: Deb, M. L.; Bhuyan, P. J. *Synlett* **2008**, 325–328.

(21) For an account, see: Tsuchimoto, T. *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 752–765.

(22) Yamamoto, H.; Ishihara, K. *Acid Catalysis in Modern Organic Synthesis*; Wiley-VCH: Weinheim, 2008.