Indium Catalysis

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Indium-Catalyzed Heteroaryl–Heteroaryl Bond Formation through Nucleophilic Aromatic Substitution**

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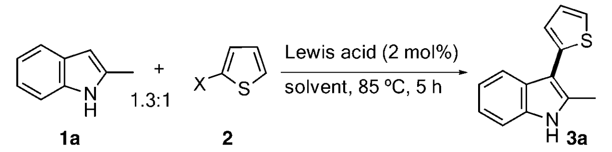
Heteroaromatic molecules bearing heteroaryl–heteroaryl bonds are an important class of building blocks found in a variety of areas; for example, optoelectronic materials,[1] liquid crystals,[2] biological compounds,[3] and ligands for asymmetric catalysis.[4] Over the past 35 years, transition-metal-catalyzed cross-coupling reactions have been chiefly responsible for making (hetero)aryl–(hetero)aryl bonds.[5] On the other hand, nucleophilic aromatic substitution (S_NAr) has actually been studied to construct such biaryl linkages since the 1940s.[6] However, aromatic compounds, which are intrinsically electron-rich, are in general unreactive toward nucleophilic substitution.[7] Therefore, two aryl substrates with entirely opposite electronic demands must be arranged to realize biaryl synthesis by the S_NAr reaction. Thus, electron-rich aryl nucleophiles with highly electropositive metals (e.g. Li^+, Mg^{2+}, Zn^{2+}) and/or electron-poor aryl electrophiles with one or more strong electron-withdrawing groups (EWGs; e.g. CF_3, NO_2, CN, CO_2R) have each been the aryl substrate of choice.[8] More than a stoichiometric amount of promoter is also often necessary.[8c,p,q] These requisites may have limited the widespread applicability of biaryl synthesis based on S_NAr. We envisioned that catalytic biaryl synthesis by S_NAr independent of such activated aryl substrates would be an attractive alternative to the transition-metal-catalyzed cross-coupling strategy. Herein, we report the first example of a catalytic heteroaryl–heteroaryl bond-forming reaction based on S_NAr without using both the heteroarylmetal nucleophile and heteroaryl electrophile substituted with EWGs.

Table 1: Effect of changing X.[a]



X	Conv. of **2** [%][b]	Yield of **3a** [%][c]
I	3	< 1
Br	2	< 1
Cl	5	< 1
NO_2	9	< 1
CN	5	< 1
OMe (**2a**)	99	35
OAc	24	< 1
OTf	> 99	< 1

[a] Reaction conditions: **1a** (0.325 mmol), **2** (0.250 mmol), $In(OTf)_3$ (5.00 μmol), 1,4-dioxane (1.0 mL), 85 °C, 5 h. [b] Determined by GC analysis. [c] Determined by ^1H NMR spectroscopy. Tf = SO_2CF_3.

Initially, we studied the effect of changing the leaving group X in thiophene derivatives **2** (acting as electrophiles) in the indium-catalyzed reaction of 2-methylindole (**1a**; acting as a nucleophile; Table 1). On treatment of **1a** and **2** bearing various halides (X = I, Br, Cl) with 2 mol % of $In(OTf)_3$ (Tf = SO_2CF_3) in 1,4-dioxane at 85 °C for 5 h, no desired reaction occurred. Neither the nitro nor cyano groups, which often behave as leaving groups in S_NAr reactions, worked at all. In sharp contrast, **2a**, having a methoxy group, reacted with **1a** to give thienylindole **3a** in 35 % yield, while the related oxygen-based leaving groups such as OAc and OTf gave disappointing results, despite their better leaving ability compared with OMe.[9] Next, we tested other solvents in the reaction of **1a** with **2a** (Table 2). The ethereal solvent DME, which is similar to 1,4-dioxane, was efficient while other solvents made the reaction sluggish. After thorough investigations on a co-solvent for 1,4-dioxane and DME, we found that the yield of **3a** was markedly increased to 80 % in a mixed solvent system, consisting of 1,4-dioxane and toluene (25:1). Other indium salts as well as metal triflates were less effective (Table 3). No reaction occurred without a catalyst. With $In(OTf)_3$ as a catalyst, the fine-tuning of the solvent volume finally raised the yield up to 86 %. The results in Table 3 might

Table 2: Effect of solvents.[a]

Solvent	Conv. of **2a** [%][b]	Yield of **3a** [%][c]
1,4-dioxane	99	35
DME	71	53
CH_3CH_2CN	44	25
$ClCH_2CH_2Cl$	36	21
PhCl	10	2
$PhCH_3$	12	8
1,4-dioxane/$PhCH_3$[d]	99	80
DME/$PhCH_3$[d]	95	73

[a] Reaction conditions: **1a** (0.325 mmol), **2a** (0.250 mmol), $In(OTf)_3$ (5.00 μmol), solvent (1.0 mL), 85 °C, 5 h. [b] Determined by GC analysis. [c] Determined by ^1H NMR spectroscopy. [d] The solvent ratio is 25:1 (1.0 mL:40 μL). DME = dimethoxyethane.

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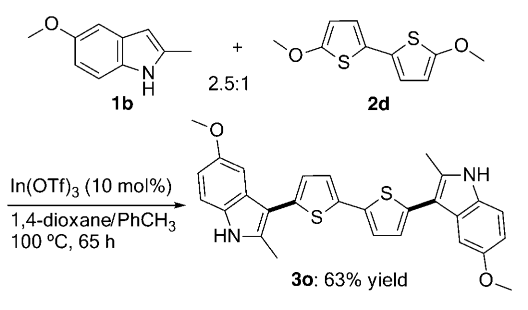
Table 3: Effect of Lewis acids.[a]

Lewis acid	Conv. of **2a** [%][b]	Yield of **3a** [%][c]
In(OTf)$_3$	99	80
In(ONf)$_3$	>99	74
In(NTf$_2$)$_3$	38	18
InCl$_3$	<1	<1
Cu(OTf)$_2$	81	59
AgOTf	99	73
Bi(OTf)$_3$	98	73
Sc(OTf)$_3$	45	18
Y(OTf)$_3$	13	4
Yb(OTf)$_3$	24	8
none	<1	<1
In(OTf)$_3$[d]	>99	86

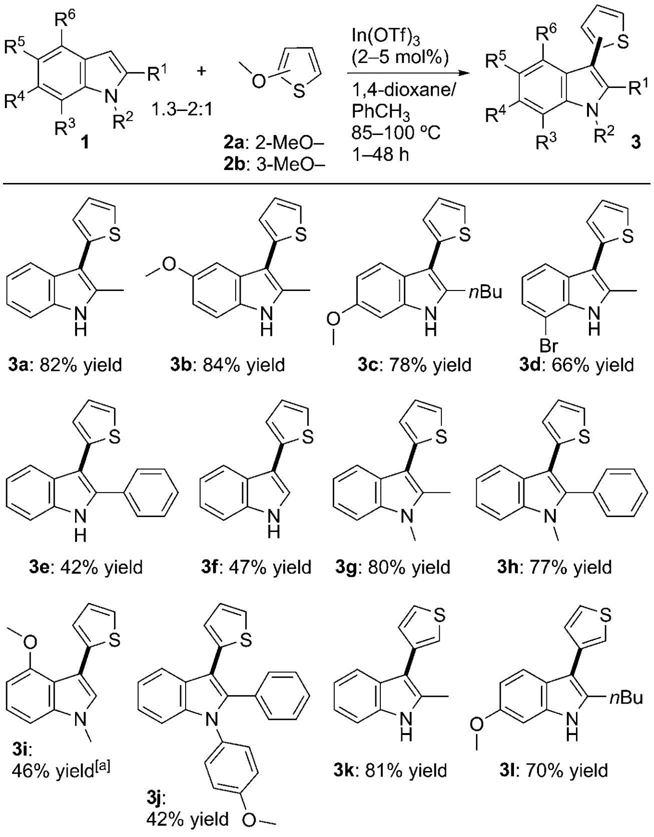
[a] Reaction conditions: **1a** (0.325 mmol), **2a** (0.250 mmol), Lewis acid (5.00 μmol), 1,4-dioxane/PhCH$_3$ (1.0 mL:40 μL), 85 °C, 5 h. [b] Determined by GC analysis. [c] Determined by ^{1}H NMR spectroscopy. [d] Used 1,4-dioxane/PhCH$_3$ [0.5 mL:40 μL (12.5:1)]. Nf$=$SO$_2$C$_4$F$_9$.

indicate that Lewis acids consisting of a rather soft metal and strong electron-withdrawing ligands tend to be favorable as catalysts, owing to the lower catalytic activity of the hard Lewis acids with strong electron-withdrawing ligands such as Sc-, Y-, and Yb(OTf)$_3$ and of the soft Lewis acid with weaker electron-withdrawing ones like InCl$_3$.[10] Notably, **3a** is accessible in one step from commercially available **1a** and **2a**; this is important because presynthesis of heteroarylmetal nucleophiles and heteroaryl electrophiles substituted with EWGs is not desired.

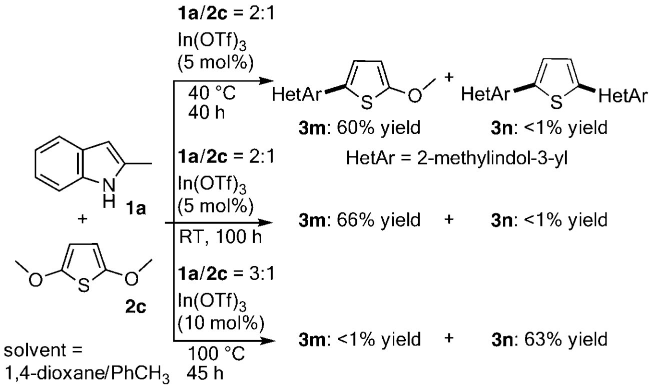
We next examined the substrate scope. As shown in Scheme 1, indoles **1** with Me, *n*Bu, OMe, Br, Ph, and/or *p*-MeOC$_6$H$_4$ groups displaced the OMe group from **2a** to afford **3b**–**3j**, where 1,2,3-triarylindole **3j**, having a fully extended π-conjugation system, is included. The OMe groups on indole substrates remained intact, thus showing remarkable chemoselectivities (see **3b**, **3c**, **3i**, **3j**, and **3l**). 3-Methoxythiophene (**2b**) also reacted with **1** to give **3k** and **3l**. Even more electron-rich 2,5-dimethoxythiophene (**2c**; as compared with **2a**) also participated in this reaction (Scheme 2). The interesting aspect is that the appropriate choice of reaction conditions enables exclusive access to either the single or double substitution of **2c**, thus leading to **3m** or **3n**, respectively.[11] The single substitution even proceeded at room temperature in a higher yield. Potentially useful quaterheteroaryl **3o** was obtained directly by the double substitution of **2d** with **1b** [Eq. (1)].



(1)

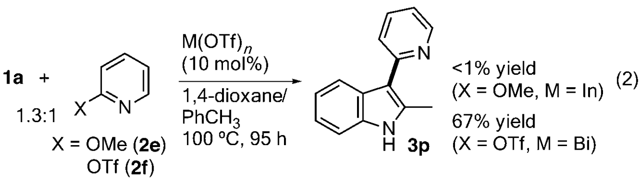


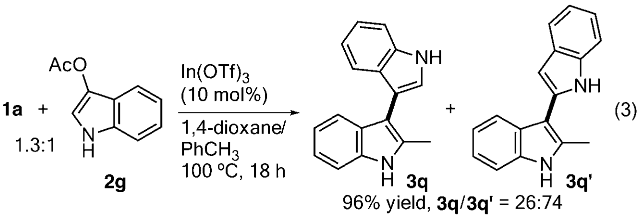
Scheme 1. Indium-catalyzed S$_N$Ar reaction of various indoles **1** with **2a** or **2b**. Yields of isolated **3a**–**3l** are shown here. Further details on reaction conditions for each reaction are provided in the Supporting Information. [a] In(ONf)$_3$ (10 mol%) instead of In(OTf)$_3$ was used.

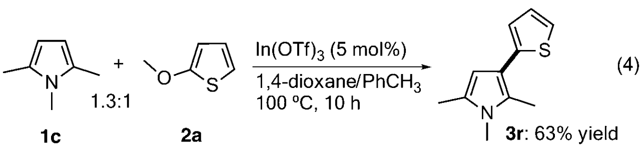


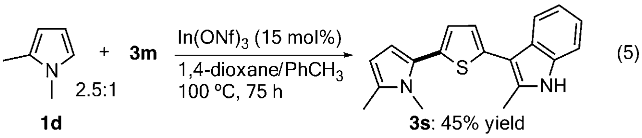
Scheme 2. Indium-catalyzed S$_N$Ar reaction of **1a** with **2c**.

The strategy is also applicable to the synthesis of other bi- and ter-heteroaryls. While the In(OTf)$_3$-catalyzed reaction of **1a** with **2e** bearing the OMe group delivered no desired product, replacing **2e** with **2f** having the OTf group and replacing In(OTf)$_3$ with Bi(OTf)$_3$ altered the result drastically, giving pyridylindole **3p** in 67% yield [Eq. (2)]. 3-Acetoxyindole (**2g**) is an excellent electrophile in terms of the reaction efficiency, but unfortunately not with respect to the regiochemistry [Eq. (3)].[12] We then found that pyrroles **1c**



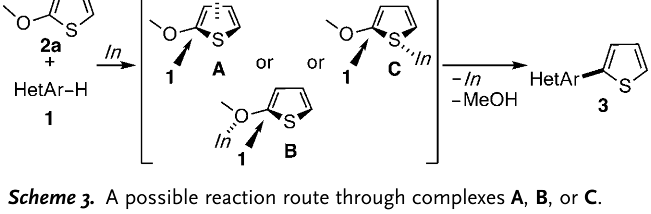




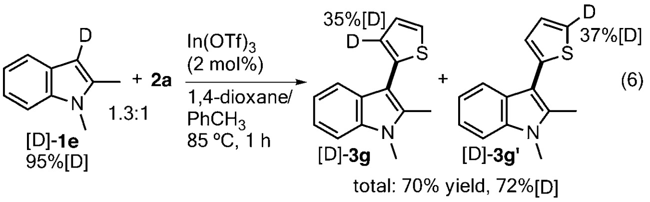


and **1d** also work well as nucleophiles [Eqs. (4) and (5)]. As Equation (5) shows, the substitution of the OMe group in **3m**, which was prepared as shown in Scheme 2, with 1,2-dimethylpyrrole (**1d**) provided ter-heteroaryl **3s** that is connected regularly in the order of pyrrole, thiophene, and indole rings. In this case, In(ONf)$_3$ was a superior catalyst to its triflate salt.[13]

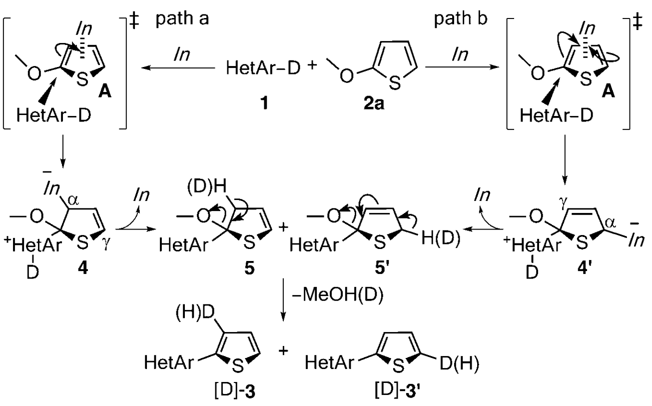
A possible route for this reaction is depicted in Scheme 3, which exemplifies the reaction of **2a** with HetAr–H **1**. At least three coordination modes of **2a** to InX$_3$ (*In*; complexes **A**, **B**, and **C**) appear to be possible as triggers of this reaction. To gain insight into the details, we performed the reaction of deuterium-labeled indole [D]-**1e** (95% [D]) with **2a** under the standard conditions [Eq. (6)]. The reaction gave [D]-**3g** and [D]-**3g′** incorporating a deuterium atom on the C3′- or C5′-poition of the thiophene ring with 72% total deuterium content, thus suggesting that a carbon–indium bond trapped by D$^+$ is formed during the reaction. Therefore, complex **A** in which the carbon atoms of **2a** coordinate directly to the *In* appears to be the most plausible, as well demonstrated in the S$_N$Ar reaction via π complexes between transition metals and arenes.[14] Heteroaryl rings with higher π-electron density are thought to be more favorable for complexation with an electrophilic *In*^{III} atom,[15] thereby they are activated more efficiently. Accordingly, the findings that **2c** with two methoxy groups is much more reactive than **2a** and that thiophenes **2** with electron-withdrawing groups (halides, NO$_2$, CN, OTf) are inactive also support the validity of the reaction proceeding via complex **A** (Scheme 1, Scheme 2, and Table 1).



Scheme 3. A possible reaction route through complexes **A**, **B**, or **C**.



Taking the above observations into consideration, possible mechanisms are depicted in Scheme 4, which shows the reaction of HetAr–D **1** and **2a**.[16] Although it is still unclear at present which one of either path a or path b is in operation, allylindium-type intermediates **4** and/or **4′** would be formed first by the nucleophilic attack of **1** to complex **A**,[17] in which the *In* moiety can be regarded as a tentative EWG to make **2a** electrophilic enough to react. Subsequent transfer of the deuterium atom from the HetAr$^+$–D to the α site and/or γ site in the allylindium unit would give **5** and/or **5′**.[18] The elimination of MeOH(D) for the re-aromatization would lead to [D]-**3** and [D]-**3′**. The 23% loss of the D atom (95% deuteration of [D]-**1e** to total 72% deuteration of [D]-**3g** and [D]-**3g′**) should be ascribed to the final step in which both MeOH and MeOD would be eliminated.



Scheme 4. Possible reaction mechanisms.

In summary, for the first time, we have achieved catalytic heteroaryl–heteroaryl bond formation based on the S$_N$Ar reaction using two easily available heteroaryl substrates that require no activating groups. We also considered the reason why heteroaryl electrophiles **2** without EWGs work well, based on the mechanistic studies on which complex **A** is the plausible coordination mode. In general, transition-metal-catalyzed cross-coupling using indolyl- and pyrrolylmetal compounds is impractical since their presynthesis requires multiple steps.[19] Our strategy will thus be highly useful in such cases.

Experimental Section

Synthesis of **3a** (Scheme 1): In(OTf)$_3$ (2.8 mg, 5.0 μmol) was added to a 20 mL Schlenk tube, which was heated at 150 °C in vacuo for 2 h and then filled with argon. To this were added 1,4-dioxane (0.5 mL) and toluene (40 μL), and the resulting solution was stirred at RT for 10 min before 2-methylindole (42.6 mg, 0.325 mmol) and 2-methoxythiophene (28.5 mg, 0.250 mmol) were added successively. After stirring at 85 °C for 5 h, a saturated NaHCO$_3$ aqueous solution (0.5 mL) was added and the aqueous phase was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine and then dried over anhydrous Na$_2$SO$_4$. Filtration and evaporation of the solvent and subsequent column chromatography on silica gel (*n*-hexane/EtOAc = 6:1) gave 2-methyl-3-(thiophen-2-yl)-1*H*-indole (**3a**; 45.6 mg, 82 %).

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[12] Separate treatment of **3q** or **3q′** with In(OTf)$_3$ (10 mol %) in 1,4-dioxane/toluene (25:1) at 100 °C for 18 h resulted in quantitative recovery of each starting material **3q** or **3q′**, respectively, thus indicating that no isomerization occurs between **3q** and **3q′** under the conditions. As previously demonstrated, formation of **3q′** may possibly be attributed that a cationic intermediate leading to **3q′** is formed via migration of the 2-methylindol-3-yl group from C3′ to C2′ in a cationic intermediate for **3q**: N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185 – 3189; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125 – 3129, and references therein.

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[16] In the cases of **2f** and **2g**, we cannot presently exclude other routes via coordination modes other than the type such as complex **A**.

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