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Coupling and Cyclization of *o*-Iodoanilines and Propargylic Bromides via Allenes: An Efficient Entry to Indomethacin

Can Zhu[†] and Shengming Ma*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China, and Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai, 200062, P. R. China

masm@sioc.ac.cn

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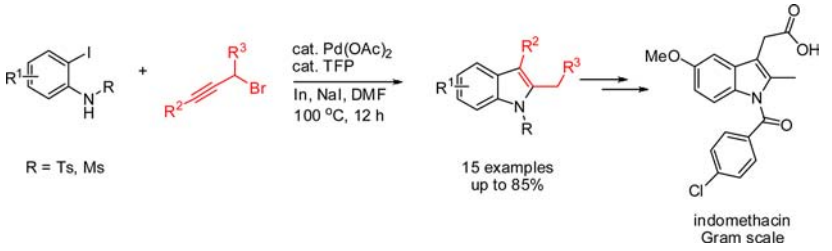
ABSTRACT



A sequential allene synthesis and cyclization has been realized in a one-pot manner. A Pd(0)-catalyzed one-pot reaction of *N*-Ts or -Ms 2-iodoanilines and propargylic bromides afforded indoles with pharmaceutical importance highly efficiently with diversity via sequential carbon−carbon bond coupling forming allenes and azapalladation. With this newly established methodology, an efficient approach to indomethacin, an anti-inflammatory drug (NSAID), has been accomplished.

Allenes are a class of compounds with interesting reactivities owing to the presence of two cumulative carbon−carbon double bonds.[1] Functionalized allenes have been proven to be efficient starting materials for the synthesis of potentially useful carbo- and heterocycles,[2] especially, the transition metal-catalyzed cyclizations of allenes with a nucleophilic functionality which have been demonstrated to be very powerful (Scheme 1).[3] Here the allenes with a nucleophilic functionality have been pre-prepared usually through tedious procedures. Based on our recent effort toward the development of an efficient synthesis of allenes,[4] we envisioned that the seamless combination of efficient allene synthesis and cyclization would greatly improve the efficiency of such approaches. The challenge will be the identification of the suitable transition metal catalyst(s), which may nicely work for

[†] Chinese Academy of Sciences.
[‡] East China Normal University.

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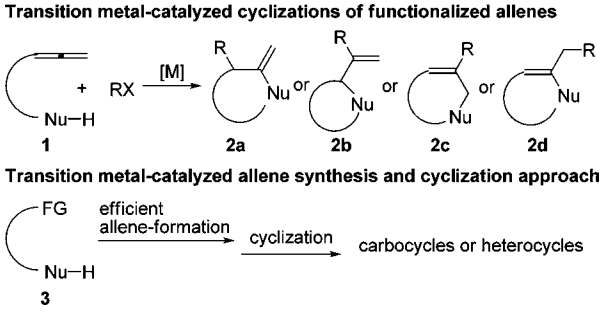
both allene synthesis and cyclization. We wish to report here the realization of such a concept with a palladium catalyst working for both steps, providing a diverse and efficient approach to indoles.

Scheme 1. Cyclization of Functionalized Allenes and the Allene Synthesis–Cyclization Approach[a]

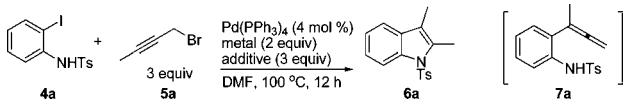


[a] Nu = nucleophilic unit.

We first approached such a concept by applying the coupling of organic halides with an amine functionality with propargylic/allenylic metallic reagents.[5,6] We were initially attempting the Suzuki coupling reaction as well as the Negishi coupling reaction of *N*-tosyl 2-iodoaniline **4a** and allenylic/propargylic metallic reagents for the synthesis of *o*-aminophenylallenes;[7] however, the attempt failed, most probably due to the presence of the *o*-amine functionality (for details, see the Supporting Information).

Our further work began with the palladium(0)-catalyzed coupling of *N*-tosyl 2-iodoaniline **4a** with 1-bromobut-2-yne **5a** given the fact that propargylic bromide is much more reactive toward metals forming allenylic/propargylic organometallic reagents in situ. When the reaction was carried out in *N*,*N*-dimethylformamide (DMF) at 100 °C catalyzed by 4 mol % $Pd(PPh_3)_4$ in the presence of 2.0 equiv of metal such as Zn, Al, Mg, and In, disappointing results were obtained (entries 1–4, Table 1). Surprisingly, when In was chosen as the reductant with the addition of NaI, the indole product **6a** was obtained directly in 81% yield (entry 5, Table 1), and the presence of its allene precursor **7a** was not detected, indicating smooth direct cyclization to the indole product **6a** following the allene formation step via coupling;[8–10] other metals such as Zn, Al, and Mg together with NaI as the additive failed to execute such a transformation (entries 6–8, Table 1). NaI may help to generate the indium reagent and increase the group-transfer ability of the *in situ* generated indium reagent. Further screening led to the observation that LiCl, LiI, or KI failed to show better performance (entries 9–11, Table 1).

Table 1. Palladium-Catalyzed Cross-Coupling Reaction and Cyclization of **4a** with **5a**[a]



entry	metal	additive	yield of **6a** (%)[b]
1	Zn	–	–[c]
2	Al	–	–[d]
3	Mg	–	–
4	In	–	–
5	**In**	**NaI**	**81**
6	Zn	NaI	–[e]
7	Al	NaI	–[f]
8	Mg	NaI	–
9	In	LiCl	30
10	In	LiI	73
11	In	KI	69

[a] The reaction was carried out using **4a** (c = 0.17 M), **5a** (3.0 equiv), metal (2.0 equiv), additive (3.0 equiv), and $Pd(PPh_3)_4$ (4 mol %) at 100 °C in DMF. [b] Determined by ^{1}H NMR analysis with nitromethane as the internal standard. [c] **4a** recovered in 71% yield as determined by ^{1}H NMR analysis. [d] **4a** recovered in 59% yield as determined by ^{1}H NMR analysis. [e] **4a** recovered in 25% yield as determined by ^{1}H NMR analysis. [f] **4a** recovered in 98% yield as determined by ^{1}H NMR analysis. Ts = 4-methylbenzenesulfonyl.

With the inspiring results in hand, we worked toward further optimization of the reaction conditions by applying the ligand effect (Table 2). $Pd(OAc)_2$ together with different phosphine ligands was screened (entries 2–6, Table 2), and fortuitously, with the electron-rich tris(2-furyl)phosphine (TFP) as the ligand, the yield of **6a** was improved to 91% (entry 6, Table 2)! Thus, $Pd(OAc)_2$ (4 mol %), TFP (8 mol %), In (2.0 equiv), and NaI (3.0 equiv) in DMF at 100 °C were defined as the optimal reaction conditions for further study.

The scope of the reaction was then investigated by using the optimal reaction conditions (Table 3). We first studied the cyclization reaction of *N*-tosyl 2-iodoaniline **4a** with different propargylic bromides. When R^2 is H, methyl, *n*-Pr, allyl, or cinnamyl, the reaction showed moderate to good results (entries 1–4 and 7, Table 3). Aryl-substituted

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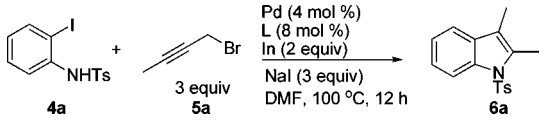
Table 2. Optimization of the Reaction Conditions for the Pd-Catalyzed Cross-Coupling Reaction and Cyclization of **4a** with **5a**[a]



entry	catalyst/ligand	yield of **6a** (%)[b]
1	$Pd(PPh_3)$	81
2	$Pd(OAc)_2/PPh_3$	61
3	$Pd(OAc)_2$/L1[c]	21
4	$Pd(OAc)_2$/L2[d]	53
5	$Pd(OAc)_2$/L3[e]	26[f]
6	**$Pd(OAc)_2$/TFP**[g]	**91**

[a] The reaction was carried out using **4a** (c = 0.17 M), **5a** (3.0 equiv), In (2.0 equiv), NaI (3.0 equiv), palladium complex (4 mol %), and ligand (8 mol %) at 100 °C in DMF. [b] Determined by ^{1}H NMR analysis with nitromethane as the internal standard. [c] L1 = $MePPh_2$. [d] L2 = tris(4-methoxyphenyl)phosphine. [e] L3 = tris(2,4,6-trimethoxyphenyl)-phosphine. [f] **4a** recovered in 5% yield as determined by ^{1}H NMR analysis. [g] TFP = tris(2-furyl)phosphine.

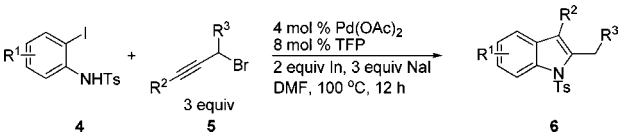
propargylic bromides led to the corresponding products in moderate yields (entries 5−6, Table 3). The reaction also worked with secondary propargylic bromide (entry 8, Table 3). It is worth mentioning that various substituents on the benzene ring were observed to be compatible under the standard reaction conditions, exhibiting diversity: Different R^1 groups, such as fluoro, chloro, bromo, and methoxy at the 4-position (entries 9−12, Table 3) and chloro at the 5-position (entry 13, Table 3), may be introduced to the indole unit, leading to the corresponding indole derivatives in good yields. It is also practical to conduct the reaction of **4a** and **5a** to afford **6a** in 82% yield on gram scale (entry 14, Table 3).

The structure of **6a**−**m** was further confirmed by the X-ray single crystal diffraction study of **6d** (Figure 1).[11]

Further studies showed that the substituent group of the nitrogen atom also greatly influenced the reaction. As observed, *N*-Ts-substituted 2-iodoaniline **4a** (Ts = 4-methylbenzenesulfonyl) afforded the indole product **6a** in 85% yield, while the reaction of *N*-Ms-substituted 2-iodoaniline **4g** (Ms = methanesulfonyl) afforded corresponding product **6n** in 76% yield. However, when we chose *N*-*p*-Ns-substituted 2-iodoaniline **4h** (*p*-Ns = 4-nitrobenzenesulfonyl) as the starting material, a trace amount of indole derivative **6o** was formed (Scheme 2).

(11) Crystal data for **6d**: $C_{19}H_{19}NO_2S$, MW = 325.42, Triclinic, Space group $P\bar{1}$, final R indices [$I > 2s(I)$], R_1 = 0.0540, wR_2 = 0.1531, R indices (all data), R_1 = 0.0651, wR_2 = 0.1652, a = 9.1257(10) Å, b = 9.1641(10) Å, c = 10.7395(12) Å, α = 101.582(2)°, β = 92.848(2)°, γ = 103.302(2)°, V = 851.90(16) Å^3, T = 293(2) K, Z = 2, reflections collected/unique: 5173/3337 (R(int) = 0.0182), number of observations [$> 2s(I)$] 2655; parameter: 228. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 919206 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.

Table 3. Palladium-Catalyzed One-Pot Synthesis of Polysubstituted Indoles from 2-Iodoanilines **4** and Propargylic Bromides **5**[a]



	4	**5**		
entry	R^1	R^2	R^3	yield of **6** (%)[b]
1	H (**4a**)	Me	H (**5a**)	85 (**6a**)
2	H (**4a**)	H	H (**5b**)	54 (**6b**)
3	H (**4a**)	*n*-Pr	H (**5c**)	72 (**6c**)
4	H (**4a**)	Allyl	H (**5d**)	77 (**6d**)[c]
5	H (**4a**)	Ph	H (**5e**)	65 (**6e**)
6	H (**4a**)	*p*-$MeOC_6H_4$	H (**5f**)	57 (**6f**)
7	H (**4a**)	cinnamyl	H (**5g**)	76 (**6g**)
8[d]	H (**4a**)	*n*-Bu	Et (**5h**)	43 (**6h**)
9	4-F (**4b**)	Me	H (**5a**)	85 (**6i**)
10	4-Cl (**4c**)	Me	H (**5a**)	84 (**6j**)
11	4-Br (**4d**)	Me	H (**5a**)	73 (**6k**)
12	4-MeO (**4e**)	Me	H (**5a**)	74 (**6l**)
13	5-Cl (**4f**)	Me	H (**5a**)	77 (**6m**)
14[e]	H (**4a**)	Me	H (**5a**)	82 (**6a**)

[a] The reaction was conducted at 100 °C in DMF with **4** (c = 0.17 M), **5** (3.0 equiv), In (2.0 equiv), and NaI (3.0 equiv) in the presence of $Pd(OAc)_2$ (4 mol %) and TFP (8 mol %). [b] Yield of isolated product. [c] Purity (95%) determined by using CH_3NO_2 as the internal standard. [d] The reaction was conducted at 85 °C with LiCl (3.0 equiv) instead of NaI (3.0 equiv). [e] Gram-scale reaction was conducted with **4a** (1.0071 g) and **5a** (1.0751 g) providing **6a** (0.6610 g).

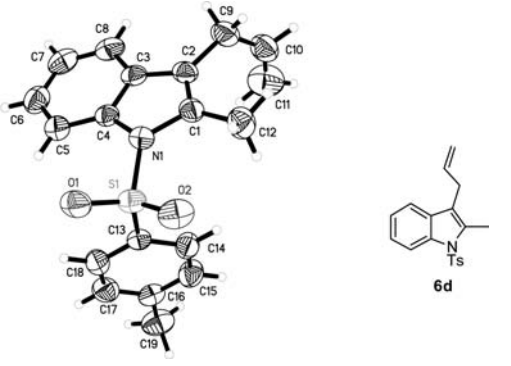


Figure 1. ORTEP drawing of **6d**.

Indomethacin (**12**) is a clinically used non-steroid anti-inflammatory drug (NSAID) to reduce fever, pain, stiffness, and swelling.[13] We demonstrated the potential of this method by applying it to the synthesis of indomethacin on gram scale:[13d,14] It is easy to conduct the reaction of **4e** and **5d** to afford **6p** in 76% yield. Subsequent detosylation[12] and *N*-acylation[14a] led to **9** in 74% yield. Dihydroxylation[15]

Scheme 2. Studies on the Reactivity Using Different *N*-Substituted 2-Iodoanilines

and two-step oxidation[15,16] gave indomethacin (**12**) in 55% yield from **9** (Scheme 3).

In conclusion, we have developed a one-pot sequential reaction for the diverse and efficient synthesis of polysubstituted indoles starting from the readily available diversified 2-iodoanilines and propargylic bomides, involving the intermediacy of allenes. This tandem coupling−cyclization reaction is believed to proceed via palladium(0)-catalyzed carbon−carbon bond formation, involving organoindium reagents generated in situ,[17,18] and cycloisomerization. This protocol has been applied to the gram scale synthesis of indomethacin; thus, this chemistry will be of high interest for organic and medicinal chemists for further studies in related areas. Further studies in this area are currently underway in our laboratory.

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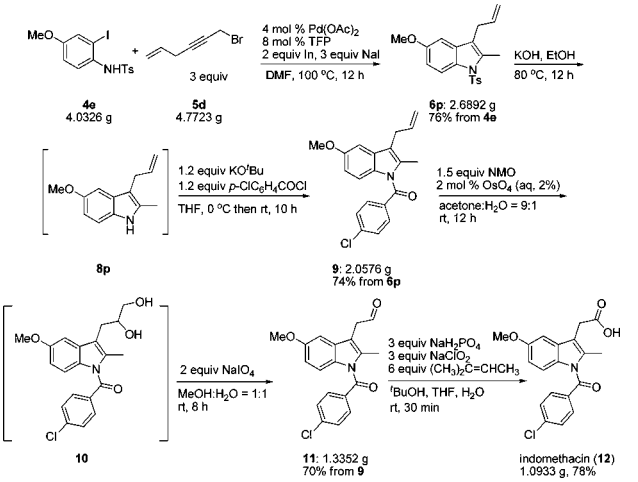
Scheme 3. Approach to Indomethacin (**12**) on Gram Scale



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Supporting Information Available. Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.