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Palladium-Catalyzed Synthesis of 1*H*-Indenes and Phthalimides via Isocyanide Insertion

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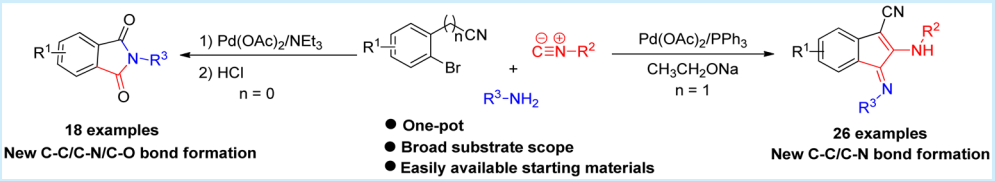
Supporting Information

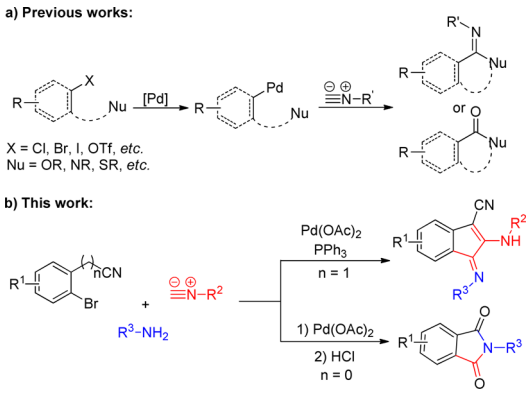


ABSTRACT: A new and versatile multicomponent domino strategy has been developed for the synthesis of a series of 1*H*-indene and phthalimide derivatives from simple and readily available starting materials. This process operating under mild conditions shows a broad substrate scope with moderate to excellent yields.

Indenes are key structural units, widely found in pharmaceutical drugs,[1] natural products,[2] and functional materials.[3] They can also be used as valuable ligands in tailored metallocene complexes for olefin polymerization.[4] For these reasons, many methods have been developed for the construction of an indene skeleton.[5−9] Among them, the transition-metal-catalyzed [3 + 2] cyclization[6] and cycloaddition reactions,[7] Brønsted or Lewis acid catalyzed Friedel−Crafts cyclization,[8] and the ring expansion of substituted cyclopropenes are notable examples.[9] Despite these advances, they often suffered from some limitations (e.g., tedious synthetic sequences, special starting materials, harsh conditions, and narrow functional group compatibility), which greatly limited their applications. Moreover, chemo- and regioselective synthesis of polysubstituted indene derivatives still remains challenging.[10] Therefore, the development of simple and efficient methods to construct polysubstituted indenes from readily available starting materials in one step is highly desirable.

Isocyanides represent an important class of organic molecules which have a broad range of applications in biomedical chemistry and materials science owing to their diverse variations.[11] In the past decades, transition-metal-catalyzed multicomponent reactions (MCRs) involving isocyanides have attracted great attention as a powerful tool in organic synthesis.[12] Most of these strategies involved the formation of aryl- or alkenyl-palladium species and sequential coupling with different nucleophiles to afford various heterocycle compounds (Scheme 1a).[13,14] Although much progress has been achieved in this area, the exploration of different nucleophilic partners to trap the active Pd intermediates should be very important. To the best of our knowledge, the use of an sp^3 carbon atom as a nucleophilic partner to capture the active palladium species has been less explored.[15] Based on our continuous interest in the development of isocyanides,[16] we report an efficient and convenient route for the synthesis of 1*H*-indene and phthalimide derivatives via palladium-catalyzed multicomponent reactions involving isocyanide insertion (Scheme 1b).

Scheme 1. Palladium-Catalyzed MCRs of Isocyanides



Initially, 2-(2-bromophenyl)acetonitrile (**1a**), isonitrile (**2a**), and aniline (**3a**) were treated in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (10 mol %), and NEt_3 (2 equiv) in DMSO at 100 °C for 12 h, and the desired 1*H*-indene product **4aaa** was observed in 77% yield (see entry 1 of Table S1 in the Supporting Information (SI)). Notably, in the absence of

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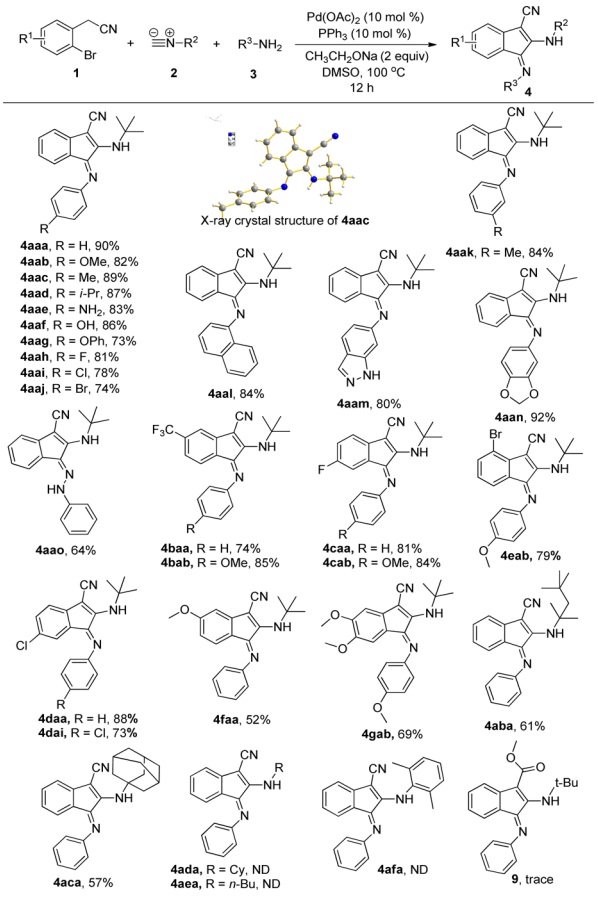
$Pd(OAc)_2$ or NEt_3, no product **4aaa** was detected (Table S1, entries 2−4). Among various solvents tested, DMSO turned out to be the most appropriate (Table S1, entries 5−8). Moreover, replacement of $Pd(OAc)_2$ with other palladium salts resulted in lower yields (Table S1, entries 9−11). The effect of base was also studied. When CH_3CH_2ONa was used as the base, a 92% yield of **4aaa** was obtained (Table S1, entries 12−18). The investigations described above revealed that the $Pd(OAc)_2/PPh_3/CH_3CH_2ONa$/DMSO system is the best combination for promoting this multicomponent reaction (Table S1, entry 18).

With the optimal reaction conditions in hand, a variety of substituted 2-(2-bromophenyl)acetonitriles, isocyanides, and anilines were examined (Scheme 2). To our delight, various

Scheme 2. Synthesis of 1*H*-Indenes Form 2-(2-Bromophenyl)acetonitriles, Isonitriles, and Amines[a]



[a]All reactions were carried out under the following conditions: **1** (0.1 mmol), **2** (0.2 mmol), **3** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (10 mol %), CH_3CH_2ONa (2.0 equiv), DMSO (0.5 mL) at 100 °C for 12 h. Isolated yield is given. ND = not detected.

anilines bearing an electron-donating or -withdrawing group at the benzene ring participated well in the reaction. Anilines **3b**−**3g** possessing an electron-rich group at the *para*-position, such as −OMe, −Me, −*i*Pr, $-NH_2$, −OH, −OPh, transferred to the desired products **4aab**−**4aag** in 82−89% yields. The reactions of anilines having an electron-deficient group at the *para*-position, including −F, −Cl, and −Br groups, furnished the corresponding products **4aah**−**4aaj** in 74−81% yields. The crystallization of compound **4aac** from anhydrous ethanol gave single crystals suitable for X-ray analysis. Aniline **3k** with a substituent at the *meta*-position also reacted smoothly and afforded the target product **4aak** in 84% yield. In addition, some bulky amines, **3l**, **3m**, and **3n**, were well tolerated in this reaction system, giving the corresponding products **4aal**, **4aam**, and **4aan** in 80−92% yields, respectively. Gratifyingly, phenylhydrazine **3o** could also be successfully transformed to the 1*H*-indene derivative **4aao** in 64% yield. Next, we examined the scope of 2-(2-bromophenyl)acetonitriles (**1b**−**1g**). It was observed that 2-(2-bromophenyl)acetonitriles with an electron-withdrawing group, such as 5-CF_3, 4-F, 4-Cl, and 6-Br, at the aryl ring were well tolerated, affording the desired products **4baa**−**4eab** in good yields (73−88%). The transformations of 2-(2-bromophenyl)acetonitriles bearing an electron-donating group, such as 5-methoxy and 4,5-dimethoxy groups, also gave the desired products **4faa** and **4gab** in 52% and 69% yields. Moreover, the sterically hindered 1,1,3,3-tetramethylbutyl isocyanide (**2b**) and adamantyl isocyanide (**2c**) were compatible with the reaction conditions, leading to the formation of **4aba** and **4aca** in 57% and 61% yields, respectively. Unfortunately, the transformations of other isocyanides substituted with an aryl group or a primary or secondary alkyl group failed to afford the corresponding products **4ada**−**4afa** under the optimized conditions. When using methyl 2-(2-bromophenyl)acetate instead of 2-(2-bromophenyl)acetonitrile **1a**, the desired product **9** was afforded in poor yield. The ester group presumably is not conducive to the formation of intermediate **B** (see Scheme 6).

Subsequently, we explored the scope of the palladium-catalyzed isocyanide insertion reaction using 2-bromobenzonitriles and anilines as starting materials. Pleasingly, the desired product phthalimide[17] **6aaa** was obtained in 21% yield with the combination of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and NEt_3 (2 equiv) in 1,4-dioxane at 80 °C for 12 h (see entry 1 of Table S2 in the SI). The reaction did not work if either $Pd(OAc)_2$ or the NEt_3 was absent (Table S2, entries 2−4). The screening of different solvents led to the discovery that toluene was the most effective, forming the product **6aaa** in 52% yield (Table S2, entries 5−8). Some bases, such as *t*-BuOK, K_2CO_3, CH_3ONa, Cs_2CO_3, and CsF, were also tested, but the reaction did not work well under these conditions (Table S2, entries 9−13). With other palladium salts a relatively lower yield of **6aaa** was observed (Table S2, entries 14−17). An obvious improvement in the yield could be obtained as the temperature was increased to 100 °C (Table S2, entries 18−19).

Fortunately, a series of phthalimides could be synthesized through this protocol. As shown in Scheme 3, anilines bearing electron-donating (e.g., 4-OMe, 4-Me, 3-Me, 2-Me, 3,5-dimethyl, 3,4-dimethyl) and electron-withdrawing (e.g., 4-F, 4-Cl, 4-Br) groups on the phenyl rings were converted to the corresponding products **6aab**−**6aar** in moderate to good yields (62−79%). It was found that the sterically hindered anilines were well tolerated regardless of the position of their substituents (e.g., 4-Me, 3-Me, 2-Me, 3,5-dimethyl, 3,4-dimethyl), providing the desired products **6aac**−**6aar** in 70−75% yields. Naphthalen-1-amine (**3l**) was also transformed to the expected product **6aal** in 70% yield. Delightfully, the benzylamine substrates **3s** and **3t** could be converted to the target phthalimides (**6aas**−**6aat**) in moderate yields as well. Furthermore, different substituents on 2-bromobenzonitriles, such as 5-OMe, 4-Me, 4-F, 4-Cl, and 5-CF_3, were fully tolerated, and the conversion delivered the desired products **6baa**−**6faa** in 42−57% yields.

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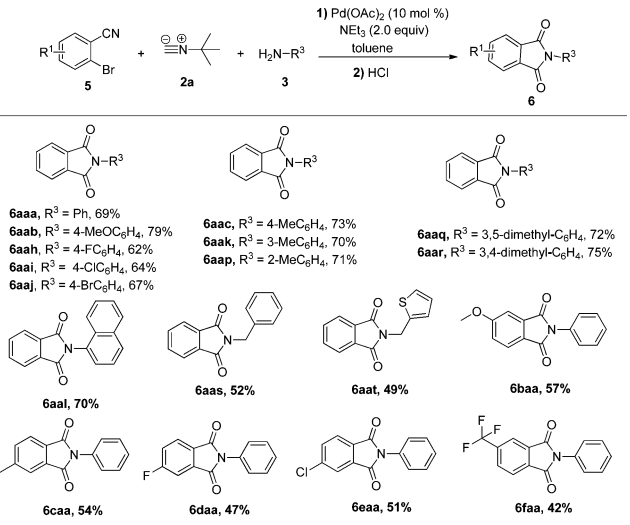
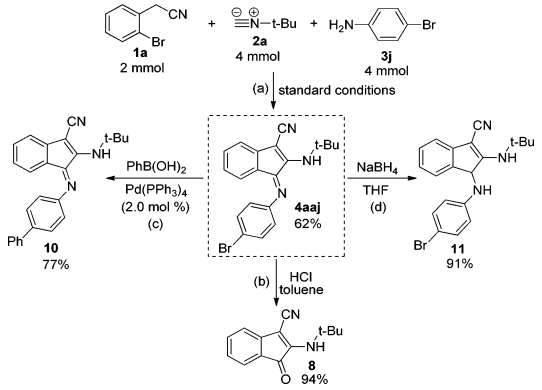
Scheme 3. Synthesis of Phthalimides Form 2-Bromobenzonitriles, *tert*-Butylisonitrile, and Amines[a]



[a]All reactions were carried out under the following conditions: **5** (0.12 mmol), **2a** (0.15 mmol), **3** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), NEt_3 (2.0 equiv), toluene (1 mL) at 100 °C for 12 h, followed by the addition of HCl (4 M, 0.5 mL) for 1 h. Isolated yield is given.

The reaction could be easily scaled up to 2 mmol under the standard conditions and delivered the desired product **4aaj** in 62% yield (Scheme 4a). The synthetic potential of these 1*H*-

Scheme 4. Scale-up Synthesis and Further Modification of 4aaj[a]

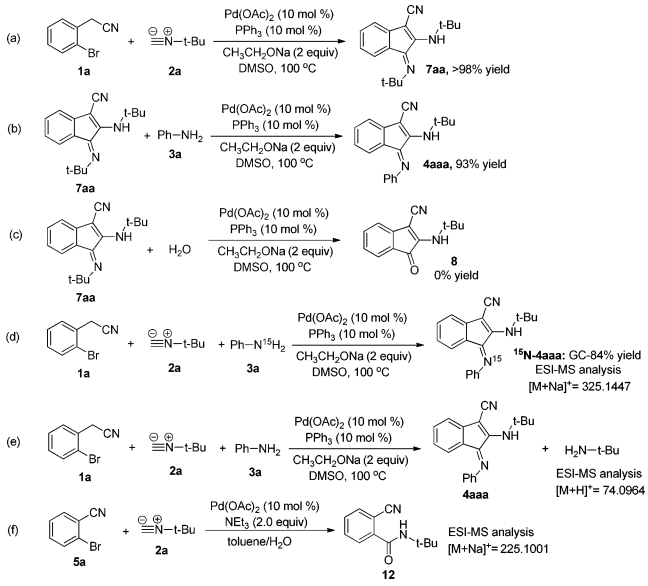


[a]For details of the reaction conditions, see the SI.

indene was demonstrated by further modification of **4aaj**. Hydrolysis of **4aaj** provided the 2-(*tert*-butylamino)-1-oxo-1*H*-indene-3-carbonitrile **8** in 94% yield (Scheme 4b). Arylation of **4aaj** afforded product **10** in 77% yield (Scheme 4c). The reduction reaction also proceeded smoothly to give product **11** in 91% yield under mild conditions (Scheme 4d).

A series of control experiments were then carried out to gain more insight into the reaction mechanism (Scheme 5). Initially, the reaction of 2-(2-bromophenyl)acetonitrile (**1a**) with *tert*-butylisonitrile (**2a**) was performed under the optimal conditions, and **7aa** was formed in 98% yield (Scheme 5a). When **7aa** was treated with aniline **3a**, the target product (*E*)-2-(*tert*-butylamino)-1-(phenylimino)-1*H*-indene-3-carbonitrile (**4aaa**) was obtained in 93% yield (Scheme 5b), which suggested that **7aa** might be an intermediate in this reaction.

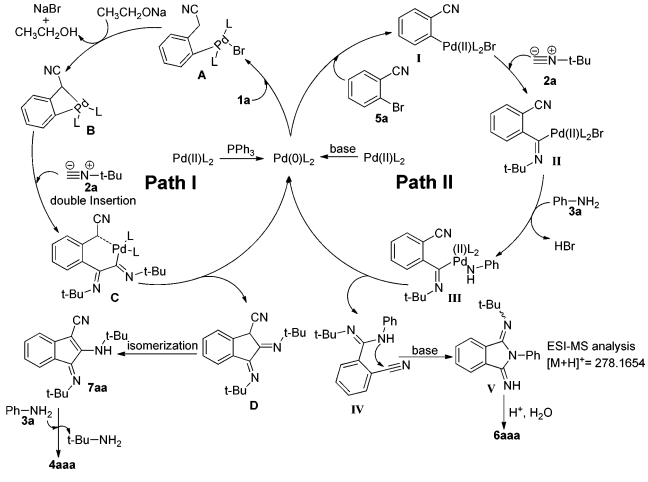
Scheme 5. Control Experiments



However, when **7aa** was treated with 2 equiv of H_2O under the optimal conditions, compound **8** could not be detected (Scheme 5c), indicating that the reaction should not undergo a hydrolysis process. Moreover, the ^{15}N-labeling experiment was also utilized to achieve more insight into this reaction process (Scheme 5d), which indicated that the nitrogen atom of imine in **4aaa** was derived from aniline **3a**. In addition, *tert*-butyl amine (m/z = 74.0964) could be detected in the reaction mixture by ESI-MS (Scheme 5e), suggesting that **4aaa** was formed through an amine exchange reaction between **3a** and **7aa**. Without **3a**, **5a** and **2a** were treated under the standard conditions (Scheme 5f), *N*-(*tert*-Butyl)-2-cyanobenzamide **12** ($[M + Na]^+$ = 225.1001) was detected in HRMS spectra, suggesting that the intermediate **II** was formed[13d] (see Scheme 6).

On the basis of the above results and previous reports, we proposed a plausible reaction mechanism for this transformation detailed in Scheme 6. In path I, oxidative addition of **1a** to the $L_2Pd(0)$ catalyst facilitates the formation of aryl palladium species **A**, which would undergo cyclopalladation with concomitant C−H bond cleavage to give a four-membered

Scheme 6. Possible Reaction Mechanism



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palladium-cyclic species **B**. Next, the double insertion of isocyanide **2a** into the Pd−C bond would produce the intermediate **C**, and reductive elimination of **C** generates the intermediate **D**. Isomerization of intermediate **D** forms compound **7aa**. Finally, the desired product **4aaa** is obtained via an amine exchange reaction between aniline **3a** and **7aa**. In path II, the first step is the formation of palladium species **I** through the oxidative addition of **5a** with $L_2Pd(0)$, followed by the insertion of **2a** to give intermediate **II**, which would react with **3a** to yield the intermediate **III**. Immediately, reductive elimination of **III** provides intermediate **IV** and $L_2Pd(0)$. Then, the nucleophilic addition of amidine to the nitrile forms intermediate **V** ($[M + H]^+ = 278.1654$). Finally, the hydrolysis of **V** under acidic conditions releases the final product **6aaa**.

In conclusion, we have successfully established a flexible and efficient strategy for the construction of 1*H*-indene and phthalimide derivatives involving palladium-catalyzed migratory insertion of isocyanides with easily available starting materials. The reaction proceeds with mild conditions and facile operation and displays wide functional group compatibility. Given these advantages, the present method may be highly useful in synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02771.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

Crystallographic data for **4aac** (CIF)

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Notes

The authors declare no competing financial interest.

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