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# Two Palladium-Catalyzed Domino Reactions from One Set of Substrates/Reagents: Efficient Synthesis of Substituted Indenes and *cis*-Stilbenoid Hydrocarbons from the Same Internal Alkynes and Hindered Grignard Reagents

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## Abstract

Two types of domino reactions from the same internal alkynes and hindered Grignard reagents based on carbopalladation, Pd-catalyzed cross-coupling reaction and C-H activation strategy are described. The realization of these domino reactions relied on the control of the use of the ligand and the reaction temperature. Our study provides an efficient access to useful polysubstituted indenes and *cis*-substituted stilbenes, and may offer new means to the development of tandem/domino reactions in a more efficient way.

The development of transition metal-catalyzed tandem or "domino" reactions, which combine two or more bond-forming reactions into one synthetic operation, represents one of the most attractive subjects in synthetic organic chemistry.[1,2] Such tandem/domino reactions allow the concomitant formation of two or more bonds with rapid increase in molecular complexity with minimized separation/purification efforts. Since arranging two or more bond-forming reactions to occur in a tandem or domino fashion is always challenging, it is not surprising to observe that almost all tandem/domino reactions were developed on a basis of one type of tandem/domino reaction per one set of substrates/reagents.[1–3] Developing two or more types of tandem/domino reactions from the same substrates and reagents, which represents a strategy that could further heighten the efficiency of conducting reactions in a tandem/domino fashion, is apparently very attractive, but remains to be largely unexplored.[4]

We have recently documented the palladium-catalyzed tandem reaction of 1,2-dhalobenzenes and 2-haloaryl tosylates with hindered Grignard reagents to form substituted fluorenes,[5] in which palladium-associated arynes were believed to be the intermediates when the reaction was carried out in the absence of phosphines or *N*-heterocyclic carbenes ligands.[5b] The triple bond nature of arynes led us to consider that alkynes might also function similarly as *in situ* generated arynes. We thus envisioned that carbopalladation of alkynes could generate vinylpalladium(II)X complexes **I** (Scheme 1).[6] **I** could then (a) undergo cyclization via C-H activation[7,8] to afford substituted indenes, which are structural constituents of metallocene-based catalysts for olefin polymerizations, of biologically active compounds and of functional materials;[9,10] and (b) undergo transmetalation followed by reductive elimination (cross-coupling process) to yield *cis*-stilbenoid hydrocarbons, which are potentially useful in the fields of molecular sensors and molecular electronics.[11,12] Therefore, two types of domino reactions, namely domino carbopalladation-cyclization to form polysubstituted indenes and

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domino carbopalladation–cross-coupling to form *cis*-stilbenoid hydrocarbons containing highly substituted phenyl groups, might be developed from the same alkynes and hindered Grignard reagents if the two competing pathways could be controlled (Scheme 1). Herein, we report our successful realization of these two types of reactions by controlling the use of ligand and the reaction temperature.

Based on the consideration that the activation of C-H bond would involve the interaction of C-H bond with $Pd^{(II)}$ center and such interaction would be disfavored at higher reaction temperature and/or in the presence of ligands, we surmised the cyclization via $sp^3$ C-H activation process would be favored in the absence of ligands and at lower reaction temperature. We thus began our study by examining the reaction of diphenylacetylene with 2-mesitylPd(II)(OAc), *in situ* generated from 2-mesitylmagnesium bromide with $Pd(OAc)_2$. We found the domino carbopalladation-cyclization product 4,6-dimethyl-2,3-diphenylindene was the major product with only $Pd(OAc)_2$ as the promoter, either at room temperature, 60 C or refluxing (Table 1, entries 1, 2, 5). The use of $PPh_3$ as a ligand decreases the formation of the cyclization product as well as slowed down the reaction (Table 1, entries 2–4). By using 4 equiv. of $PPh_3$ and in refluxing THF, the domino carbopalladation–cross-coupling product became the major product, along with the self-coupling of Grignard reagent as the main side reaction (Table 1, entry 7). Our results suggested that by controlling the use of ligand and reaction temperature, it is possible to control the domino reaction pathways.

As $Pd(II)X_2$ would be reduced to Pd(0) species after every reaction cycle, after establishing factors that influence the reaction competing pathways, we next turned our attention to develop the catalytic version of these two types of domino reactions by identifying oxidants that could oxidize Pd(0) species to Pd(II) species. We have tested several commonly available oxidants and found 1,2-dibromoethane can be served as an excellent oxidizer (Table 2). By using a stoichiometric amount of 1,2-dibromoethane and 3% $Pd(OAc)_2$, the domino carbopalladation-cyclization process proceeded smoothly to give 4,6-dimethyl-2,3-diphenylindene in excellent yield (Table 2, entry 6).

With 1,2-dibromoethane as the oxidant, a number of alkynes were examined for the $Pd(OAc)_2$-catalyzed domino carbopalladation-cyclization reaction and our results are listed in Table 3. We found that diaryl-, dialkyl- and alkylarylacetylenes were all suitable substrates. When unsymmetrical alkylarylacetylenes were employed as the substrates, we found the domino reaction occurred mainly from the alkyl sides of alkyarylacetylenes,[13] as evidenced by the ratio of two isomeric products (Table 3, entries 9–13). To determine whether other types of hydrogens (nonbenzylic 1° hydrogens, benzylic 2°, and 3° hydrogens) could also be activated under our condition, we have tested 2-ethyl-6-methylphenylmagnesium bromide and 2-isopropyl-6-methylphenylmagnesium bromide for the domino reaction. We found that the $sp^3$ C-H activation exclusively occurred at the benzylic methyl group, suggesting that nonbenzylic 1° hydrogens (nonbenzylic methyl group), 2° (ethyl group) and 3° (isopropyl group) benzylic hydrogens could not be activated (Table 3, entries 14, 15). This was further confirmed by the fact that no reaction was observed for 2,6-diethylphenylmagnesium bromide with diphenyl-acetylene (Table 3, entry 16).

By using 1,2-dibromoethane as the oxidant, 4 equivalent of $PPh_3$ relative to $Pd(OAc)_2$ and in refluxing THF, we were also able to realize the second type of domino reaction, the carbopalladation followed by cross-coupling, to form *cis*-stilbenes,[11,12] in a catalytic fashion. *cis*-Substituted stilbenes containing highly substituted phenyl groups were obtained in good yields from the same alkynes and hindered Grignard reagents that form polysubstituted indenes (Table 4). Our results also suggested that $Pd(PPh_3)_2Cl_2$-catalyzed reactions of *trans*-1,2-dibromoalkenes with Grignard reagents in refluxing THF to give *cis*-substituted stilbenes[12a] most likely also proceeded with alkynes and **I** as the reaction intermediates.[14]

In summary, we developed two types of Pd-catalyzed domino reactions from the same alkynes and hindered Grignard reagents by controlling the use of ligand and the reaction temperature. We also showed that only benzylic methyl hydrogens might be activated by Pd(II) species. Our study provided an efficient access to useful polysubstituted indenes and *cis*-substituted stilbenes from simple, commercially available starting materials/reagents. The ligand and temperature factors for controlling the domino reaction pathways identified in this study may also be applicable for other cross-coupling and C-H activation-based tandem/domino reactions. Work toward this direction is underway.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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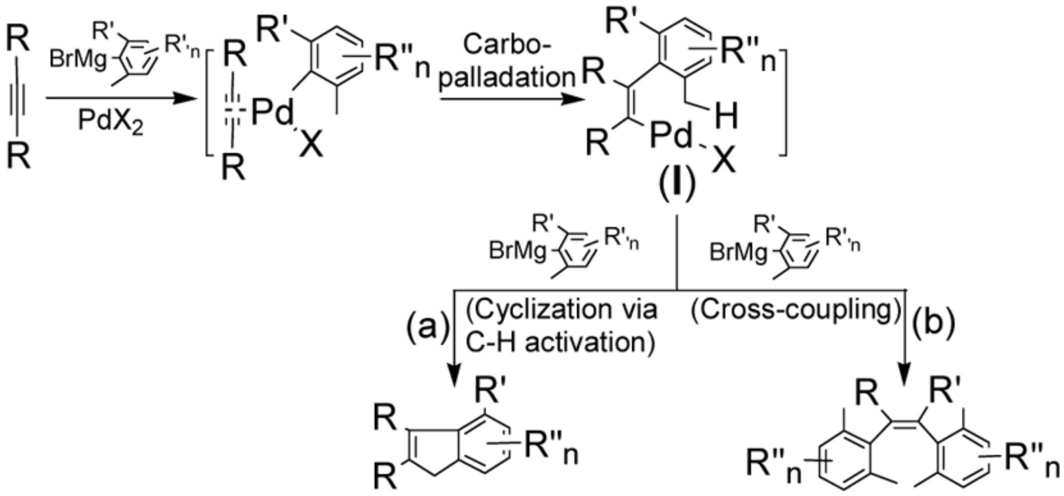
13. A similar regioselectivity trend was observed in Pd-catalyzed three-component reactions of aryl iodides, internal alkynes and arylboronic acids: Zhou C, Larock RC. J Org Chem 2005;70:3765–3777. [PubMed: 15876060]

14. $Pd(PPh_3)_2Cl_2$-catalyzed reactions of *trans*-1,2-dibromoalkenes with Grignard reagents in refluxing THF were reported to give *cis*-substituted stilbenes in excellent yields (Ref. 12a). In our hands, we found $Pd(PPh_3)_2Cl_2$-catalyzed reaction of *trans*-1,2-dibromo-1,2-diphenyl-ethene with pentamethlphenylmagnesium bromide indeed gave *cis*-substituted stilbene in 86% yield. However, we also found $Pd(PPh_3)_2Cl_2$-catalyzed reactions of *trans*-1,2-dibromo-1,2-diphenylethene or *trans*-3,4-dibromo-3-hexene with 2-mesitylmagnesium bromide or 2,6-dimethylhenylmagnesium bromide in refluxing THF gave significant amounts of substituted indenes (>18%); When the reaction temperature was 60°C, substituted indenes were obtained in 70–98% yields

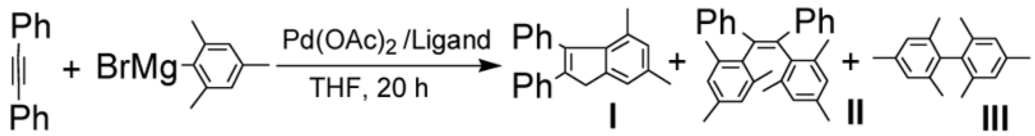


**Scheme 1.**

Domino Carbopalladation-Cyclization via *sp*$^3$ C-H Activation vs. Domino Carbopalladation-Cross-Coupling Reaction

## Table 1

Pd(OAc)$_2$-Promoted Domino Reaction of Diphenylacetylene with 2-Mesitylmagnesium Bromide [a]



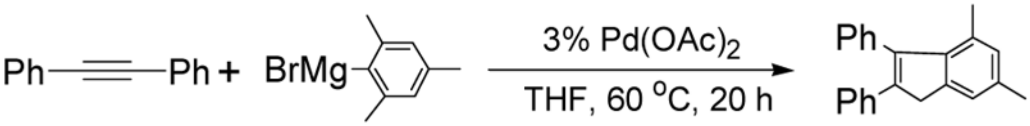
| entry | ligand | temperature | conversion | ratio[b] I | II | III |
|---|---|---|---|---|---|---|
| 1 | None | R. T. | 85% | 97 : | 2 : | 1 |
| 2 | None | 60 | 99% | 90 : | 2 : | 8 |
| 3 | 2 equiv $PPh_3$ | 60 | 75% | 81 : | 9 : | 10 |
| 4 | 4 equiv $PPh_3$ | 60 | 60% | 20 : | 24 : | 56 |
| 5 | None | Reflux | 99% | 93 : | 3.5 : | 3.5 |
| 6 | 2 equiv $PPh_3$ | Reflux | 99% | 69 : | 12 : | 19 |
| 7 | 4 equiv $PPh_3$ | Reflux | 81% | 2 : | 67 : | 31 |

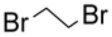
[a] Reaction conditions: diphenylacetylene (1.0 equiv), Grignard reagent (2.5 equiv), Pd(OAc)$_2$ (1 equiv), THF (2 mL), 20 h.

[b] Based on $^1$H NMR.

**Table 2**

Pd(II)-Catalyzed Domino Reaction of Diphenylacetylene with Mesitylmagnesium Bromide [a]



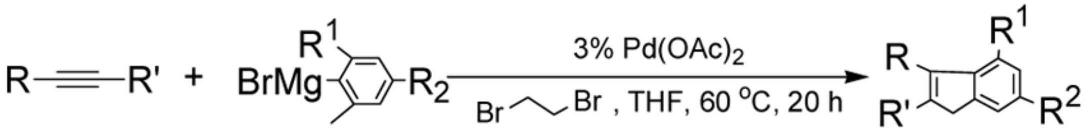
| entry | additives | yield (%) |
|---|---|---|
| 1 | None | $< 2$[b] |
| 2 | $CuCl_2$ | $< 2$[b] |
| 3 | $CuSO_4$ | $< 2$[b] |
| 4 | $FeCl_3$ | 15 |
| 5 | $Ag2CO_3$ | 5 |
| 6 |  | 87 |

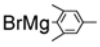
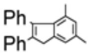
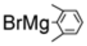
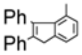
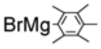
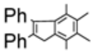
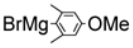
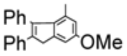
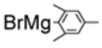
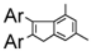
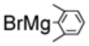
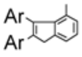
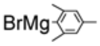
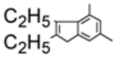
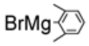
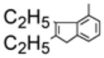
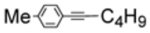
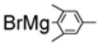
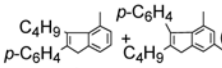
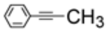
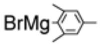
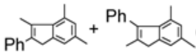
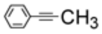
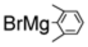
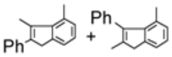
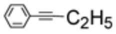
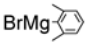
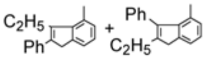
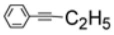
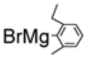
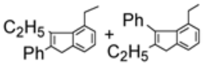
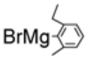
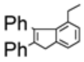
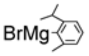
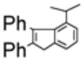
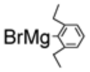
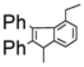
[a] Reaction conditions: diphenylacetylene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 mL).

[b] Conversion based on $^1H$ NMR

## Table 3

Pd(OAc)$_2$-Catalyzed Cyclizations of Internal Alkynes with Hindered Grignard Reagents[a]



| entry | alkyne | ArMgBr | product | yield(%)[b] |
|---|---|---|---|---|
| 1 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 87 |
| 2 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 85 |
| 3 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 81 |
| 4 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 87 |
| 5 |  |  |  | 97 |
| 6 |  |  |  | 94 |
| 7 | $C_2H_5{\equiv}C_2H_5$ |  |  | 71 |
| 8 | $C_2H_5{\equiv}C_2H_5$ |  |  | 77 |
| 9 |  |  |  (91:9)[c] | 78 |
| 10 |  |  |  (92:8)[c] | 72,[d,e] |
| 11 |  |  |  (90:10)[c] | 64,[d,f] |
| 12 |  |  |  (89:11)[c] | 85 |
| 13 |  |  |  (85:15)[c] | 67 |
| 14 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 69 |
| 15 | $\mathrm{Ph{\equiv}Ph}$ |  |  | 78 |
| 16 | $\mathrm{Ph{\equiv}Ph}$ |  |  | <2%[g] |

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[a] Reaction conditions: alkyne (1.0 equiv), Grignard reagent (2.5 equiv), Pd(OAc)$_2$ (3%), 1,2-dibromoethane (1.0 equiv.), THF (2 ml), 60 °C.

[b] Isolated yields.

[c] Ratio based on $^1$H NMR.

[d] Reaction condition: room temperature, 30 h.

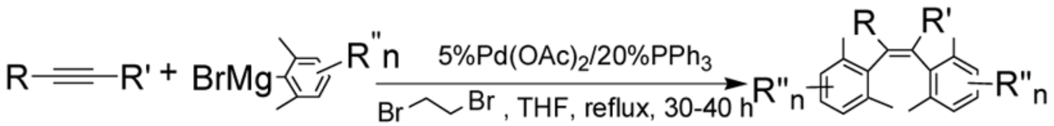
[e] 15% Crossc-oupling product was observed.

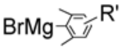
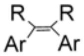
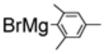
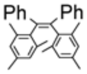
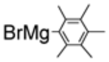
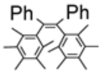
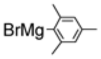
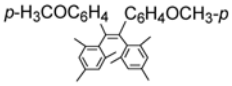
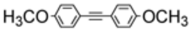
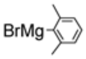
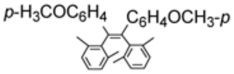
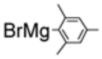
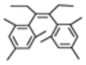
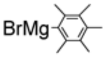
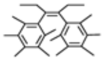
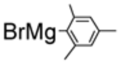
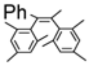
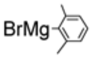
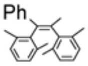
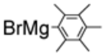
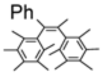
[f] 21% Cross-coupling product was observed.

[g] Reaction time: 45 h.

## Table 4

Pd(OAc)$_2$-Catalyzed Domino Carbopalladation-Cross-coupling of Internal Alkynes and Hindered Grignard Reagents [a]



| entry | $R\equiv R$ |  |  | yield(%)[b] |
|---|---|---|---|---|
| 1 | $Ph\equiv Ph$ |  |  | 71 |
| 2 | $Ph\equiv Ph$ |  |  | 65 |
| 3 |  |  |  | 72 |
| 4 |  |  |  | 69 |
| 5 | $C_2H_5\equiv C_2H_5$ |  |  | 60 |
| 6 | $C_2H_5\equiv C_2H_5$ |  |  | 81 |
| 7 | $Ph\equiv CH_3$ |  |  | 78 |
| 8 | $Ph\equiv CH_3$ |  |  | 74 |
| 9 | $Ph\equiv CH_3$ |  |  | 81 |

[a] Reaction conditions: alkyne (1.0 equiv), Grignard reagent (4.0 equiv), 1,2-dibromoethane (1.5 equiv), Pd(OAc)$_2$ (5%), PPh$_3$ (20%), THF (2 mL), refluxing, 30–40 h.

[b] Isolated yields.