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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

Cheng-Guo Dong, Pik Yeung, and Qiao-Sheng Hu*

Department of Chemistry, College of Staten Island and the Graduate Center of the City University of New York, Staten Island, New York 10314

qiaohu@mail.csi.cuny.edu

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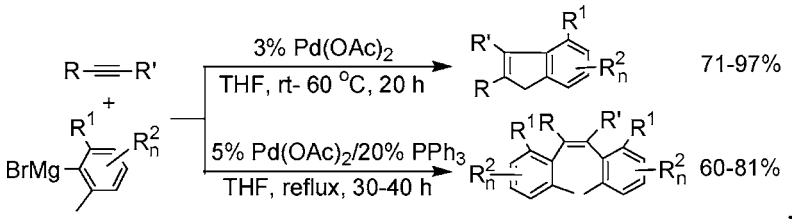
ABSTRACT



Two types of domino reactions from the same internal alkynes and hindered Grignard reagents based on carbopalladation, Pd-catalyzed cross-coupling reaction, and a 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 efficient access to useful polysubstituted indenes and cis-substituted stilbenes and may offer a new means of 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 a rapid increase in molecular complexity with minimized separation/purification efforts. Because 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 the 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 largely unexplored.[4]

We have recently documented the palladium-catalyzed tandem reaction of 1,2-dihalobenzenes and 2-haloaryl tosylates with hindered Grignard reagents to form substituted fluorenes,[5] in which palladium-associated arynes were be-

(1) (a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001−1020. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967−1983. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136 and references cited therein.

(2) (a) de Meijere, A.; von Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413−422. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (c) Ikeda, S.-i. *Acc. Chem. Res.* **2000**, *33*, 511−519. (d) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (e) Heumann, A.; Reglier, M. *Tetrahedron* **1996**, *52*, 9289−9346. (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306 and references cited therein.

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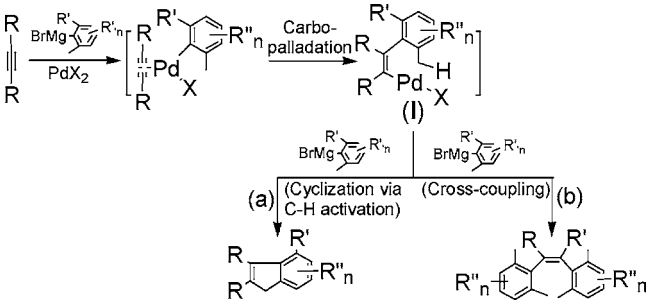
lieved to be the intermediates when the reaction was carried out in the absence of phosphines or *N*-heterocyclic carbene ligands.[5b] The triple bond nature of arynes led us to consider that alkynes might also function similarly as in situ generated arynes. We thus envisioned that carbopalladation of alkynes could generate vinylpalladium(II)X complexes **I** (Scheme 1).[6]

Scheme 1. Domino Carbopalladation−Cyclization via sp^3 C−H Activation vs Domino Carbopalladation−Cross-Coupling Reaction



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 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 ligands and the reaction temperature.

On the basis of the consideration that the activation of a C−H bond would involve the interaction of a C−H bond with a $Pd^{(II)}$ center and that such an interaction would be disfavored at higher reaction temperature and/or in the presence of ligands, we surmised the cyclization via an 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 that the domino carbopalladation−cyclization product 4,6-dimethyl-2,3-diphenylindene was the major product with only $Pd(OAc)_2$ as the promoter, at room temperature, 60 °C, or refluxing (Table 1, entries 1, 2, and 5). The use of PPh_3 as a ligand decreases the formation of the cyclization product and slows down the reaction (Table 1, entries 2−4). By using 4 equiv of PPh_3 in refluxing THF, the domino carbopalladation−cross-coupling product became the major product, along with the self-coupling of the Grignard reagent as the main side reaction (Table 1, entry 7). Our results suggested that by controlling the use of the ligand and reaction temperature, it is possible to control the domino reaction pathways.

As $Pd(II)X_2$ would be reduced to Pd(0) after every reaction cycle, after establishing factors that influence the reaction competing pathways, we next turned our attention to developing 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

(3) Selected recent examples of Pd-catalyzed tandem/domino reactions: (a) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436−14437. (b) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353−2356. (c) Leclerc, J.-P.; Andre, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711−1714. (d) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426−7427. (e) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927−4930. (f) Martins, A.; Marquardt, U.; Kasravi, N.; Alberico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937−4942. (g) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468−16476. (h) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (i) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149. (j) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701−704. (k) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103−5106. (l) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575−2578. (m) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741−3744. (n) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701−704. (o) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777−4779. (p) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454−6460. (q) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460−7461. (r) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620−1621. (s) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605−3608.

(4) For examples: (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893−2901. (b) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644−8651. Also see refs 1 and 2.

(5) (a) Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2006**, *8*, 5057−5060. (b) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289−2292.

(6) Recent reviews for carbopalladation of alkynes: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2310. (b) de Meijere, A.; von Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413−422.

(7) Recent reviews for C−H activation: (a) Dyker, G., Ed. *Handbook of C-H Transformations: Application in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; Vol. 2. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077−1101. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639.

(8) For examples of Pd-catalyzed cyclizations via sp^3 C−H activation: (a) Baudoin, O.; Herrbach, A.; Gueritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736−5740. (b) Suau, R.; Lopez-Romero, J. M.; Rico, R. D. *Tetrahedron Lett.* **1996**, *37*, 9357−9360. (c) Dyker, G. *J. Org. Chem.* **1993**, *58*, 6426−6428. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1994**, *33*, 103−105. (e) Dyker, G. *Angew. Chem., Int. Ed.* **1992**, *31*, 1023−1025.

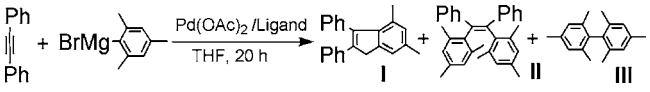
(9) (a) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205−1222. (b) Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, *13*, 2397−2399 and references therein. (c) Barbera, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296−299.

(10) Substituted indenes were typically prepared in more than one step. For recent examples of one-pot access to substituted indenes with different substitution patterns from 2-(2-(1-alkynyl)phenyl)malonates or 2-(2-halophenyl)malonate: (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325−3327. (b) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963−4966. Also see: (c) Kuninobu, Y.; Nishina, Y.; Takai, K. *Org. Lett.* **2006**, *8*, 2891−2893. (d) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423−15430.

(11) (a) Rathore, R.; Lindeman, S. V.; Kochi, J. K. *Angew. Chem.* **1998**, *110*, 1665−1667; *Angew. Chem., Int. Ed.* **1998**, *37*, 1585−1587. (b) Irie, M. *Chem. Rev.* **2000**, *100*, 1685−1716.

(12) The most efficient preparation methods reported so far involve the use of 1,2-dibromoalkenes with hindered Grignard reagents: (a) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832−14833. For other methods: (b) Maeda, K.; Okamoto, Y.; Morlender, N.; Haddad, N.; Eventova, I.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9686−9689. (c) Bottino, F. A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 77−81.

Table 1. $Pd(OAc)_2$-Promoted Domino Reaction of Diphenylacetylene with 2-Mesitylmagnesium Bromide[a]

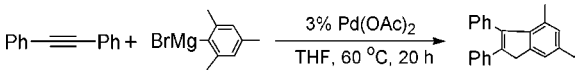


entry	ligand	temp	conversion	ratio[b] I	II	III
1	none	rt	85%	97	2	1
2	none	60	99%	90	2	8
3	2 equiv of PPh_3	60	75%	81	9	10
4	4 equiv of PPh_3	60	60%	20	24	56
5	none	reflux	99%	93	3.5	3.5
6	2 equiv of PPh_3	reflux	99%	69	12	19
7	4 equiv of PPh_3	reflux	81%	2	67	31

[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 ^1H NMR.

available oxidants and found 1,2-dibromoethane can be used 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).

Table 2. Pd(II)-Catalyzed Domino Reaction of Diphenylacetylene with Mesitylmagnesium Bromide[a]

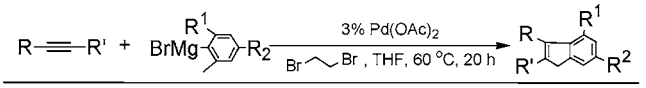


entry	additives	yield (%)
1	none	<2[b]
2	$CuCl_2$	<2[b]
3	$CuSO_4$	<2[b]
4	$FeCl_3$	15
5	Ag_2CO_3	5
6	Br Br	87

[a] Reaction conditions: diphenylacetylene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 mL). [b]Conversion based on ^1H NMR.

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 alkylarylacetylenes,[13] as evidenced by the ratio of the two isomeric products (Table 3, entries 9−13). To determine whether other types of hydrogens (nonbenzylic 1° hydrogens and benzylic 2° and 3° hydrogens) could also be activated under our conditions, 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) and 2° (ethyl group) and 3° (isopropyl group) benzylic hydrogens could not be activated (Table 3, entries 14 and 15). This was further confirmed by the fact that no reaction was observed for 2,6-diethylphenylmagnesium bromide with diphenylacetylene (Table 3, entry 16).

Table 3. $Pd(OAc)_2$-Catalyzed Cyclizations of Internal Alkynes with Hindered Grignard Reagents[a]



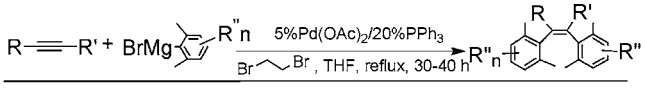
entry	alkyne	ArMgBr	product	yield(%)[b]
1	Ph−≡−Ph	BrMg	Ph, Ph	87
2	Ph−≡−Ph	BrMg	Ph, Ph	85
3	Ph−≡−Ph	BrMg	Ph, Ph	81
4	Ph−≡−Ph	BrMg-OMe	Ph, Ph, OMe	87
5	MeO-≡-OMe	BrMg	Ar, Ar	97
6	MeO-≡-OMe	BrMg	Ar, Ar	94
7	C_2H_5−≡−C_2H_5	BrMg	C_2H_5, C_2H_5	71
8	C_2H_5−≡−C_2H_5	BrMg	C_2H_5, C_2H_5	77
9	Me−≡−C_4H_9	BrMg	C_4H_9, p-C_6H_4 + C_4H_9, p-C_6H_4 (91:9)[c]	78
10	−≡−CH_3	BrMg	Ph + Ph (92:8)[c]	72[d,e]
11	−≡−CH_3	BrMg	Ph + Ph (90:10)[c]	64[d,f]
12	−≡−C_2H_5	BrMg	C_2H_5, Ph + Ph, C_2H_5 (89:11)[c]	85
13	−≡−C_2H_5	BrMg	C_2H_5, Ph + Ph, C_2H_5 (85:15)[c]	67
14	Ph−≡−Ph	BrMg	Ph, Ph	69
15	Ph−≡−Ph	BrMg	Ph, Ph	78
16	Ph−≡−Ph	BrMg	Ph, Ph	< 2%[g]

[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 ^1H NMR. [d]Reaction conditions: room temperature, 30 h. [e]15% cross-coupling product was observed. [f]21% cross-coupling product was observed. [g]Reaction time: 45 h.

By using 1,2-dibromoethane as the oxidant and 4 equiv of PPh_3 relative to $Pd(OAc)_2$ in refluxing THF, we were also able to realize the second type of domino reaction, carbopalladation followed by cross-coupling, to form *cis*-stilbenes,[11,12] in a catalytic fashion. Cis-substituted stilbenes

(13) A similar regioselectivity trend was observed in Pd-catalyzed three-component reactions of aryl iodides, internal alkynes, and arylboronic acids: Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765−3777.

Table 4. $Pd(OAc)_2$-Catalyzed Domino Carbopalladation−Cross-Coupling of Internal Alkynes and Hindered Grignard Reagents[a]



entry	R−≡−R	BrMg−R'	R, R / Ar, Ar	yield(%)[b]
1	Ph−≡−Ph	BrMg−	Ph, Ph	71
2	Ph−≡−Ph	BrMg−	Ph, Ph	65
3	H_3CO− −OCH$_3$	BrMg−	*p*-$H_3COC_6H_4$, $C_6H_4OCH_3$-*p*	72
4	H_3CO− −OCH$_3$	BrMg−	*p*-$H_3COC_6H_4$, $C_6H_4OCH_3$-*p*	69
5	C_2H_5−≡−C_2H_5	BrMg−		60
6	C_2H_5−≡−C_2H_5	BrMg−		81
7	Ph−≡−CH_3	BrMg−	Ph	78
8	Ph−≡−CH_3	BrMg−	Ph	74
9	Ph−≡−CH_3	BrMg−	Ph	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.

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 ligands and the reaction temperature. We also showed that only benzylic methyl hydrogens might be activated by Pd(II) species. Our study provided 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.

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Supporting Information Available: General procedures and product characterizations for palladium-catalyzed domino reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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(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-diphenylethene with pentamethylphenylmagnesium 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-dimethylphenylmagnesium 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.