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Rh(I)-Catalyzed Decarbonylation of Diynones via C–C Activation: Orthogonal Synthesis of Conjugated Diynes

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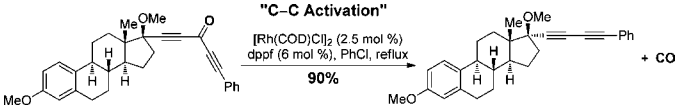
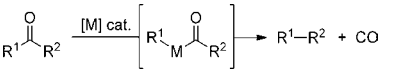
ABSTRACT



Utilization of C–C bond activation as a unique mode of reactivity for constructing C–C bonds provides new strategies for preparing important organic molecules. Development of a Rh(I)-catalyzed C–C activation of diynones to synthesize symmetrical and unsymmetrical conjugated diynes through decarbonylation is reported. This C–C cleavage strategy takes advantage of the innate reactivity of conjugated ynones without relying on any ring strain or auxiliary directing group. This alkynation method also has orthogonal properties compared to typical cross-coupling reactions.

Nonmetathesis-based transition-metal-catalyzed C–C bond activation has recently emerged as a unique platform for developing new catalytic transformations.[1] Among various activation modes, C–C cleavage assisted by an adjacent carbonyl group has become an increasingly recognized strategy due to the high occurrence of ketones in organic molecules.[1b,d,j] In particular, oxidative insertion of metals into the ketone α C–C bond followed by CO extrusion and reductive elimination (namely decarbonylative C–C cleavage/coupling, as shown in Scheme 1) represents an underutilized but attractive method to form C–C bonds.[2]

Scheme 1



The elegant work by Murakami/Ito,[3] Kondo,[4] and Yamamoto[5] has demonstrated catalytic pathways for decarbonylation of four-membered ketones leading to ring contraction or expansion (Figure 1A). More recently, Shi et al.[6] disclosed a Rh-catalyzed biaryl synthesis through C–C decarbonylation/coupling using a pyridyl group as an auxiliary directing group (ADG, Figure 1B). In contrast to these two strategies, catalytic decarbonylative C–C cleavage/coupling with linear ketones lacking ring strain or ADGs remains largely underdeveloped.[7] Conjugated diynes, namely 1,3-diynes, are an important structural

(1) For recent reviews on C–C activation, see: (a) Rybtchiski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (b) Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97. (c) M. E. van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (d) Jun, C. H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1. (f) Jun, C. H.; Park, J. W. *Top. Organomet. Chem.* **2007**, *24*, 117. (g) Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (h) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (i) W. D. Jones, W. D. *Nature* **1993**, *364*, 676. (j) Kondo, T.; Mitsudo, T. A. *Chem. Lett.* **2005**, *34*, 1462. (k) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (l) Korotvicka, A.; Necas, D.; Kotora, M. *Curr. Org. Chem.* **2012**, *16*, 1170. (m) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740.

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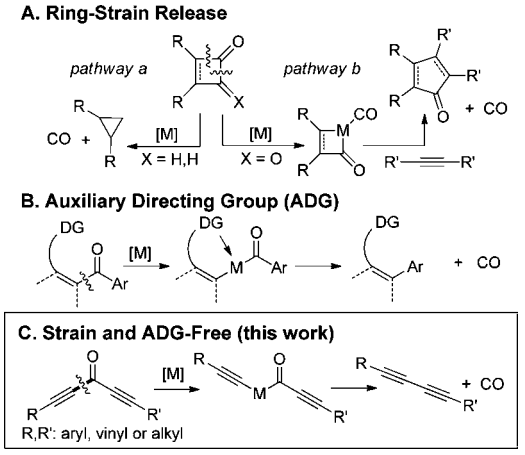
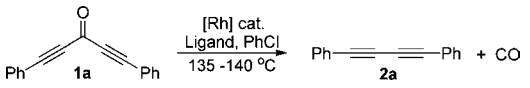


Figure 1. General strategies for transition metal-catalyzed C−C activation involving decarbonylation.

motif found in a diversity of molecules ranging from materials to natural products.[8] Their preparation generally relies on Cu- or Pd-mediated coupling reactions,[9] such as Glaser−Hay,[10,11] Cadiot−Chodkiewicz,[12] or Sonogashira reactions.[13] Although highly effective, high-loading or stoichiometric reagents (e.g., oxidants) are often needed (particularly for preparing unsymmetrical diynes, *vide infra*). Given the importance of diynes, the development of alternative, ideally orthogonal methods for synthesizing these moieties is of significant value. Here, we describe our development of a Rh(I)-catalyzed decarbonylation of conjugated diynones to 1,3-diynes via strain and ADG-free C−C activation (Figure 1C).

Müller's seminal study in 1969 on stoichiometric reactions between conjugated diynones and Wilkinson's complex $[Rh(PPh_3)_3Cl]$ shows the feasibility for decarbonylation of ynones.[14] However, a catalytic transformation has not been realized to date. We postulated that the challenge for developing an efficient catalytic decarbonylation of diynones is attributed to the difficulty of removing CO from the Rh center, as the $Rh(CO)(PPh_3)_2Cl$ complex generated from Müller's conditions proved to be unreactive.[14a] Inspired by the aldehyde decarbonylation reactions,[15] we envisioned that such a challenge could be addressed by using a bidentate phosphine ligand bearing a wide bite angle, because, first, CO dissociation, which is expected to be the turnover-limiting step, could be accelerated due to the bulkiness of the ligand[15] and, second, reductive elimination leading to the formation of the diyne products would also be enhanced.[16]

Table 1. Selected Optimization of Decarbonylation of Diynone **1a**[a]



entry	cat.	cat. loading (mol %)	ligand	bite angle (deg)[c]	time (h)	yield[b] (%)
1	$[Rh(COD)Cl]_2$	5	dppe	85	8	42
2	$[Rh(COD)Cl]_2$	5	dppp	91	8	73
3	**$[Rh(COD)Cl]_2$**	**5**	**dppf**	**96**	**8**	**99**
4	$[Rh(COD)Cl]_2$	5	dppb	98	24	32 (57)
5	$[Rh(COD)Cl]_2$	5	DPEphos	103	24	36 (53)
6	$[Rh(COD)Cl]_2$	5	XANTphos	111	24	41(51)
7	**$[Rh(COD)Cl]_2$**	**2.5**	**dppf**	**96**	**24**	**91**
8	$[Rh(COE)_2Cl]_2$	2.5	dppf	–	24	67
9	$[Rh(C_2H_4)_2Cl]_2$	2.5	dppf	–	24	73
10	$[Rh(COD)(CH_3CN)_2]^+ BF_4^-$	2.5	dppf	–	24	47
11	$[Ir(COD)Cl]_2$	2.5	dppf	–	24	N.R.[d]
12	$Ru_3(CO)_{12}$	2.5	dppf	–	24	N.R.[d]

[a] Conditions: diynone **1a** (0.21 mmol), [Rh]/ligand = 1:1.2, PhCl (0.1 M). [b] Isolated yields; yield in parentheses is based on recovered starting material. [c] See ref 18 for the bite-angle values. [d] N.R. = No Reaction.

To test our hypothesis, we attempted the catalytic decarbonylation using phenyl-diynone **1a** as the model substrate (Table 1). By subjecting **1a** to 5 mol % $[Rh(COD)Cl]_2$ and 12 mol % bidentate phosphine ligand (dppe, dppp, and dppf) in chlorobenzene (PhCl) at 135−140 °C, full conversion of the starting material was achieved within 8 h (Table 1, entries 1−3).[17] While decomposition products were observed using dppe and dppp, dppf proved highly selective for this transformation and a quantitative yield was obtained (Table 1, entry 3).[18] The use of bidentate phosphine ligands was crucial for catalyst turnover, as use of PPh_3, PCy_3, or no phosphine ligands only resulted in < 10% yield. Nonetheless, we discovered that the catalyst loading can be lowered to 2.5 mol % and the desired product was still obtained in 91% yield after

(7) (a) For Rh-catalyzed decarbonylations of 1,2- and 1,3-diketones, see: Reference 2a. (b) For a Rh-mediated decarbonylation of cyclodecanone and -pentanone, see: Reference 3a. (c) For a recent Rh-mediated decarbonylation of aryl ketones, see: Daugulis, O.; Brookhart, M. *Organometallics* **2004**, *23*, 527.

(8) For typical reviews, see: (a) *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2006. (b) *Chemistry of Acetylenes*; Cadiot, P., Chodkiewicz, W., Eds.; Marcel Dekker: New York, 1969.

(9) For a recent review, see: Siemson, P.; Livingston, R. C.; Diedrich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

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(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(14) (a) Müller, E.; Segnitz, A.; Langer, E. *Tetrahedron Lett.* **1969**, *14*, 1129. (b) Müller, E.; Segnitz, A. *Liebigs Ann. Chem.* **1973**, 1583. (c) For a related transformation involving carbonyl migration, see: Müller, E.; Segnitz, A. *Synthesis* **1970**, 147.

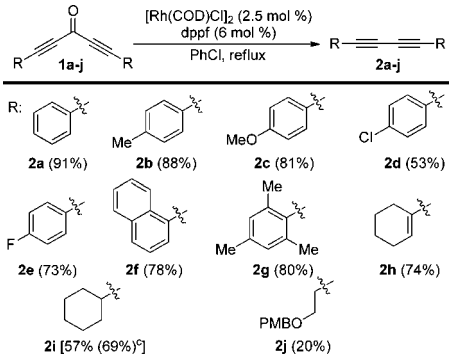
(15) For seminal work of bidentate ligand-assisted decarbonylation of aldehydes, see: Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083.

(16) For a kinetic study of the bite-angle effect on reductive eliminations, see: Marcone, J. E.; Moloy, K. G. *J. Am. Chem. Soc.* **1998**, *120*, 8527.

(17) Chlorobenzene was found to be the optimal solvent, whereas use of toluene proved to be inefficient.

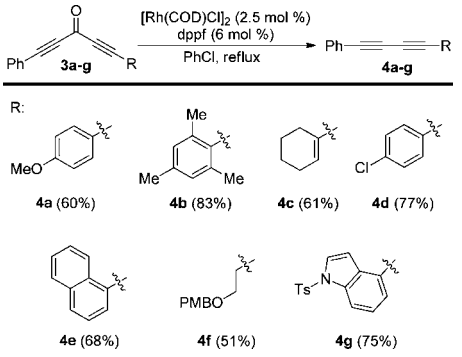
(18) For average ligand bite angles, see: (a) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519. (b) van Leeuwen, P. W. N. M.; Kamer, P. D. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

Scheme 2. Substrate Scope of Rh-Catalyzed Decarbonylation of Symmetrical Diynones[a,b]



[a] Conditions: diynone (0.19−0.21 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), dppf (6 mol %), PhCl (0.1 M), reflux, 16−24 h. [b] Isolated yields. [c] Yield in parentheses is based on recovered starting material.

Scheme 3. Substrate Scope of Rh-Catalyzed Decarbonylation of Unsymmetrical Diynones[a,b]



[a] Conditions: diynone (0.19−0.21 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), dppf (6 mol %), PhCl (0.1 M), reflux, 16−24 h. [b] Isolated yields.

24 h (Table 1, entry 7). Furthermore, addition of a Lewis acid ($ZnCl_2$) did not promote the reaction to occur at lower temperature.[19]

The substrate scope was explored first with symmetrical diynones (Scheme 2). A range of diynone substrates underwent decarbonylation to give the corresponding diynes. For example, aryl-substituted diynones with various electronic properties gave products in good to excellent yields (**2a**−**e**). Sterically hindered substrates **1f**−**g** were also examined and no major decrease in yield or reactivity was observed, even with relatively bulky mesityl substituents.[20] In addition, alkenyl- and alkyl-substituted diynones also afforded the desired diyne products **2h**−**j**. With the substrate-containing homopropargylic PMB-ether **1j**, we observed slight decomposition and isomerization of the starting material, thus leading to a decreased yield (see Supporting Information).

Classical methods for the synthesis of unsymmetrical diynes (from monoalkynes) generally rely on either using a large excess of one coupling partner under Glaser−Hay conditions or employing alkynyl halides (prepared from halogenation of terminal alkynes) under Cadiot-Chodkiewicz conditions.[9] Our C−C activation method provides an alternative way to prepare unsymmetrical diynes (Scheme 3).[21] Of note, the substituents that led to relatively low yields in the symmetrical substrates (e.g., p-Cl-phenyl **2d** and PMB ether **2j**) showed improved reactivity in the unsymmetrical case **4d** and **4f**, respectively. In addition, the protected indole moiety in **4g** is compatible under the decarbonylation conditions. Furthermore, when unsymmetrical diynones were used, only unsymmetrical diyne products were isolated and no symmetrical products, such as diphenyl bisacetylene, were observed. This indicates that the catalytic process is an intramolecular process and no intermolecular transfer of acetylenic units takes place.

A catalytic cycle is proposed for the Rh-catalyzed decarbonylation of diynones (Figure 2). The initial step likely involves substrate coordination to the Rh(I) through either one or both acetylenes to give complex **I** (step 1). Promoted by proximity, Rh(I) would oxidatively insert into the C−C bond α to the carbonyl group to generate acyl-Rh(III) acetylide **II** (step 2), despite the inertness of the $sp-sp^2$ σ-bond.[22] Subsequent elimination of CO (step 3) followed by reductive elimination of the resultant bisacetylide **III** (step 4) would provide the conjugated diyne. Note that the first three steps in the catalytic cycle are in principle all reversible. Finally, influenced by the bidentate phosphine ligand, the CO would be extruded from the metal center through ligand exchange with the diynone substrate, allowing the resulting Rh(I) complex **I** to re-enter the catalytic cycle.

The synthetic value of the Rh-catalyzed decarbonylation of diynones has been further demonstrated in the derivatization of natural products, such as citronellal, myrtenal, and ethinyl estradiol (Scheme 4). A number of interesting aspects were found: (1) ynones can be prepared from the corresponding aldehydes[23,24] with no need to isolate the alkyne intermediates (e.g., synthesis of ynone **8**, Scheme 4A); (2) the sensitive four-membered ring of myrtenal remained intact (Scheme 4B); (3) for unsymmetrical-diyne synthesis, this method has advantages over the

(19) We recently demonstrated that using $ZnCl_2$ can promote catalytic C−C activation: Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567.

(20) In comparison, triisopropylsilyl-containing substrates resulted in no reaction.

(21) (a) For a Cu-catalyzed unsymmetrical diyne synthesis via decarboxylative cross-coupling, see: Yu, M.; Pan, D.; Jia, W.; Chen, W.; Jiao, N. *Tetrahedron Lett.* **2010**, *51*, 1287. (b) For a lithium dialkynyldialkylborate-mediated unsymmetrical diyne synthesis, see: Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 1078.

(22) For examples of activation of sp^2-sp alkyne C−C bonds, see: (a) Baddley, W. H.; Panattonni, C.; Bandoli, G.; Clemente, D. A.; Belluco, U. *J. Am. Chem. Soc.* **1971**, *93*, 5590. (b) Anderson, G. K.; Lumetta, G. J.; Siria, J. W. *J. Organomet. Chem.* **1992**, *434*, 253. (c) Müller, C.; Iverson, C. N.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc.* **2001**, *123*, 9718. For recent reviews on activation of C−CN bonds, see: (d) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097. (e) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (f) Bonesi, S. M.; Fagnoni, M. *Chem.—Eur. J.* **2010**, *16*, 13572.

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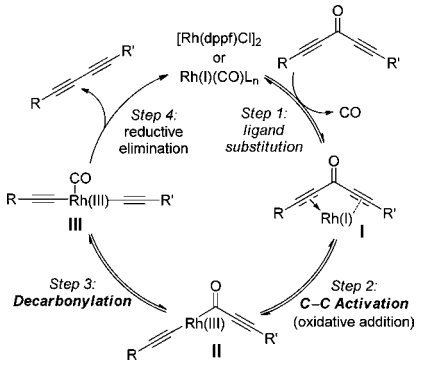
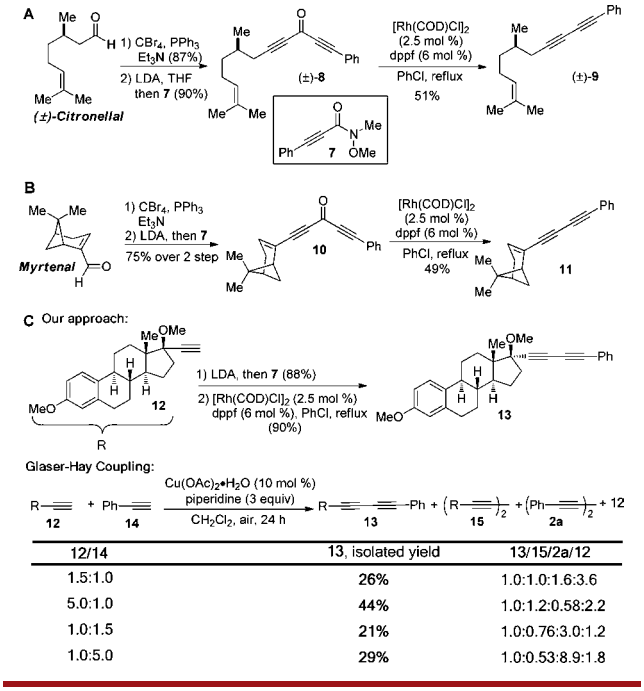


Figure 2. Putative catalytic cycle of Rh-catalyzed decarbonylation of diynones.

Scheme 4. Applications in Natural-Product Modification



12/14	13, isolated yield	13/15/2a/12
1.5:1.0	26%	1.0:1.0:1.6:3.6
5.0:1.0	44%	1.0:1.2:0.58:2.2
1.0:1.5	21%	1.0:0.76:3.0:1.2
1.0:5.0	29%	1.0:0.53:8.9:1.8

catalytic Glaser–Hay coupling.[25] For example, ethinyl estradiol-derived unsymmetrical diyne **13** was synthesized in 79% yield over two steps from alkyne **12** using our approach (Scheme 4C). Although use of Glaser–Hay coupling would save one operation, this reaction gave much lower yields and a complex mixture of hetero- and homodimers that are difficult to separate.[26]

Furthermore, we found that this C–C activation-based alkynation method also has orthogonal reactivity to typical cross-coupling reactions. While it is well established that aryl iodides and bromides are highly reactive under Pd- or Cu-catalyzed coupling conditions,[9] our study shows that under

(25) The modified Glaser–Hay reaction conditions were adopted from a recent report, see: Balaraman, K.; Kesavan, V. *Synthesis* **2010**, 3461.

(26) Doi, T.; Orita, A.; Matsuo, D.; Saijo, R.; Otera, J. *Synlett* **2008**, 55.

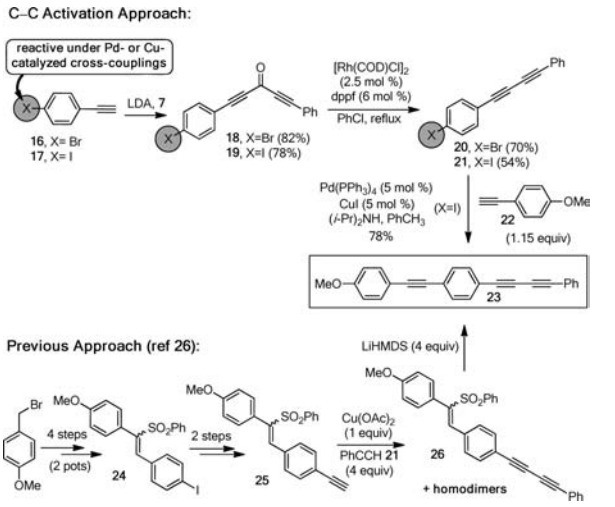


Figure 3. Orthogonal reactivity to the Pd/Cu-catalyzed couplings.

the Rh-catalyzed decarbonylation conditions the C–C bond was selectively cleaved instead of the C–X bonds. The diyne products **20** and **21** containing aryl halides (Br and I) were provided in good yields (Figure 3). Further Sonogashira coupling with terminal alkyne **22** gave an interesting ynediyne compound **23** that previously required eight steps to prepare.[26]

In summary, we have developed the first catalytic de carbonylation of diynones to prepare conjugated diynes. This C–C activation reaction takes advantage of the innate reactivity of ynones without relying on ADG or ring-strain release, which, to our knowledge, constitutes the only other approach for catalytic cleavage/functionalization of sp–sp^2 C–C bonds besides the established C–CN activation.[22d–f] It is noteworthy that the reaction conditions are pH/redox neutral and highly atom-economical. Given that (1) the reaction substrates (diynones) are readily available and (2) the reaction conditions are orthogonal to the cross-couplings, this catalytic transformation is expected to serve as an important alternative means to prepare conjugated diynes. It is also anticipated that the use of C–C cleavage as a distinct mode of reactivity in C–C formation reactions, as described in this report, would have broad implications for the discovery of new types of transformations.

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Supporting Information Available. Experimental procedures and spectroscopic data (^{1}H, ^{13}C NMR; IR; HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.