Organic Letters
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

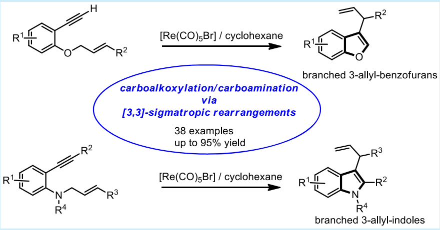
Rhenium-Catalyzed Intramolecular Carboalkoxylation and Carboamination of Alkynes for the Synthesis of C3-Substituted Benzofurans and Indoles

Ming-Guang Rong, Tian-Zhu Qin, and Weiwei Zi*

State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: A rhenium-catalyzed carboalkoxylation and carboamination of alkyne is reported. This reaction provides an efficient route to synthesize de novo C3-substituted benzofurans and indoles under mild conditions in moderate to good yields. Mechanistic studies revealed that the rhenium played the role of a π acid catalyst to activate the alkynes, followed by a charge-accelerated [3,3]-sigmatropic rearrangement.



Transition metal-catalyzed hydroalkoxylation and hydroamination of alkynes provide reliable methods for synthesizing C2-substituted benzofurans and indoles from readily available *o*-alkynylphenols or *o*-alkynylanilines[1] (Scheme 1a). For C3-substituted indoles and benzofurans, synthetic methods are still very limited.[2] Blum recently reported oxyboration and aminoboration of alkynes,[3] giving 3-borylated benzofurans and indoles, which could be converted to C3-substituted indoles and benzofurans through further cross-coupling reactions (Scheme 1b). Monteiro disclosed a palladium-catalyzed cyclization of allyl phenyl ether to give 3-allyl benzofurans.[4] This reaction involved the intermediacy of π-allylic palladium species, which was generated by oxidative insertion of a C−N bond into palladium (Scheme 1c). As a contrast, Fürstner reported a carbocation shift mechanism for Pt(II)-catalyzed transformation of *o*-alkynylphenol ethers[5] (Scheme 1d). For substrates with a cinnamyl group, only linear allylic rearrangement products were obtained in both of these systems.

Homogeneous rhenium-catalyzed transformation of alkynes has drawn an increasing amount of interest from the synthetic community.[6] A key feature of these reactions is the facile formation of rhenium vinylidenes from terminal alkynes, which could further undergo various transformations.[7] During the investigation of insertion of C−H into rhenium vinylidenes, we discovered an unprecedented rhenium-catalyzed carboalkoxylation/carboamination of alkynes, which selectively afforded rearranged, branched benzofuran and indole products in good yields (Scheme 1e). In this reaction, the intermediacy of rhenium vinylidene was ruled out; instead, the rhenium played the role of a π acid catalyst to activate the alkynes,[8−10] followed by a charge-accelerated [3,3]-sigmatropic rearrangement.[11,12] Herein, we disclose the details of this discovery.

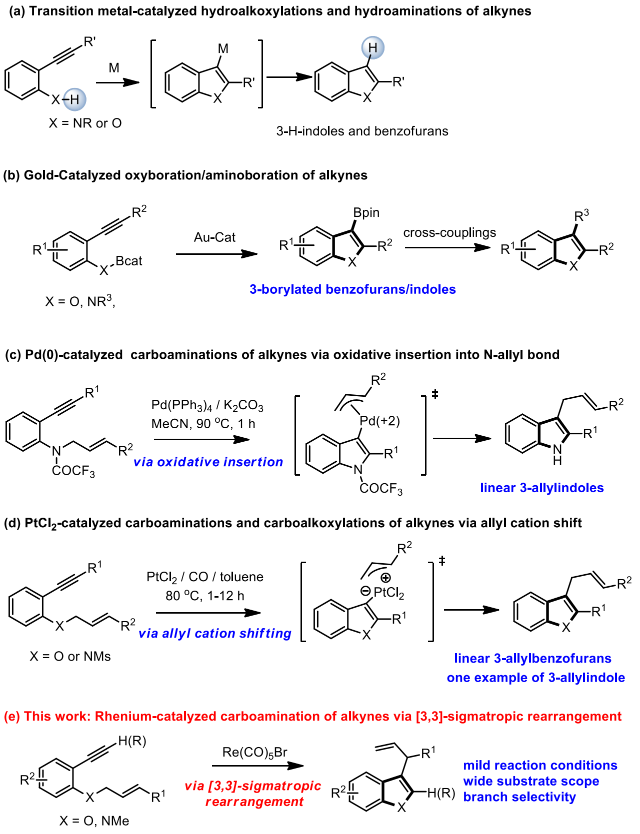
Our research was initiated with reaction of **1a** with 5 mol % Re(CO)$_5$Br in toluene at 70 °C, which gave carboalkoxylation product **2a** in 49% yield, together with a 22% yield of linear product **2a′** (Table 1, entry 1). Traditional π acid catalyst Ph$_3$PAuSbF$_6$ was examined, but it failed to catalyze this transformation[13] (entry 2). Rh(cod)$_2$OTf, [Ir(cod)Cl]$_2$, and Mn(CO)$_5$Br were also tested; however, no **2a** or **2a′** was detected with these catalysts (entries 3−5, respectively). We then investigated the effect of the ligand on this reaction. With 5 mol % Ph$_3$P or bipyridine, the reaction was completely shut down, which revealed that CO was a key ligand for rhenium in this transformation (entries 6 and 7). Using NaBAr$^F_4$ to remove the bromide in Re(CO)$_5$Br to generate a cationic Re$^+$ could not help to improve the yield (entry 8). After various solvents, such as DCE, dioxane, *p*-xylene, and cyclohexane (entries 9−12, respectively), had been screened, we found that the carboalkoxylation reaction proceeded most efficiently in cyclohexane. Under such conditions, desired product **2a** was isolated in 65% yield, together with a relatively lower yield of **2a′** (**2a**:**2a′** ratio of >4.3:1, entry 12). Improved results were obtained by switching the nucleophilic group of the substrate from oxygen to nitrogen, by which carboamination product indole **4a** was obtained in 86% yield with excellent regioselectivity (entry 13).

With the optimized reaction conditions in hand, we first explored the scope of this rhenium-catalyzed carboalkoxylation reaction to prepare C3-substituted benzofurans (Scheme 2). When R^1 was a phenyl ring, *p*-Br, CF$_3$-substituted substrates reacted smoothly, giving desired products **2b** and **2c** in moderate yields. When R^1 groups were alkyl groups, the reactions also worked well and improved yields were obtained (**2d**−**2g**). A 1,3-diene moiety was tolerated in this reaction, giving rearrangement product **2h** bearing a skipped 1,4-diene in 51% yield. If the R^4 group were not a H atom, internal

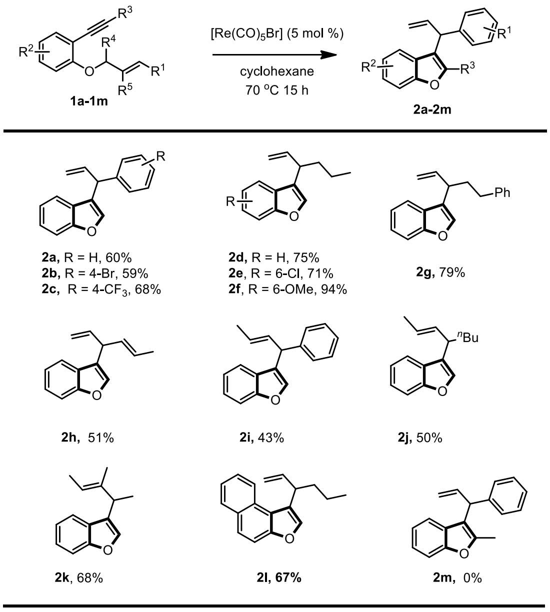
Received: May 7, 2019

DOI: 10.1021/acs.orglett.9b01619
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Pioneering Works about the Synthesis of C3-Substituted Benzofurans and Indoles



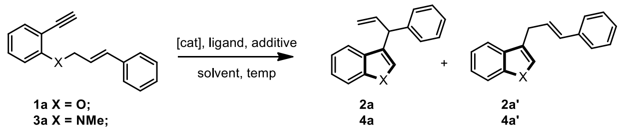
Scheme 2. Rhenium-Catalyzed Carboalkoxylation of Alkynes To Prepare Benzofurans



alkene products such as **2i** and **2j** would form, yet with slightly decreased yields. Furthermore, an example with $R^1 = R^4 = R^5 =$ Me was examined, giving **2k** in a 68% yield. Lastly, the reaction could be used to prepare naphthalene ring-fused furan **2l**. However, for an internal alkyne substrate (R^3 = Me), no desired 2,3-disubstituted benzofuran **2m** could be obtained under the standard reaction conditions.

Encouraged by these results, we next investigated the scope of the carboamination reaction to prepare C3-substituted indoles (Scheme 3). The R^1 group on the aromatic ring was first investigated. As shown in **4a–4e**, a range of electronically modulating substituents, including F, Me, CF_3, and ester groups, at the C6 positions were well tolerated, giving the desired indole scaffolds in good yields (**4a–4e**). Starting from various substituted cinnamyl groups (R^3 was 4-CF_3, 4-Br, or 2-Me), indoles **4f–4h** were obtained in 79–94% yields. A thiophene type product **4i** also could be prepared efficiently by this method. To increase the variety of groups on nitrogen in

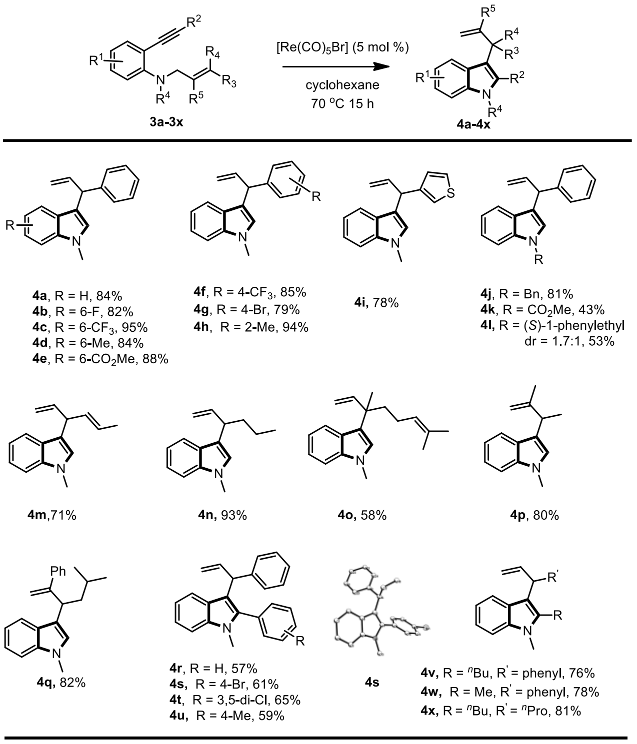
Table 1. Optimization of the Reaction Conditions[a]



entry	substrate	[M]	additive[b]	solvent	2a:2a′ ratio[c]	yield (%)[c] of 2a
1	**1a**	$Re(CO)_5Br$		toluene	2.2:1	49
2	**1a**	PPh_3AuSbF_6		toluene	–	0
3	**1a**	$Rh(cod)_2OTf$		toluene	–	0
4	**1a**	$[Ir(cod)Cl]_2$		toluene	–	0
5	**1a**	$Mn(CO)_5Br$		toluene	–	0
6	**1a**	$Re(CO)_5Br$	PPh_3	toluene	–	0
7	**1a**	$Re(CO)_5Br$	bipyridine	toluene	–	0
8	**1a**	$Re(CO)_5Br$	$NaBAr^F_4$[e]	toluene	1.1:1	21
9	**1a**	$Re(CO)_5Br$		DCE	1.4:1	50
10	**1a**	$Re(CO)_5Br$		dioxane	1.6:1	49
11	**1a**	$Re(CO)_5Br$		*p*-xylene	2.5:1	53
12	**1a**	$Re(CO)_5Br$		cyclohexane	4.3:1	65
13[d]	**3a**	$Re(CO)_5Br$		cyclohexane	>30:1	86

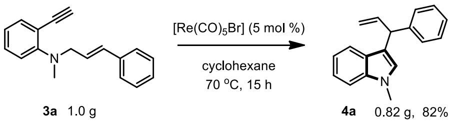
[a] Reactions were performed with 0.1 mmol of substrate and 5 mol % metal catalyst in 1 mL of solvent at 70 °C under an argon atmosphere for 15 h. [b] With 5 mol % PPh_3, 5 mol % bipyridine, or 5 mol % $NaBAr^F_4$. [c] Determined by ^1H NMR analysis with $C_2H_2Br_4$ as an internal standard. [d] The yield and ratio refer to the corresponding **4a** and **4a′**. [e] $NaBAr^F_4$ = sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate.

Scheme 3. Rhenium-Catalyzed Carboamination of Alkynes To Prepare Indoles



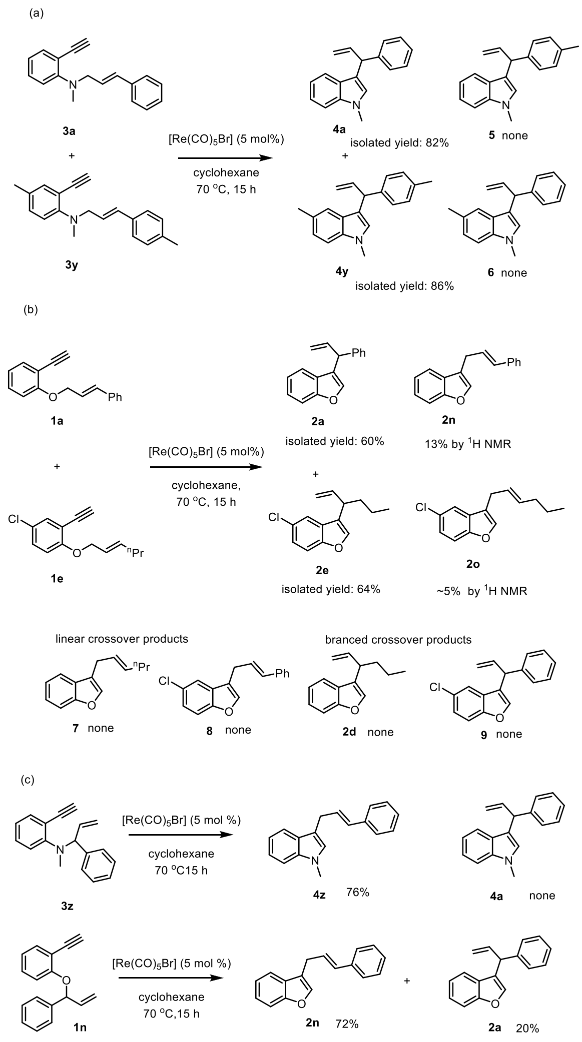
indoles, NBn and NCO$_2$Me were examined, affording the corresponding products **4j** and **4k** in 81% and 43% yields, respectively. When (*S*)-1-phenylethyl was introduced to the substrate, diastereoselectivity was observed but in a low ratio (dr = 1.7:1; **4l**). Moreover, aliphatic allylic migration cyclization products could be prepared (**4m** and **4n**), and even a quaternary carbon center could be constructed when employing a geranyl-tethered amine as the substrate (**4o**). The R^5 group could be Me or Ph other than H, and comparable yields were found (**4p** and **4q**). Finally, we found the carboamination reaction had a substrate scope that was better than that of the carbalkoxylation reaction. As for internal alkynes (R^3 = Ph or alkyl groups), the reactions furnished a series of 2,3-substituted indoles in moderate to good yields (**4r**−**4x**).[14] To demonstrate the scalability of this methodology, we performed a gram-scale reaction (Scheme 4). The carboamination of **3a** proceeded smoothly to afford desired 3-substituted indole **4a** in 82% isolated yield after 15 h at 70 °C.

Scheme 4. Scalability of the Carboamination of 3a



To gain some insights into the mechanism, controlled experiments were conducted. A mixture of **3a** and **3y** in a 1:1 ratio was subjected to the reaction, and intramolecular cyclization products **4a** and **4y** were generated in 82% and 86% isolated yields, respectively. No crossover products **5** and **6** were observed, which indicated that a concerted [3,3]-sigmatropic rearrangement other than a carbocation demetalation[15] step was involved (Scheme 5a). A crossover experiment between **1a** and **1e** was also conducted (Scheme 5b). In this case, besides normal products **2a** and **2e**, linear **2n** was also formed. However, neither branched crossover products (**2d** and **9**) nor linear crossover products (**7** and **8**) was detected. Moreover, starting from branched starting material **3z**, linear rearrangement product **4z** was formed exclusively. A similar result was observed for **1n**; however, minor branched **2a** was also isolated (Scheme 5c). On the basis of the results presented above, we rationalized that the [1,3]-rearrangement for the O-tethered substrate was also undergoing a concerted pathway.[16]

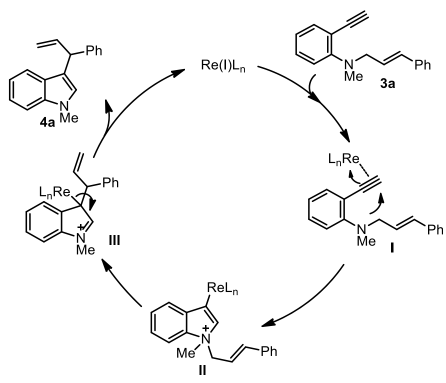
Scheme 5. Controlled Experiments



A plausible mechanism for this reaction is shown in Scheme 6 by using **3a** as a model substrate. Cationic Re(I) first activates the alkyne moiety in **3a**, followed by nucleophilic attack from a nitrogen atom, giving intermediate **II** immediately. A charge-accelerated [3,3]-sigmatropic rearrangement of **II** then gives species **III**, which followed a demetalation step to give desired 3-substituted cyclization product **4a** and regenerate the rhenium catalyst.

In summary, we have developed an efficient cationic Re(I)-catalyzed carboalkoxylation and carboamination reaction, which provided a de novo synthesis of C3-substituted benzofurans and indoles. This reaction represents a rare

Scheme 6. Proposed Catalytic Cycle



example of using rhenium as a π acid catalyst, by which novel branch selectivities were demonstrated compared to the previously reported linear selectivities of the platinum catalyst. Controlled experiments supported a concerted [3,3]-sigmatropic rearrangement other than a carbocation shift mechanism.[17] Further work on the asymmetry of this reaction and detailed mechanistic studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01619.

Experimental details and complete analytical data (PDF)

Accession Codes

CCDC 1914271 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zi@nankai.edu.cn.

ORCID

Weiwei Zi: 0000-0002-7842-0174

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National “Young Thousand Talents Plan”, the National Natural Science Foundation of China (21871150), and the Fundamental Research Funds for the Central Universities. The authors gratefully acknowledge the State Key Laboratory of Elemento-organic Chemistry and the College of Chemistry of Nankai University for generous start-up financial support.

■ REFERENCES

(1) (a) Perea-Buceta, J. E.; Wirtanen, T.; Laukkanen, O.-V.; Makelä, M. K.; Nieger, M.; Melchionna, M.; Huittinen, N.; Lopez-Sanchez, J. A.; Helaja, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11835–11839. (b) Kumaran, E.; Leong, W. K. *Tetrahedron Lett.* **2014**, *55*, 5495–5498. (c) RubioMarques, P.; Rivero-Crespo, M. A.; Leyva-Pérez, A.; Corma, A. *J. Am. Chem. Soc.* **2015**, *137*, 11832–11837. (d) Allegretti, P. A.; Huynh, K.; Ozumerzifon, T. J.; Ferreira, E. M. *Org. Lett.* **2016**, *18*, 64–67. (e) Witham, C. A.; Huang, W.; Tsung, C. K.; Kuhn, J. N.; Somorjai, G. A.; Toste, F. D. *Nat. Chem.* **2010**, *2*, 36–41. (f) Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5162–5165. (g) Rubio-Marqus, P.; Rivero-Crespo, M. A.; Leyva-Pérez, A.; Corma, A. *J. Am. Chem. Soc.* **2015**, *137*, 11832–11837. (h) Cook, A. K.; Copéret, C. *Organometallics* **2018**, *37*, 1342–1345. (i) Li, B.; Ju, Z.; Zhou, M.; Su, K.; Yuan, D. *Angew. Chem., Int. Ed.* **2019**, *58*, 7687–7691.

(2) (a) Qu, C. H.; Zhang, S.; Du, H.; Zhu, C. *Chem. Commun.* **2016**, *52*, 14400–14403. (b) Ilies, L.; Isomura, M.; Yamauchi, S.-i.; Nakamura, T.; Nakamura, E. *J. Am. Chem. Soc.* **2017**, *139*, 23–26. (c) Watanabe, T.; Mutoh, Y.; Saito, S. *J. Am. Chem. Soc.* **2017**, *139*, 7749–7752.

(3) (a) Hirner, J. J.; Faizi, D. J.; Blum, S. A. *J. Am. Chem. Soc.* **2014**, *136*, 4740–4745. (b) Chong, E.; Blum, S. A. *J. Am. Chem. Soc.* **2015**, *137*, 10144–10147. (c) Issaian, A.; Tu, K. N.; Blum, S. A. *Acc. Chem. Res.* **2017**, *50*, 2598–2609.

(4) (a) Monteiro, N.; Balme, G. *Synlett* **1998**, *1998*, 746–747. (b) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, *2003*, 2115–2134.

(5) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025.

(6) For reviews, see: (a) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938–1953. (b) Hua, R.; Jiang, J.-L. *Curr. Org. Synth.* **2007**, *4*, 151–174.

(7) (a) Mao, G.; Huang, Q.; Wang, C. *Eur. J. Org. Chem.* **2017**, *2017*, 3549–3564. (b) Fukumoto, Y.; Daijo, M.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 8762–8765. (c) Hori, S.; Murai, M.; Takai, K. *J. Am. Chem. Soc.* **2015**, *137*, 1452–1457. (d) Iwasawa, N.; Watanabe, S.; Ario, A.; Sogo, H. *J. Am. Chem. Soc.* **2018**, *140*, 7769–7772. (e) Xia, D.; Wang, Y.; Du, Z.; Zheng, Q.-Y.; Wang, C. *Org. Lett.* **2012**, *14*, 588–591. (f) Murai, M.; Uemura, E.; Hori, S.; Takai, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 5862–5866. (g) Murai, M.; Uemura, E.; Hori, S.; Takai, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 5862–5866.

(8) For selective reviews of alkyne activation, see: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (c) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776–1782. (d) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (f) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712. (g) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358–1367. (h) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589.

(9) For rhenium as a π acid catalyst, see: (a) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468–470. (b) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760–15761.

(10) For our studies of alkyne activation, see: (a) Zheng, Y.; Zi, W. *Tetrahedron Lett.* **2018**, *59*, 2205–2213. (b) Wang, H. F.; Wang, S. Y.; Qin, T. Z.; Zi, W. *Chem. - Eur. J.* **2018**, *24*, 17911–17914. (c) Zheng, Y.; Guo, L.; Zi, W. *Org. Lett.* **2018**, *20*, 7039–7043. (d) Rong, M.-G.; Qin, T.-Z.; Liu, X.-R.; Wang, H.-F.; Zi, W. *Org. Lett.* **2018**, *20*, 6289–6293.

(11) For selective reviews of [3,3]-sigmatropic rearrangements, see: (a) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597–643. (c) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133–3148. (d) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2556–2591.

(12) For selective examples of charge-accelerated [3,3]-sigmatropic rearrangements, see: (a) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 9726–9727. (b) Valerio, V.; Madelaine, C.; Maulide, N. *Chem. - Eur. J.* **2011**, *17*, 4742–4745. (c) Eberhart, A. J.; Cicoira, C.; Procter, D. J. *Org. Lett.* **2013**, *15*, 3994–3997. (d) Shrives, H. J.; Fernández-Salas, J. A.; Hedtke, C.; Pulis, A. P.;

Procter, D. *Nat. Commun.* **2017**, *8*, 14801. (e) Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. *Angew. Chem., Int. Ed.* **2017**, *56*, 2212−2215. (f) Kaldre, D.; Klose, I.; Maulide, N. *Science* **2018**, *361*, 664−667. (g) He, Z.; Shrives, H. J.; Fernández-Salas, J. A.; Abengózar, A.; Neufeld, J.; Yang, K.; Pulis, A. P.; Procter, D. J. *Angew. Chem., Int. Ed.* **2018**, *57*, 5759−5764. (h) Wu, H.; Zi, W.; Li, G.; Lu, H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2015**, *54*, 8529−8532. (i) Šiaučiulis, M.; Sapmaz, S.; Pulis, A. P.; Procter, D. J. *Chem. Sci.* **2018**, *9*, 754−759.

(13) For Au-catalyzed carboalkoxylation of alkyne, see: (a) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474−1475. (b) Faza, O. N.; López, C. S.; de Lera, A. R. *J. Org. Chem.* **2011**, *76*, 3791−3796. (c) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600−12603. (d) Pawar, S. K.; Wang, C. D.; Bhunia, S.; Jadhav, A. M.; Liu, R. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559−7563. (e) Adcock, H. V.; Langer, T.; Davies, P. W. *Chem. - Eur. J.* **2014**, *20*, 7262−7266. (f) Banerjee, S.; Senthilkumar, B.; Patil, N. T. *Org. Lett.* **2019**, *21*, 180−184.

(14) CCDC 1914271 (**4s**) 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.

(15) For examples of carbocation demetalation, see: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473−4475. (b) Dube, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062−12063. (c) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649−2651. (d) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972−12975.

(16) The authors thank the reviewers for the suggestion of the experiments depicted in parts b and c of Scheme 5.

(17) During the preparation of the manuscript, a $PtCl_2$-catalyzed carboamination of alkyne via [3,3]-sigmatropic rearrangement was reported: Mirzaei, A.; Peng, X.-S.; Wong, H. N. C. *Org. Lett.* **2019**, *21*, 3795−3798.