# Sequential Difunctionalization of 2-Iodobiphenyls by Exploiting the Reactivities of a Palladacycle and an Acyclic Arylpalladium Species

Dushen Chen, Guangfa Shi, Hang Jiang, Yu Zhang, and Yanghui Zhang*

Department of Chemistry, and Shanghai Key Lab of Chemical Assessment and Sustainability, Tongji University, 1239 Siping Road, Shanghai, 200092, P. R. China

S *Supporting Information*

ABSTRACT: A novel sequential difunctionalization reaction of 2-iodobiphenyl has been developed by exploiting the distinct reactivities of a palladacycle and an acyclic arylpalladium species. In this tandem reaction, an in situ formed dibenzopalladacyclopentadiene reacts selectively with an alkyl halide, after which the thus formed acyclic arylpalladium species selectively undergoes a Heck reaction with an alkene. This work demonstrates the strong relationship between the coordination mode of a transition metal complex and its reactivity, which could shed light on the mechanisms of other transition-metal-catalyzed reactions and offer the opportunity to develop other synthetically enabling organic transformations.
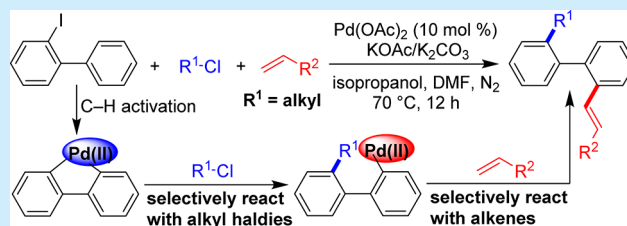
Transition metal catalysts are particularly versatile in organic synthesis and allow for a wide range of organic reactions to be developed.[1] A pervasive theme in catalysis research is that the coordination environment and the redox state of the metal have a dramatic impact on reactivity.[2] Hence, it is important to study the relationship between the coordination mode of organometallic intermediates and their reactivity in elementary steps along the reaction coordinate, so as to better understand the overall underlying mechanism and to develop new reactions.

Metallacycles are important organometallic compounds and are often intermediates in transition-metal catalysis. They have been extensively studied over the years and have found diverse applications in organic synthesis.[3] Because of their unique cyclic structure, metallacycles may exhibit reactivity patterns that are different from those of common acyclic organometallic complexes. In this context, dibenzometallacyclopentadienes are particularly intriguing to our research group,[4] because they contain two aryl-metal bonds. There exists an opportunity to difunctionalize these species, providing biphenyls with newly installed functional groups at the 2- and 2′-positions. Therefore, we sought to dibenzometallacyclopentadienes as a model to probe the relationship between the coordination mode of palladium and the resultant reactivity with different coupling partners.

The reactions of transition-metal complexes with organic halides and alkenes represent two of the most fundamental classes of elementary reactions in catalysis.[5] More significantly, these two types of reactions proceed via distinct pathways.[6] Therefore, we envisioned that organic halides and alkenes could possess differentiated reactivities toward metallacycles and acyclic organometallic species, and that this reactivity pattern could be exploited in a productive catalytic cycle.
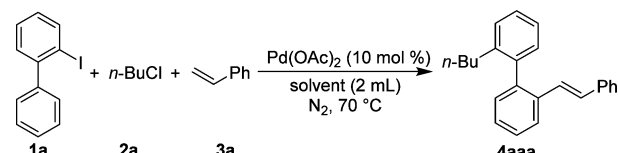
Herein, we report our success in the sequential alkylation/alkenylation of dibenzopalladacyclopentadienes by exploiting the divergent reactivity of palladacycle and acyclic arylpalladium intermediates with alkyl halides and alkenes. The dibenzopalladacyclopentadienes were obtained from 2-iodobiphenyls via C–H activation.[7,8] This reaction conceptually represents how new reactions can be developed through a detailed understanding of the relationship between a metal's coordination mode and its reactivity. The selectivity with which the palladacycle reacts with alkyl halides suggests that metallacycles could provide a generally useful mode of reactivity for developing alkylation reactions with alkyl halides.

We commenced our study by investigating the reaction of 2-iodobiphenyl with *n*-butyl chloride and styrene. After an extensive survey of reaction conditions, the desired difunctionalized biphenyl product was obtained in 10% yield in the presence of $Pd(OAc)_2$ and KOAc in DMF (Table 1, entry 1). The yield increased to a lesser extent when 2 equiv K_2CO_3 and 5 equiv *n*-BuCl were added (entries 2 and 3). At this stage, we envisioned that the catalytic cycle would start with the oxidative addition of **1a** to a Pd(0) species. If it was the case, we reasoned that the addition of a reductant would improve the yield by accelerating the reduction of Pd(II) to Pd(0). Notably, the yield increased dramatically to 50% when 2 equiv methanol was added (entry 4), and was further improved to 60% by using *i*-PrOH as the reductant (entry 5). Gratifyingly, a yield of 82% was observed in the presence of 5 equiv K_2CO_3 (entry 6). The reaction gave lower yield or no product formation in other solvents (entries 7–9). The product was not observed when the reaction was carried out under an air atmosphere (entry

Table 1. Survey of the Reaction Conditions

entry	*n*-BuCl (equiv)	KOAc (equiv)	K₂CO₃ (equiv)	reductant (equiv)	solvent	yield (%)[a]
1	3	4			DMF	10
2	3	4	2		DMF	15
3	5	4	2		DMF	20
4	5	4	2	MeOH (2)	DMF	50
5	5	4	2	IPA (2)	DMF	60
6	5	4	5	IPA (2)	DMF	82 (80)[b]
7	5	4	5	IPA (2)	DMA	24
8	5	4	5	IPA (2)	THF	
9	5	4	5	IPA (2)	CH₃CN	
10	5	4	5	IPA (2)	DMF	[c]
11	5	4	5	IPA (2)	DMF	54[d]
12	5	4	5	IPA (2)	DMF	8[e]

[a]The yields were determined by ¹H NMR analysis of the crude reaction mixture using CHCl₂CHCl₂ as the internal standard. [b]Isolated yield. [c]Under air atmosphere. [d]5 equiv *n*-BuBr. [e]5 equiv *n*-BuI. IPA = isopropyl alcohol.

10). This could be due to unwanted oxidation of the catalytically active Pd(0) species by O₂, which would suppress the reaction. *n*-Butyl bromide was also a competent coupling partner, albeit in a lower yield (entry 11), and *n*-butyl iodide was almost completely unreactive (entry 12).

The substrate scope was next examined. We first investigated the performance of a range of alkenes under the optimized reaction conditions. Thus, a variety of styrene derivatives were tested. As shown in Figure 1, reactions employing styrenes with alkyl substituents on the arene gave the desired products in
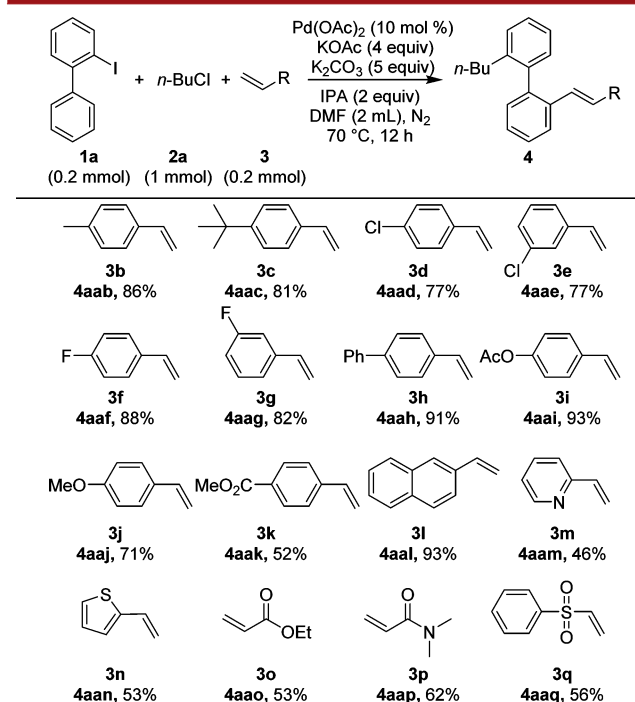

Figure 1. Alkene scope. Isolated yield.

high yields (**4aab** and **4aac**). Both chloro and fluoro groups, either at *para* or *meta* position, were well-tolerated (**4aad**–**4aag**). Styrenes containing other common functional groups, including phenyl, acetoxy, methoxy, and ester groups, were also reactive, affording the difunctionalized products in moderate to excellent yields (**4aah**–**4aak**). The reaction with 2-vinyl-naphthalene was also high-yielding (**4aal**). Notably, the protocol was compatible with heteroaryl olefins, including 2-vinylpyridine and 2-vinylthiophene (**4aam** and **4aan**). Next, the compatibility of other alkenes was examined. Alkenes containing an electron-withdrawing substituent, such as an ester, amide, or sulfonyl group, underwent the difunctionaliza-tion reaction successfully in moderate yields (**4aao**–**4aaq**).

Subsequently, we investigated the substrate scope with respect to the alkyl chloride coupling partner. As shown in Figure 2, linear primary alkyl chlorides containing a variety of
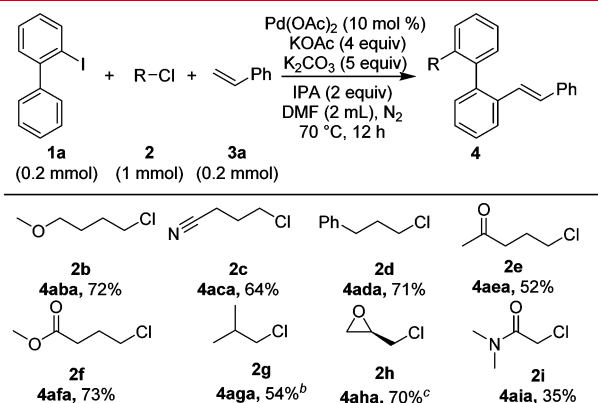
Figure 2. Alkyl chloride scope. Isolated yield. (b) 100 °C. (c) A mixture of two diastereomers.

functional groups effectively underwent the difunctionalization reaction under the standard conditions to yield the alkylated products (**4aba**–**4afa**). The more branched substrate, isobutyl chloride, was also suitable (**4aga**). Notably, 2-(chloromethyl)-oxirane was compatible with the protocol, forming two diastereomers in a 1:1 ratio in an overall yield of 70% (**4aha**). α-Chloroacetamide was also reactive, albeit in a low yield (**4aia**). Unfortunately, the secondary alkyl chloride, 2-chloroalkane, was not suitable, and no alkylated products were observed.

Finally, the compatibility of various substituted 2-iodobi-phenyl derivatives was examined using **2a** and **3a** as the reactants. A range of symmetrically substituted 2-iodobiphenyls were subjected to the standard conditions. As shown in Figure 3, dimethylated substrates were reactive (**4baa** and **4caa**), and both fluoro and chloro groups were tolerated in the reaction (**4daa**–**4faa**). Substrates containing two trifluoro- methyl or two phenyl groups underwent the reaction in high yields (**4gaa** and **4haa**), and even a tetraalkoxy 2-iodobiphenyl was found to be suitable (**4iaa**). The *ortho*-subsituted substrate, 2-iodo-2′-methylbiphenyl, was not reactive.

2,2′-Disubstitued biphenyls can be found in a number of natural and synthetic products. In particular, they are essential structural motifs in many pharmaceutically active compounds.[9] The reaction we developed may provide convenient access to 2,2′-disubstitued biphenyls for drug discovery and biological studies.

To gain insight into the mechanism of the difunctionalization reaction, we designed the experiment shown in Scheme 1. Two
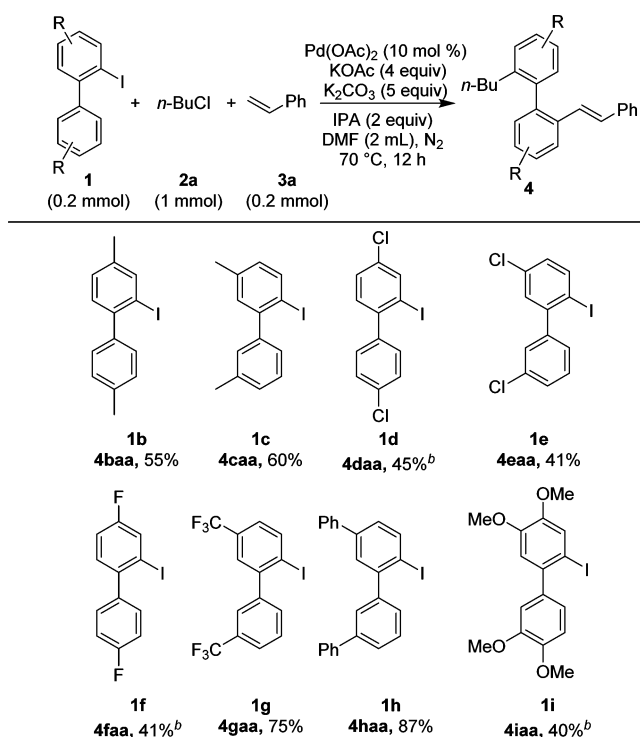
Figure 3. 2-Iodobiphenyl scope. Isolated yield. (b) 100 °C.

Scheme 1. Mechanistic Studies[a]
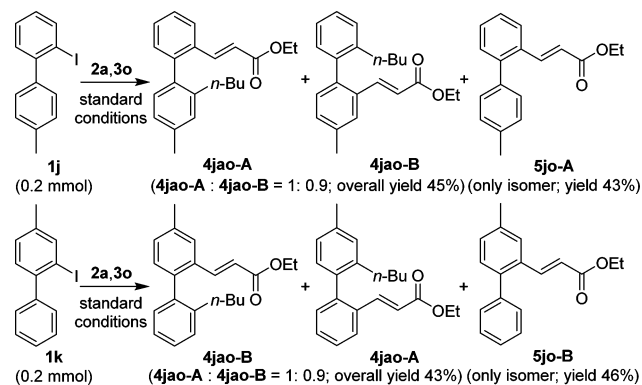
[a]Isolated yield.

reactions were performed, one with substrate **1j** and the other with substrate **1k**. Each was allowed to react with ethyl acrylate and *n*-BuCl under the standard conditions. The reaction with **1j** led to two isomeric difunctionalized products (**4jao-A** and **4jao-B**) in a ratio of 1:0.9. The reaction with **1k** also provided both products in a 1:0.9 ratio. This outcome is consistent with the two reactions proceeding via a common dibenzopallada-cyclopentadiene intermediate. Furthermore, in these two reactions, a direct alkenylated product (**5jo-A** for **1j**; **5jo-B** for **1k**) was formed. Direct Heck alkenylation took place at only the carbon originally bearing an iodo group; the other isomer with acrylate on the distal phenyl ring opposite to the iodo group was not observed. On the basis of these results, we can conclude that the Heck alkenylated products result from the direct reaction of ethyl acrylate with an acyclic arylpalladium species that is formed from the oxidative addition of 2-iodobiphenyl to Pd(0) and a palladacycle is not involved in this pathway to form the Heck alkenylated byproduct. It should be

mentioned that the Heck products were the major byproducts in the difunctionalization reactions. Moreover, no direct butylated products were observed. This indicates that the alkyl chloride does not react with the acyclic arylpalladium species under the reaction conditions.

Furthermore, the coupling of 2-iodobiphenyl with *n*-BuCl in the absence of an alkene was also invesitgated. Surprisingly, the reaction provided three products: monobutylated biphenyl **6aa** and two dibutylated products (**6aa-A** and **6aa-B**) in a ratio of 1:1 (Scheme 2). To gain insight into the operative mechanism

Scheme 2. Alkylation of 2-Iodobiphenyl[a]
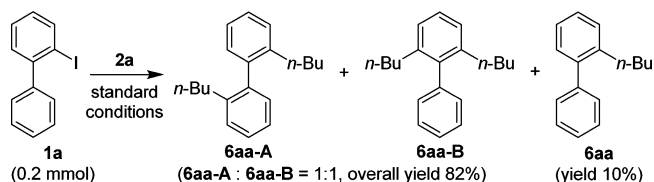
[a]Isolated yield. The ratio of **6aa-A** and **6aa-B** was determined by GC–MS and ^{1}H NMR

in this butylation reaction, additional experiments were designed and performed.[10] First, the alkylation reaction was carried out under deuterated conditions. All of the products were fully deuterated at the 2 or 2′ positions. Furthermore, when simple iodobenzene was used, no alkylated products were observed. All of these experimental results are consistent with a dibenzopalladacyclopentadiene intermediate, rather than a simple open-chain arylpalladium species as the reactive intermediate in the alkylation of 2-iodobiphenyl, even for the monobutylated product **6aa**. To the best of our knowledge, this reaction is the first example of alkylation of diarylmetallacyclepentadienes. For transition-metal-catalyzed transformations, reactions involving alkyl halides are often challenging.[11,12] The dibenzometallacycles have a reactivity profile that is distinct from those of common arylpalladium species and exhibit unique reactivity toward alkyl halides. This strategy may be extended to other metallacycles and offer further opportunities for developing novel alkylation reactions.

In principle, the difunctionalized products could arise from Heck alkenylation followed by olefin-directed C−H alkylation with alkyl chloride. To examine this possibility, we subjected premade **5jo-A** to the standard reaction conditions with *n*-BuCl. The alkylated product was not observed, which rules out this possibility.

A mechanism that is consistent with these findings is shown in Scheme 3. The catalytic cycle starts with the oxidative addition of 2-iodobiphenyl to a Pd(0) species to afford arylpalladium(II) complex **A**. Subsequent C−H activation forms the key intermediate dibenzopalladacyclopentadiene **B**. Alternatively, arylpalladium(II) species **A** can undergo a Heck reaction with the alkene, yielding the observed olefinated biphenyl byproduct. Intermediate **B** selectively reacts with the alkyl chloride to give alkylated complex **D**, via either an oxidative addition (**C**) or metathesis pathway (**C′**). Complex **D** is an acyclic arylpalladium(II) species, so it reacts selectively with the alkene to generate difunctionalized biphenyl as the final product, releasing Pd(0) to close the catalytic cycle.

In conclusion, we have demonstrated that dibenzopallada-cyclopentadienes have unique reactivity that is distinct from that of common acyclic organometallic complexes. While dibenzopalladacyclopentadienes selectively react with alkyl

Scheme 3. Proposed Mechanism

halides, acyclic arylpalladium(II) species selectively undergo Heck reactions with alkenes. By exploiting these two distinct reactivity modes, we successfully developed a novel sequential difunctionalization reaction of dibenzopalladacyclopentadienes derived from C–H activation of 2-iodobiphenyls. This tandem reaction provides convenient access to a variety of 2,2′-disubstituted biphenyls. Efforts to study the reactivity of dibenzopalladacyclopentadienes in other reactions and to apply this strategy in investigating the reactivity of other metallacycles are 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.6b00753.

> Detailed experimental procedures, spectroscopic data and characterization of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhangyanghui@tongji.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, 2nd completed revised and enlarged ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002.

(2) *Organotransition Metal Chemistry: From Bonding to Catalysis*; Hartwig, J. F., Ed.; University Science Books: Sausalito, CA, 2010.

(3) (a) Cook, T. R.; Stang, P. J. *Chem. Rev.* **2015**, *115*, 7001. (b) Beweries, T.; Rosenthal, U. *Nat. Chem.* **2013**, *5*, 649. (c) Reichard, H. A.; Micalizio, G. *Chem. Sci.* **2011**, *2*, 573. (d) Dupont, J.; Consorti, C. S.; Spencer, S. *Chem. Rev.* **2005**, *105*, 2527. (e) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055.

(4) Steffen, A.; Ward, R. M.; Jones, W. D.; Marder, T. B. *Coord. Chem. Rev.* **2010**, *254*, 1950.

(5) (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed..; Meijere, A., de Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

(6) Collman, J. P., Ed. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

(7) (a) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694. (b) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (c) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (d) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.

(8) Recent reviews on transition-metal-catalyzed C–H activation: (a) *C–H Activation: Topics in Current Chemistry, Vol. 292*; Yu, J.-Q., Shi, Z., Eds.; Springer: Berlin Heidelberg, 2010. (b) Miao, J.; Ge, H. *Eur. J. Org. Chem.* **2015**, *36*, 7859. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (f) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (g) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (h) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (i) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (j) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (k) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (l) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (m) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (n) Carbon–Carbon σ-Bond Formation via C–H Bond Functionalization in *Comprehensive Organic Synthesis*, 2nd ed.; Zhang, Y. H., Shi, G. F., Yu, J. -Q, Eds.; Elsevier: Oxford, 2014.

(9) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268 and references cited therein..

(10) For the detailed mechanistic studies, see the Supporting Information, Scheme S1. A detailed mechanism was proposed, see the Supporting Information, Scheme S2.

(11) (a) Gu, J.; Wang, X.; Xue, W.; Gong, H. *Org. Chem. Front.* **2015**, *3*, 1411. (b) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (d) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (e) Netherton, M. R.; Fu, G. C. *Top. Organomet. Chem.* **2005**, *14*, 85. (f) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(12) For selected examples of Pd-catalyzed C–H alkylations with alkyl halides, see: (a) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574. (b) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531. (c) Zhu, R.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (d) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950. (e) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (f) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.-S.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (g) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (h) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.