Organic LETTERS

Letter

pubs.acs.org/OrgLett

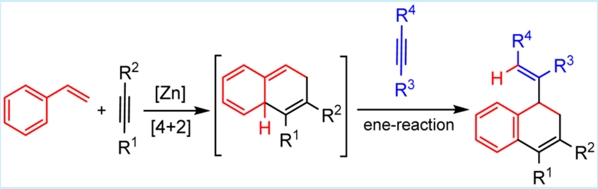
Styrene as 4π-Component in Zn(II)-Catalyzed Intermolecular Diels–Alder/Ene Tandem Reaction

Min Zheng, Feng Wu, Kai Chen,* and Shifa Zhu*

Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, 510640, P. R. China

Ⓢ *Supporting Information*

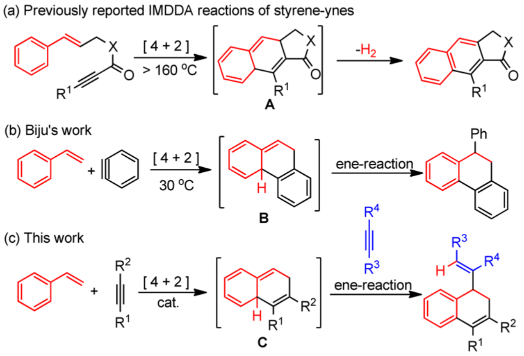
ABSTRACT: A mild Zn-catalyzed intermolecular Diels–Alder/ene tandem reaction with styrene as a 4π-component is reported. A variety of dihydronaphthalene products could be prepared in moderate to good yields. Moreover, a combination of DFT calculations and experiments was performed to further understand the mechanism of this unique tandem reaction.



The Diels–Alder reaction is one of the most useful pericyclic reactions to construct the six-membered carbocyclic compounds.[1] The Diels–Alder reaction typically involves the 4π-electron of the conjugated diene and 2π-electron of the dienophile. In comparison with the conjugated diene, the Diels–Alder reaction using styrene as a 4π-component is, however, much less developed, in which the unfavorable dearomatization should occur.

Since 1963, intramolecular didehydro-Diels–Alder (IMDDA) reactions of styrene-ynes to construct naphthalenes and other polycyclic aromatic hydrocarbons have attracted much attention. However, the IMDDA reaction required harsh reaction conditions (e.g., high temperature or microwave-assisted conditions), which often resulted in the polymerization of styrene.[2] In 2015, Brummond et al. reported the mechanistic study of the thermal IMDDA reaction of styrene-ynes, and they found that the naphthalene product was formed via the loss of hydrogen gas from the initially formed cycloadduct **A** (Scheme 1a).[3] As a more straightforward and convenient way to prepare the naphthalene derivatives, the intermolecular Diels–Alder reaction of styrene (4π-component) with an alkyne (2π-component) was much more challenging and highly under-developed.[4] Biju et al. has taken advantage of benzyne as an effective dienophile to react with styrene under mild conditions (Scheme 1b).[5] As our continuing efforts to develop tandem reactions based on alkynes,[6] we desire to develop a more general intermolecular Diels–Alder/ene-tandem reaction between styrene as a 4π-component and alkynes as a 2π-component (Scheme 1c).

Scheme 1. Diels–Alder Reactions Involving Styrene and Alkyne

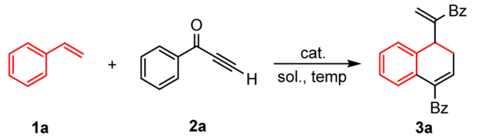


Initially, the reaction between an electron-deficient alkyne, ethynyl phenyl ketone **2a**, and styrene was chosen as the model reaction. No reaction occurred in the absence of a Lewis acid catalyst (Table 1, entry 1). It is well-known that the Diels–Alder reactions involving alkynones and 1,3-dienes could be promoted by a Lewis acid, which can decrease the electron density of the triple bond via coordination to the alkynone's carbonyl group and lead to a lower LUMO (the lowest unoccupied molecular orbital) energy.[7] The reaction of **1a** and **2a** was then carried out at room temperature in DCE in the presence of different Lewis acids. We are gratified to find that the reaction could be activated by a variety of Lewis acid catalysts, such as In(OTf)$_3$, ZnCl$_2$, Fe(OTf)$_3$, AlCl$_3$, and BF$_3$·Et$_2$O, yielding the dihydronaphthalene **3a** in 18–60% yields (entries 2–6). Among these Lewis acid catalyzed reactions, the best result was observed in the presence of ZnCl$_2$, and **3a** was afforded in 60% yield (entry 3). When the Brønsted acid TFA was used as the catalyst, the product **3a** was obtained in 28% yield (entry 7). The yield of **3a** dropped to less than 5% when a 1:1 ratio mixture of ZnCl$_2$ and TFA was applied (entry 8). The yield of **3a** can be enhanced to 76% when the temperature was increased to 60 °C (entry 9); however, further increasing the temperature to 80 °C resulted in a lower yield (entry 10). Neither increasing nor decreasing the amount of styrene **1a** can improve the reaction yield (entries 11–12). Other solvents such as MeCN and THF were also investigated in this model reaction. An inferior result was observed in MeCN, and no

Received: May 25, 2016

DOI: 10.1021/acs.orglett.6b01511

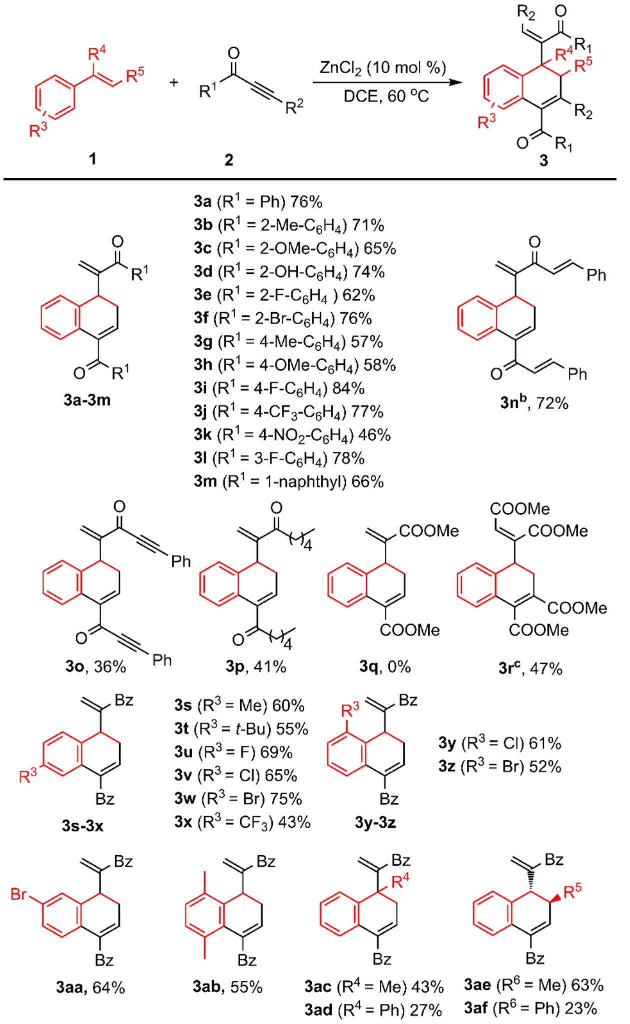
Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (10%)	1a (equiv)	temp (°C)	solvent	3a (%)
1	none	2.0	rt–60	DCE	n.r.
2	$In(OTf)_3$	2.0	rt	DCE	33
3	$ZnCl_2$	2.0	rt	DCE	60
4	$Fe(OTf)_3$	2.0	rt	DCE	22
5	$AlCl_3$	2.0	rt	DCE	38
6	$BF_3{\cdot}Et_2O$	2.0	rt	DCE	18
7	TFA	2.0	rt	DCE	28
8	$ZnCl_2$/TFA[b]	2.0	rt	DCE	<5
9	**$ZnCl_2$**	**2.0**	**60**	**DCE**	**76**[c]
10	$ZnCl_2$	2.0	80	DCE	55
11	$ZnCl_2$	1.0	60	DCE	41
12	$ZnCl_2$	2.5	60	DCE	74
13	$ZnCl_2$	2.0	60	MeCN	63
14	$ZnCl_2$	2.0	60	THF	n.r.

[a] The reaction was conducted in a sealed Schlenk tube with **1a** (0.50 mmol), **2a** (0.25 mmol) in DCE (2 mL), 12 h, under N_2. The yield was determined by ^1H NMR using CH_3NO_2 as an internal standard. Bz: benzoyl. [b] 10 mol % $ZnCl_2$ and 10 mol % TFA were used. [c] Isolated yield.

Scheme 2. Substrate Scopes[a]



[a] The reaction was conducted in a sealed Schlenk tube with **1a** (0.50 mmol), **2a** (0.25 mmol), $ZnCl_2$ (10 mol %) in DCE (2 mL) at 60 °C under N_2 for 12 h. Isolated yields are given. Bz: benzoyl. [b] ZnI_2 as catalyst, rt, 24 h. [c] 150 °C in toluene, 12 h.

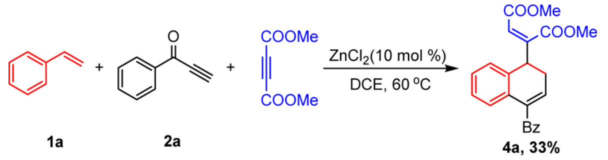
reaction occurred in THF at all, which may result from the coordination between zinc and solvent (entries 13 and 14).[8]

With the optimized reaction conditions in hand (Table 1, entry 9), the substrate scope was then explored (Scheme 2). It was found that the catalytic system could be successfully applied to a wide scope of alkynones **2**. For example, in addition to phenyl alkynone **2a**, other terminal aryl alkynones with different substituents at the phenyl group can serve as effective substrates as well, yielding the products **3a**–**m** in moderate to good yields (46–84%). It seems that the reactions are not very sensitive to the electronic effects of the alkynone substrates. Both the alkynones with electron-donating and -withdrawing groups functioned well under the catalytic conditions. The functional groups of methoxyl, hydroxyl, and nitro were well tolerated (**3c**, **3d**, **3h**, **3k**). Besides aryl alkynones, the alkenyl- and alkynyl-substituted alkynones can also be used as effective substrates, affording the desired products **3n** and **3o** in 72% and 36% yields, respectively. Alkyl alkynone transferred to the corresponding dihydronaphthalene **3p** in 41% yield. Further substrate screening showed that the internal alkynone was not an effective substrate for this reaction. Methyl propiolate was ineffective for this transformation as well (**3q**). An internal alkyne showed much lower reactivity, probably due to the steric hindrance. The extremely electron-poor dimethyl acetylenedicarboxylate (DMAD), which is typically an excellent dienophile for the traditional [4 + 2] reactions,[9] however, is not effective in our reaction. The reaction cannot occur until the temperature was enhanced to 150 °C (**3r**, 47%). The electron-deficient alkenes, such as methyl acrylate, dimethyl maleate, or phenyl vinyl-ketone, were not effective dienophiles for this transformation.

In addition to styrene, the styrene derivatives **1** with different substituents can be successfully employed in the reaction (**3s**–**3af**). Similarly, these reactions were not sensitive to the electronic effects of the styrene substrates. The styrene derivatives with both electron-donating and -withdrawing substituents on phenyl ring could be converted into the dihydronaphthalenes **3s**–**3ab** smoothly, with the yields ranging from 43% to 75%. It is noted that the reactions occurred well even when bulkier α- or β-substituted styrenes were applied as the substrates (**3ac**–**af**). It was found that α- or β-methylstyrene (**3ac**, **3ae**) was a better 4π-component than α- or β-phenyl styrene (**3ad**, **3af**).

After having established the intermolecular two-component Diels–Alder/ene-tandem reaction as a reliable and efficient synthetic process to synthesize diverse dihydro-naphthalenes, we are especially interested in investigating the possibility of the three-component tandem reaction, in which two different alkynes were used instead of the same alkyne in the above-mentioned tandem reaction. We desire that one alkyne can take part in the Diels–Alder process while the other alkyne participates in the subsequent ene reaction. Between these two steps, the Diels–Alder reaction was believed to be the rate-determining process for the tandem reaction. As mentioned above, the internal alkynone DMAD showed much lower reactivity toward the initial Diels–Alder reaction than the terminal alkynones, whereas DMAD can be a better dienophile in the following ene reaction based on the traditional observations.[7,10] To verify our hypothesis, the three-component tandem reaction of alkynone **2a**, DMAD, and styrene was then carried out. To our delight, the desired dihydronaphthalene product **4a** could be obtained in 33% yield (Scheme 3).

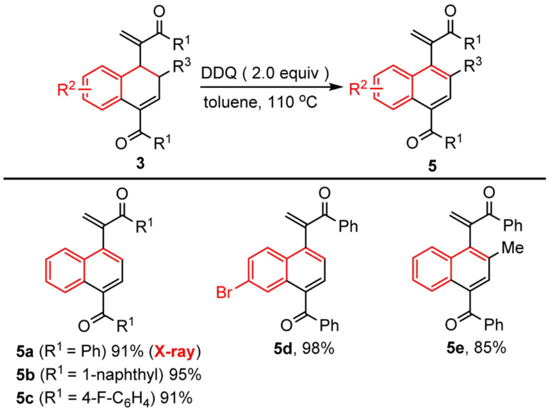
Scheme 3. Three-Component Reaction[a]



[a] The reaction was conducted with **1a** (0.50 mmol), **2a** (0.25 mmol), DMAD (1.25 mmol), ZnCl$_2$ (10 mol %) in DCE (2 mL), 60 °C under N$_2$, and 12 h. Bz: benzoyl.

With the dihydronaphthalene derivatives in hand, we also explored their further transformations. As shown in Scheme 4, the dihydronaphthalene products could be oxidized smoothly into the naphthalenes in excellent yields (**5a**–**f**, 85–98%) by DDQ as the oxidant. The structure of **5a** has been determined by the single crystal X-ray analysis.

Scheme 4. Oxidation of Dihydronaphthalene[a]

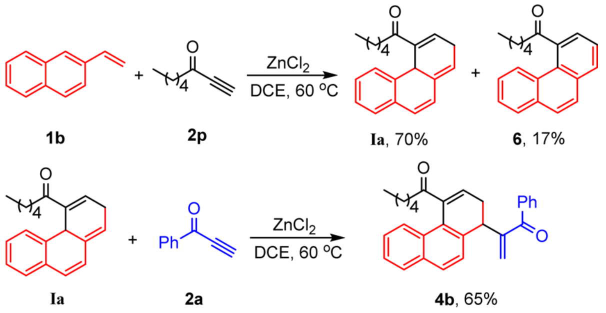


[a] The reaction was conducted with **3** (1 mmol), **DDQ** (2 mmol) in toluene under 110 °C for 12 h. Yields of the isolated products are given.

To understand the ZnCl$_2$-catalyzed tandem Diels–Alder/ene reaction, a DFT calculation was then carried out (see Supporting Information for the calculation detail).[11] The ene reaction is mechanistically similar to the Diels–Alder reaction since both reactions can proceed through a concerted cyclic transition state involving six electrons.[7,12] The coordination of zinc to the carbonyl oxygen of alkynone **2a** can decrease the LUMO energy of dienophile, which would accelerate the Diels–Alder and ene reactions. The free energy barrier for the Diels–Alder reaction was about 23.5 kcal/mol. Due to the disruption of aromaticity, the hydrogen at the 1-position of intermediate **I** could be easily released to a proton acceptor such as **2a**. Then, an ene reaction could take place through a cyclization transition state involving six electrons, requiring an activation free energy of 17.8 kcal/mol. The potential energy surface revealed that the rate-determining step is the Diels–Alder reaction via **TS1**, and the reaction is highly exergonic (−74.1 kcal/mol).

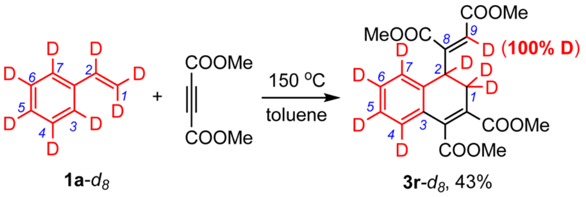
To testify the proposed reaction mechanism, a series of control experiments have been carried out. In order to observe or characterize the proposed dearomatization intermediate **I**, 2-vinylnaphthylene **1b** (with increasing aromatic content) was then used as the 4π-component diene. The desired intermediate **Ia** could be successfully isolated in 70% yield when alkynone **2p** was used as the dienophile. The reaction was accompanied by another inseparable oxidation product **6** in 17% yield. The intermediate **Ia** could subsequently react with phenyl alkynone **2a**, affording the target three-component tandem reaction product **4b** in 65% yield (Scheme 5).

Scheme 5. Control Experiments



Furthermore, to gain additional insight into the hydrogen transfer process of the ene reaction, a deuterium labeling study was also performed. As shown in Scheme 6, the reaction of deuterated styrene with DMAD under the same conditions in Scheme 2 provided the product **3r**-d_8 in 43% yield with 100% D-transfer from C-3 to C-9, which indicated that the ene reaction is a concerted process. All these control reaction results from Schemes 5 and 6 were perfectly consistent with the reaction mechanism proposed in Figure 1.

Scheme 6. Deuterium Labeling Experiment



In conclusion, a mild Zn-catalyzed intermolecular Diels–Alder/ene tandem reaction with styrene as a 4π-component is reported. The reaction was initiated by a Diels–Alder reaction between 4π-component styrene and a dienophile alkynone, followed by an ene reaction with another dienophile, leading to the dihydronaphthalene products in moderate to good yields. The reaction pathway was rationalized by DFT calculations, and the key intermediate was isolated when 2-vinylnaphthalene was used as the 4π-component. This study could not only help the understanding of the Diels–Alder reaction with styrene as 4π-component but also provide a general and efficient protocol to synthesize dihydronaphthalene derivatives. Further studies on additional application of this Diels–Alder/ene cascade reaction and Diels–Alder reactions with styrene involved as a 4π-component are underway in our laboratory.

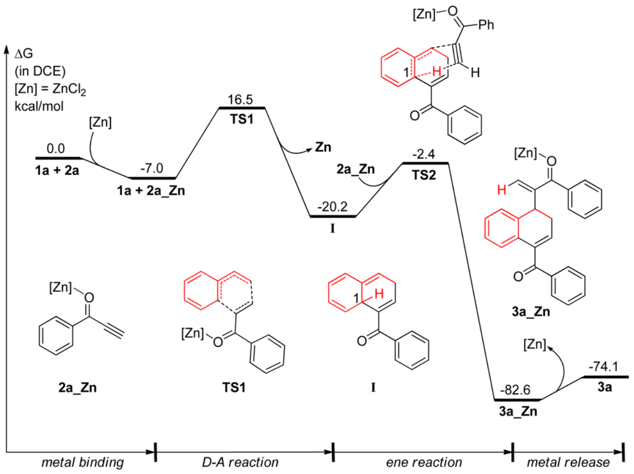


Figure 1. DFT-computed free energy profile.[11]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01511.

Typical experimental procedure, characterization for all products, and DFT calculation details (PDF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cekchen@scut.edu.cn.
*E-mail: zhusf@scut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Ministry of Science and Technology of the People's Republic of China (2016YFA0602900), the NSFC (21372086, 21422204), Guangdong Natural Science Foundation (2014A030313229, 2016A030310433), China Postdoctoral Science Foundation (2015M582378, 2016T90777), and the Fundamental Research Funds for the Central Universities, SCUT for financial support of this research. Prof. Li Zhang from SYSU is specially acknowledged for her help in language polishing.

■ REFERENCES

(1) (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (b) Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771. (c) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779. (d) Fringuelli, F.; Taticchi, A. *The Diels−Alder reaction: Selected practical methods*; John Wiley & Sons; Chichester, U.K., 2002. (e) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, *6*, 3115.

(2) (a) Klemm, L. H.; Gopinath, K. W. *Tetrahedron Lett.* **1963**, *4*, 1243. (b) Klemm, L. H.; Klemm, R. A.; Santhanam, P. S.; White, D. V. *J. Org. Chem.* **1971**, *36*, 2169. (c) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571. (d) Chackalamannil, S.; Doller, D.; Eagen, K. *Tetrahedron Lett.* **2002**, *43*, 5101. (e) Ruijter, E.; Garcia-Hartjes, J.; Hoffmann, F.; van Wandelen, L. T. M.; de Kanter, F. J. J.; Janssen, E.; Orru, R. V. A. *Synlett* **2010**, *2010*, 2485. (f) Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 5390.

(3) Kocsis, L. S.; Kagalwala, H. N.; Mutto, S.; Godugu, B.; Bernhard, S.; Tantillo, D. J.; Brummond, K. M. *J. Org. Chem.* **2015**, *80*, 11686.

(4) (a) Jiang, J.-L.; Ju, J.; Hua, R. *Org. Biomol. Chem.* **2007**, *5*, 1854. (b) Kolis, S. P.; Chordia, M. D.; Liu, R.; Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2218. (c) Wang, S. R.; Xie, Z. *Tetrahedron* **2012**, *68*, 5269.

(5) (a) Dilling, W. L. *Tetrahedron Lett.* **1966**, *7*, 939. (b) Wolthuis, E.; Cady, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 555. (c) Harrison, R.; Heaney, H.; Jablonski, J. M.; Mason, K. G.; Sketchley, J. M. *J. Chem. Soc. C* **1969**, 1684. (d) Bhojgude, S. S.; Bhunia, A.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2014**, *16*, 676. (e) Bhojgude, S. S.; Thangaraj, M.; Suresh, E.; Biju, A. T. *Org. Lett.* **2014**, *16*, 3576.

(6) (a) Ma, J.; Chen, K.; Fu, H.; Zhang, L.; Wu, W.; Jiang, H.; Zhu, S. *Org. Lett.* **2016**, *18*, 1322. (b) Liang, R.; Chen, K.; Zhang, Q.; Zhang, J.; Jiang, H.; Zhu, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 2587. (c) Ma, J.; Zhang, L.; Zhu, S. *Curr. Org. Chem.* **2015**, *20*, 102. (d) Zhu, S.; Zhang, Q.; Chen, K.; Jiang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 9414. (e) Zhu, S.; Huang, X.; Zhao, T.-Q.; Ma, T.; Jiang, H. *Org. Biomol. Chem.* **2015**, *13*, 1225. (f) Liang, R.; Jiang, H.; Zhu, S. *Chem. Commun.* **2015**, *51*, 5530. (g) Liang, R.; Ma, T.; Zhu, S. *Org. Lett.* **2014**, *16*, 4412. (h) Zhu, S.; Huang, H.; Zhang, Z.; Ma, T.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 6113. (i) Zhu, S.; Hu, L.; Jiang, H. *Org. Biomol. Chem.* **2014**, *12*, 4104. (j) Zhu, S.; Guo, Z.; Huang, Z.; Jiang, H. *Chem. - Eur. J.* **2014**, *20*, 2425. (k) Ma, J.; Jiang, H.; Zhu, S. *Org. Lett.* **2014**, *16*, 4472. (l) Zhu, S.; Zhang, Z.; Huang, X.; Jiang, H.; Guo, Z. *Chem. - Eur. J.* **2013**, *19*, 4695. (m) Zhu, S.; Xiao, Y.; Guo, Z.; Jiang, H. *Org. Lett.* **2013**, *15*, 898. (n) Zhu, S.; Liang, R.; Jiang, H.; Wu, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10861. (o) Zhu, D.; Ma, J.; Luo, K.; Fu, H.; Zhang, L.; Zhu, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 8452. (p) Zhang, J.; Xiao, Y.; Chen, K.; Wu, W.; Jiang, H.; Zhu, S. *Adv. Synth. Catal.* **2016**, *358*, DOI: 10.1002/adsc.201600266.

(7) (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200.

(8) (a) Wang, H.; Kehr, G.; Fröhlich, R.; Erker, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 4905. (b) Mikhalitsyna, E. A.; Tyurin, V. S.; Nefedov, S. E.; Syrbu, S. A.; Semeikin, A. S.; Koifman, O. I.; Beletskaya, I. P. *Eur. J. Inorg. Chem.* **2012**, *2012*, 5979.

(9) (a) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472. (b) Wender, P. A.; Jeffreys, M. S.; Raub, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 9088. (c) Mackay, W. D.; Johnson, J. S. *Org. Lett.* **2016**, *18*, 536.

(10) Fernandez, I.; Bickelhaupt, F. M. *J. Comput. Chem.* **2012**, *33*, 509.

(11) DFT calculations were performed with the Gaussian 09 program. The relative Gibbs free energies were given at the [SMD(DCE), M062X/(6-311++G(d,p), SDD)]//B3LYP/(6-31G(d), Lanl2DZ) theoretical level. See Supporting Information for calculation details.

(12) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.