Polycyclic Aromatic Hydrocarbons

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Synthesis of Multiply Substituted Polycyclic Aromatic Hydrocarbons by Iridium-Catalyzed Annulation of Ring-Fused Benzocyclobutenol with Alkyne through C–C Bond Cleavage

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Abstract: *The first iridium-catalyzed intermolecular cyclization between alkynes and ring-fused benzocyclobutenols (RBCB) through C–C bond cleavage is described. A variety of elusive polycyclic aromatic hydrocarbons (PAHs) with multiple substituents are obtained in good yields under mild conditions. This procedure provides a unique and expeditious tool for the synthesis of PAHs.*

Polycyclic aromatic hydrocarbons (PAH) with extended π-conjugated systems have attracted immense interest because of their broad application in organic, optical, and electronic materials.[1] Generally, the properties and stability of PAHs depend heavily on their structural features.[2] For examples, angular PAHs with arm-chair peripheries are more stable than linear PAHs with zig-zag peripheries when exposed to light and air (Figure 1).[3] As a result, angular PAHs are commonly considered as promisingly practical organic materials.[4] On the other hand, many compounds based on angular PAHs such as phenanthrene have exhibited remarkable pharmacological activities.[5] Currently, the common synthetic methods for the preparation of PAHs employ intramolecular cyclization,[6] in which the substrate scope and product diversity are quite limited as a result of the use of precursor compounds which themselves require multi-step preparative methods. Therefore, the development of a convenient intermolecular approach to highly substituted angular PAHs remains challenging and is of great significance for multiple fields of chemistry, pharmaceuticals, and material sciences.

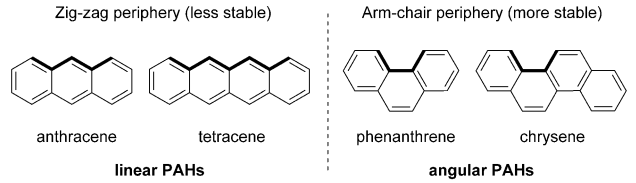
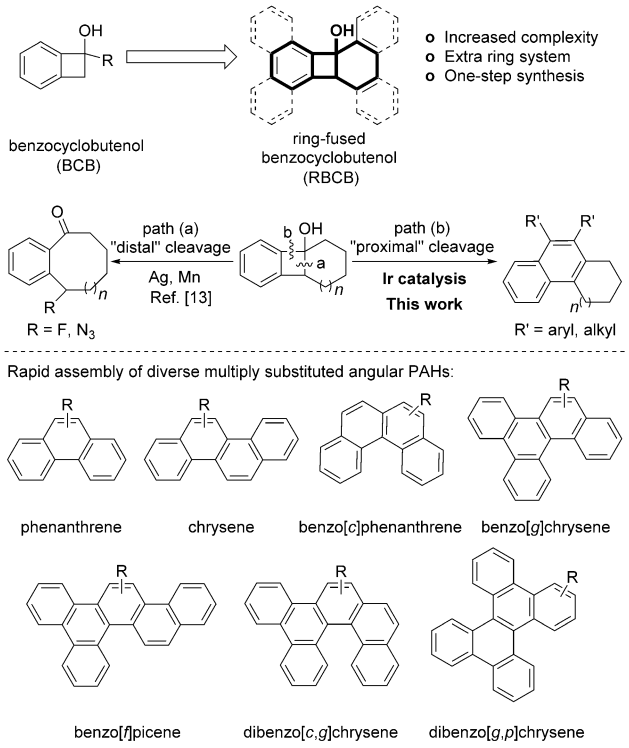


Figure 1. Linear and angular PAHs with different stabilities.

Benzocyclobutenols (BCB) are frequently employed as privileged building blocks for the construction of complex cyclic molecules and natural products.[7,8] Recently, Murakami et al. and Wang et al. reported the rhodium-catalyzed cyclization of BCB with alkynes or diazo esters, respectively.[7b,e] However, the reactions required high temperature (100 °C), the utility of products was not fully demonstrated, and most importantly, the preparation of BCB usually requires tedious synthetic routes.[9] We are interested in ring-fused benzocyclobutenols (RBCB) as they can be easily obtained using a one-step synthesis from commercially available aryl bromides and cyclic ketones.[10] In particular, the presence of additional rings provide a platform suitable for further aromatization (Scheme 1, top). The benzocyclobutyl C–C bond can be cleaved in "distal" or "proximal" pathway.[7,11,12] We recently reported the silver- or manganese-catalyzed



Scheme 1. C–C cleavage of RBCB and its applications in the synthesis of a diverse range of angular PAHs.

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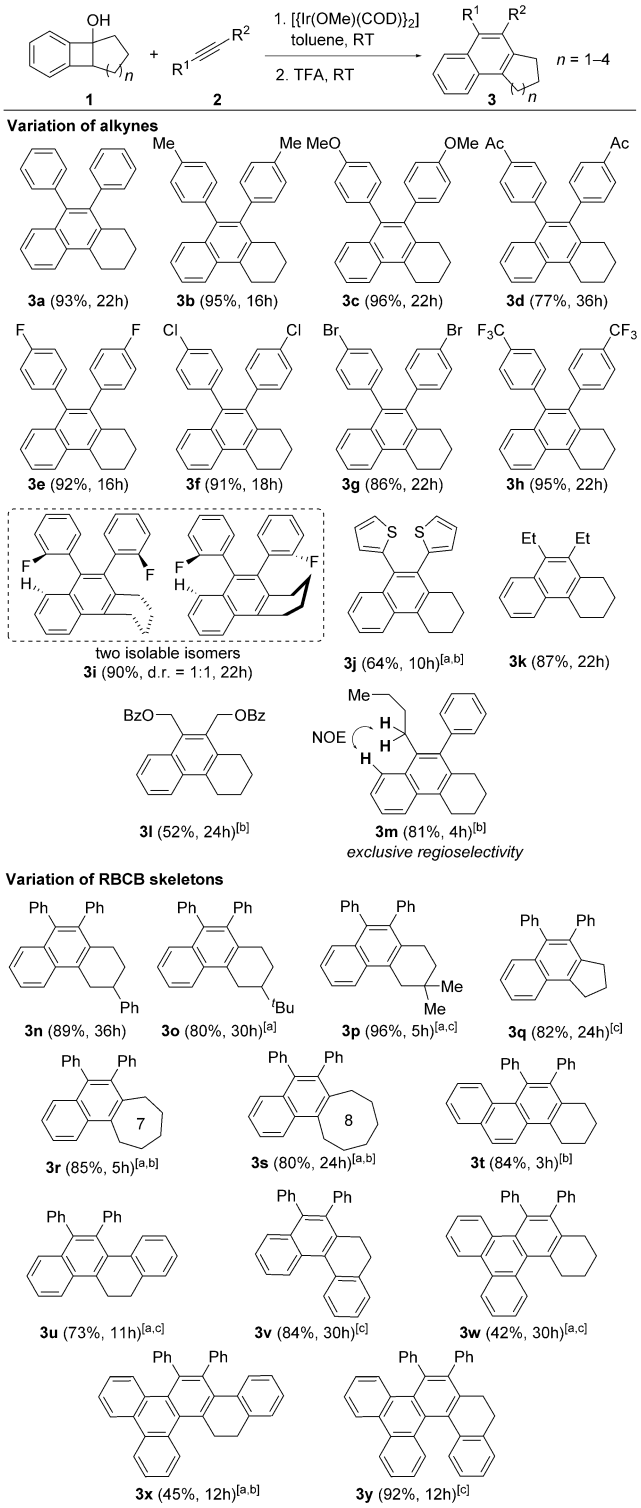
distal C–C bond cleavage of RBCB to generate medium-sized carbocyclic fluorides or azides (Scheme 1, path (a)).[13] Inspired by these findings, it is conceivable that the cyclization of alkyne with RBCB by means of proximal C–C cleavage might lead to polyaromatic compounds. Herein, we disclose the first iridium-catalyzed annulation of RBCB with alkynes to efficiently produce a variety of multiply substituted PAHs in good yields (Scheme 1, path (b)). The proximal C–C bond is regioselectively cleaved under mild conditions, mostly at room temperature.

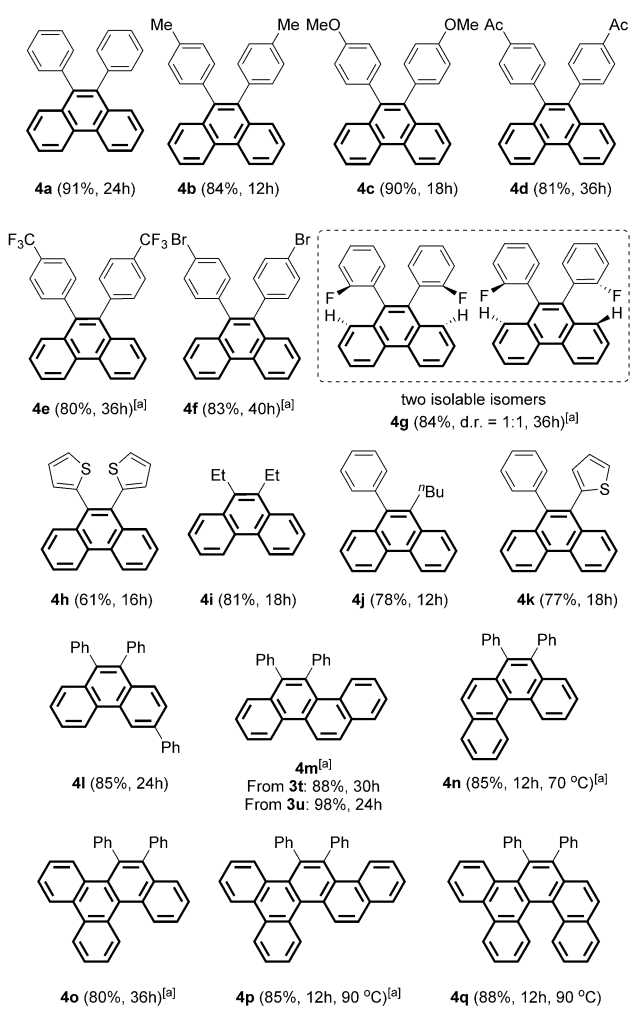
Our investigation of the annulation reaction commenced with the examination of reaction parameters, including catalysts and solvents. The use of many transition-metal catalysts (for example, $Pd(OAc)_2$, $[Rh(PPh_3)_3Cl]$, $[\{Rh(COD)Cl\}_2]$, $[\{RhCp^*Cl_2\}_2]$, and $[\{Ru(cymene)Cl_2\}_2]$; COD = 1,5-cyclooctadiene, Cp* = pentamethylcyclopentadienyl) failed to give the expected product. To our delight, $[\{Rh(OH)(COD)\}_2]$ and $[\{Ir(OMe)(COD)\}_2]$ enabled the reaction, with the iridium catalyst giving a higher yield than the rhodium catalyst at room temperature. Among the organic solvents screened, toluene delivered the best yields. After considerable efforts, the optimized reaction conditions were defined and subsequently employed for the evaluation of substrate scope (Scheme 2). Initially, a variety of alkynes were tested, showing good functional-group tolerance for the reaction conditions. Generally, the electron-rich alkynes provided better yields than electron-poor ones (**3a–c** versus **3d**). Halogenated alkynes (F, Cl, and Br) exhibited remarkable performance in the annulation reaction (**3e–g**). In particular, the presence of the bromide in **3g** provides opportunity for later functionalization of the molecule through cross-coupling reactions. The reaction afforded CF_3-containing polycyclic product **3h** in excellent yield. Interestingly, in the cases of *ortho*-substituted diarylalkyne, a couple of isomers were generated in 1:1 ratio and could be separated by column chromatography on silica gel (**3i**). In addition to aryl alkynes, heteroaryl and alkyl alkynes were also suitable substrates to furnish the corresponding adducts in synthetically useful yields (**3j–m**). Notably, only a single regioisomer was obtained when unsymmetric alkyne was applied (**3m**), indicating an exclusive regioselectivity. After completing our assessment of functional-group tolerance, we set about investigating the generality of the RBCB unit by varying its framework. The presence of either aryl or alkyl group on the ring did not compromise the high yields (**3n–p**). Aside from the six-membered ring-fused BCB, the five, seven, and eight-membered ring-fused substrates could also readily generate the products **3q–s**, although elevated temperatures were required. This result is particularly useful as these products are otherwise difficult to prepare. Significantly, the addition of an extra ring system to RBCB could easily increase the product complexity, giving rise to the desired polycyclic compounds in satisfactory yields (**3t–y**).

With a diverse range of polycyclic precursors in hand, we then embarked on their transformation into PAHs. The aromatization occurred smoothly in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature. A variety of representative molecules from Scheme 2 were selected and converted into the corresponding

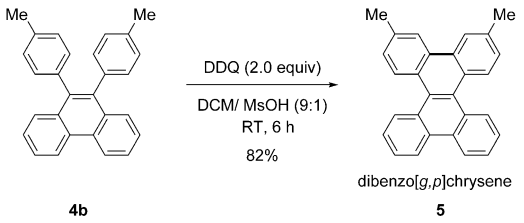


Scheme 2. Substrate scope for the annulation reaction of RBCB with alkynes. Conditions: **1** (0.20 mmol), **2** (0.22 mmol), $[\{Ir(OMe)(COD)\}_2]$ (0.005 mmol, 2.5 mol %), toluene (2.0 mL), RT, then treatment with TFA (0.10 mmol, 0.5 equiv) for 1 h. Yields of isolated products given. [a] TFA (9.0 equiv). [b] 110 °C. [c] 70 °C.

PAHs (Scheme 3). Both electron-rich and electron-deficient substrates gave rise to the expected products in good yields (**4a–e**). Susceptible functional groups, such as acetyl and



Scheme 3. Preparation of angular PAHs. Conditions: **3** (0.20 mmol) and DDQ (0.60 mmol, 3.0 equiv) in CH_2Cl_2 (2.0 mL) at RT. Yields of isolated products are given. [a] DDQ (4.0 equiv).



Scheme 4. Synthesis of dibenzo[*g*,*p*]chrysene. MsOH = methanesulfonic acid, DCM = dichloromethane.

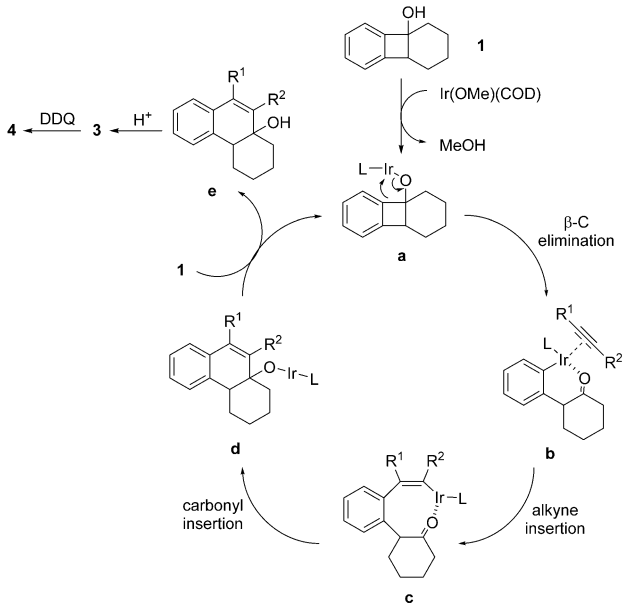


Figure 2. Proposed reaction mechanism.

bromo, remained intact under the oxidative conditions (**4d**, **4f**). Similar to its precursor **3i**, compound **4g** was also generated in the form of isomers with d.r. = 1:1, which were separable by column chromatography. Heteroaryl and alkyl substituents were also tolerated (**4h**–**k**). In addition to phenanthrenes **4a**–**l**, several elusive PAHs containing four- to six-fused aromatic rings were also readily prepared in high yields (chrysene (**4m**), benzo[*c*]phenanthrene (**4n**), benzo[*g*]chrysene (**4o**), benzo[*f*]picene (**4p**), and dibenzo[*c*,*g*]chrysene (**4q**)). Chrysene **4m** could be obtained from either **3t** or **3u** in comparable yields. It can be anticipated that additional different types of complex PAHs can be accessed by the simple manipulation of RBCB skeletons.

The utility of this method was further demonstrated by the transformation of the obtained PAHs into dibenzo[*g*,*p*]chrysene, a twisted PAH for the preparation of nonlinear-optical and liquid-crystalline materials.[14] For example, **4b** was readily converted into **5** in 82% yield at room temperature (Scheme 4).[15]

The proposed reaction mechanism is outlined in Figure 2. Initially, the incorporation of the iridium catalyst and RBCB **1** generated the iridium oxide **a**. Simultaneously, the β-carbon elimination of **a** occurred, forming the aryl–iridium species **b**. The subsequent insertion of alkynyl and carbonyl units led to the cyclized intermediate, iridium complex **d**. The protonation of **d** by **1** regenerated intermediate **a** and meanwhile released the tertiary alcohol **e**, which further reacted to form **3** by means of acid-promoted dehydration. Compound **3** could be further aromatized to PAH **4** by DDQ oxidation.

In summary, we have developed the first iridium-catalyzed intermolecular cyclization between alkynes and ring-fused benzocyclobutenols through C–C bond cleavage. The transformation exhibits good functional-group tolerance and unique regioselectivity. A variety of elusive polycyclic aromatic hydrocarbons with multiple substituents are synthesized in good yields under mild reaction conditions. This procedure provides a conceptually new and expeditious approach for the synthesis of angular PAH derivatives.

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[1] For selected reviews, see: a) R. G. Harvey, *Polycyclic Aromatic Hydrocarbons*, Wiley-VCH, New York, **1997**, pp. 43–128; b) M. M. Boorum, L. T. Scott, *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 20–31; c) M. D. Watson, A. Fechtenkötter, K. Müllen, *Chem. Rev.* **2001**, *101*, 1267–1300; d) J. E. Anthony, *Chem. Rev.* **2006**, *106*, 5028–5048.

[2] For selected reviews, see: a) J. R. Dias, *Top. Curr. Chem.* **1990**, *153*, 123–143; b) J. R. Dias, *Tetrahedron* **1993**, *49*, 9207–9220.

[3] P. Coppo, S. G. Yeates, *Adv. Mater.* **2005**, *17*, 3001–3005.

[4] For a review, see: Y. Kubozono, X. He, S. Hamao, K. Teranishi, H. Goto, R. Eguchi, T. Kambe, S. Gohda, Y. Nishihara, *Eur. J. Inorg. Chem.* **2014**, 3806–3819.

[5] a) L. Yang, L. Qin, S. W. A. Bligh, A. Bashall, C. Zhang, M. Zhang, Z. Wang, L. Xu, *Bioorg. Med. Chem.* **2006**, *14*, 3496–3501; b) L. Wei, Q. Shi, K. F. Bastow, A. Brossi, S. L. Morris-Natschke, K. Nakagawa-Goto, T. Wu, S. Pan, C. Teng, K. Lee, *J. Med. Chem.* **2007**, *50*, 3674–3680; c) J. Lin, S. Yang, T. Hong, S. Yu, Q. Shi, L. Wei, H. Chen, P. Yang, K. Lee, *J. Med. Chem.* **2009**, *52*, 1903–1911; d) Y. Lin, F. Wang, L. Yang, Z. Chun, J. Bao, G. Zhang, *Phytochemistry* **2013**, *95*, 242–251.

[6] For selected reviews, see: a) A. J. Floyd, S. F. Dyke, S. E. Ward, *Chem. Rev.* **1976**, *76*, 509–562; b) D. Pérez, E. Guitián, *Chem. Soc. Rev.* **2004**, *33*, 274–283; c) D. Pérez, D. Peña, E. Guitián, *Eur. J. Org. Chem.* **2013**, 5981–6013.

[7] For selected examples, see: a) A. Chtchemelinine, D. Rosa, A. Orellana, *J. Org. Chem.* **2011**, *76*, 9157–9162; b) N. Ishida, S. Sawano, Y. Masuda, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17502–17504; c) Y. Li, Z. Lin, *J. Org. Chem.* **2013**, *78*, 11357–11365; d) L. Ding, N. Ishida, M. Murakami, K. Morokuma, *J. Am. Chem. Soc.* **2014**, *136*, 169–178; e) Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 3013–3015; f) N. Ishida, N. Ishikawa, S. Sawano, Y. Masuda, M. Murakami, *Chem. Commun.* **2015**, *51*, 1882–1885.

[8] For examples in natural product synthesis, see: a) D. I. Macdonald, T. Durst, *J. Org. Chem.* **1988**, *53*, 3663–3669; b) G. A. Kraus, G. Zhao, *Synlett* **1995**, 541–542; c) I. Takemura, K. Imura, T. Matsumoto, K. Suzuki, *Org. Lett.* **2004**, *6*, 2503–2505; d) U. K. Tambar, D. C. Ebner, B. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 11752–11753.

[9] For selected examples, see: a) E. Akguen, M. B. Glinski, K. L. Dhawan, T. Durst, *J. Org. Chem.* **1981**, *46*, 2730–2734; b) D. I. Macdonald, T. Durst, *Tetrahedron Lett.* **1986**, *27*, 2235–2238; c) I. S. Aidhen, N. S. Narasimhan, *Tetrahedron Lett.* **1991**, *32*, 2171–2172; d) K. Kobayashi, M. Kawakita, M. Uchida, K. Nishimura, T. Mannami, S. Irisawa, O. Morikawa, H. Konishi, *J. Org. Chem.* **1999**, *64*, 3557–3562; e) Y. Ito, H. Takahashi, J.-Y. Hasegawa, N. J. Turro, *Tetrahedron* **2009**, *65*, 677–689.

[10] D. Rosa, A. Chtchemelinine, A. Orellana, *Synthesis* **2012**, *44*, 1885–1891.

[11] For selected reviews, see: a) A. K. Sadana, R. K. Saini, W. E. Billups, *Chem. Rev.* **2003**, *103*, 1539–1602; b) A. Flores-Gaspar, R. Martin, *Synthesis* **2013**, *45*, 563–580; c) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740–7752; *Angew. Chem.* **2011**, *123*, 7884–7896; d) I. Marek, A. Masarwa, P.-O. Delaye, M. Leibeling, *Angew. Chem. Int. Ed.* **2015**, *54*, 414–429; *Angew. Chem.* **2015**, *127*, 424–439; e) L. Souillart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410–9464; f) L. Souillart, E. Parker, N. Cramer, *Top. Curr. Chem.* **2014**, *346*, 163–194; g) T. Xu, A. Dermenci, G. Dong, *Top. Curr. Chem.* **2014**, *346*, 233–258.

[12] For examples of C–C cleavage of benzocyclobutanones, see: a) T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2012**, *51*, 7567–7571; *Angew. Chem.* **2012**, *124*, 7685–7689; b) T. Xu, H. M. Ko, N. A. Savage, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 20005–20008; c) T. Xu, N. A. Savage, G. Dong, *Angew. Chem. Int. Ed.* **2014**, *53*, 1891–1895; *Angew. Chem.* **2014**, *126*, 1922–1926; d) T. Xu, G. Dong, *Angew. Chem. Int. Ed.* **2014**, *53*, 10733–10736; *Angew. Chem.* **2014**, *126*, 10909–10912; e) F. Juliá-Hernández, A. Ziadi, A. Nishimura, R. Martin, *Angew. Chem. Int. Ed.* **2015**, *54*, 9537–9541; *Angew. Chem.* **2015**, *127*, 9673–9677.

[13] a) H. Zhao, X. Fan, J. Yu, C. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 3490–3493; b) R. Ren, H. Zhao, L. Huan, C. Zhu, *Angew. Chem. Int. Ed.* **2015**, *54*, 12692–12696; *Angew. Chem.* **2015**, *127*, 12883–12887.

[14] S. Yamaguchi, T. M. Swager, *J. Am. Chem. Soc.* **2001**, *123*, 12087–12088.

[15] T. S. Navale, K. Thakur, R. Rathore, *Org. Lett.* **2011**, *13*, 1634–1637.

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