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Highly regioselective Ru(II)-catalyzed [3+2] spiroannulation of 1-aryl-2-naphthols with alkynes via a double directing group strategy

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ABSTRACT

A highly regioselective Ru(II)-catalyzed [3+2] spiroannulation of 1-aryl-2-naphthols with internal alkynes was developed by using a novel double directing group strategy. This method was compatible with many functional groups, thus affording a variety of sterically congested spirocyclic molecules in high yields.

Transition metal-catalyzed C–H functionalization is a rapidly growing field with research going into many different areas [1]. Due to the ubiquity of C–H bonds in the starting arenes, selective cleavage of a specific C–H bond is difficult, but highly desirable. One approach to address such an issue is the use of a directing group (DG), which directs a metal catalyst to be proximal to a certain C–H bond, leading to selective activation and subsequent functionalization. As a result, a myriad of useful and economical transformations of readily available aromatic compounds have been successfully developed [2–3]. However, there are still some challenging problems to be solved. For example, extension of this approach to *meta*-substituted aromatic molecules was only partially successful. Activation of the sterically more encumbered C–H bond is less favorable, and the reactions with substrate **I** generally led to a single product **II**, or a regioisomeric mixture of **II** and **III** (Scheme 1a) [4–5]. Presumably, if the R substituent can serve as a second DG, the more difficult activation of C–H bond at the more bulky site of **I'** might be realized by chelating binding with two DGs for the formation of desired intermediate **B'** (Scheme 1b). If one DG binds more strongly with the metal catalyst, competitive side reaction for generating metallacyclic **A'** or **C'** might take place [6]. Therefore, the key to the development of such reactions is to identify two suitable DGs. Until now, very few examples within that category have been disclosed [7]. Stimulated by the previous works from our and other groups [8], in which phenolic DG was used for promoting Ru(II), Rh(III) or Pd(II)-catalyzed dearomatizing [3+2] spiroannulation of 1-aryl-2-naphthols with alkynes, we planned to explore a complementary protocol by functionalizing C–H bond at the more crowded site through the incorporation of a second DG^2 at the *meta*-position of their upper aryl ring. Herein, we present the successful execution of our new double directing group strategy for the regioselective construction of a number of sterically congested spirocycles by using two phenolic and acetylamino DGs (Scheme 1c).

As outlined in the reaction proposal, the main task was to find a suitable DG^2. Therefore, we began the study by testing a series of biaryl substrates **1** bearing another common DG besides the phenolic DG under our prior Ru(II)-catalysis conditions [8a], and the results are summarized in the Table 1. When equipped with an acetyl group ($\mathbf{1^I}$), the C–H activation took place at its *para*-position, leading to the less bulky product $\mathbf{3^I}$ in 40% yield, with no formation of the desired $\mathbf{4^I}$. Similar outcomes were observed when oxime ether and amide DGs ($\mathbf{1^{II}}$ and $\mathbf{1^{III}}$) were involved. These results indicated that the DGs for the generation of five-membered ruthenacycles might not be suitable for the double directing group strategy. Much to our delight, an acetylamino DG, which was widely used to activate C–H bonds for generating six-membered metallacycles [9], could promote the formation of anticipated product **4a** in 26% yield. However, regioisomeric **3a** was observed as the major product under the tested conditions. This experiment proved the feasibility of developing a double directing group strategy via the generation of two six-membered ruthenacycle-fused intermediate.

To improve the regiochemistry for the formation of **4a**, further optimization on the reaction parameters were performed (Table 2).

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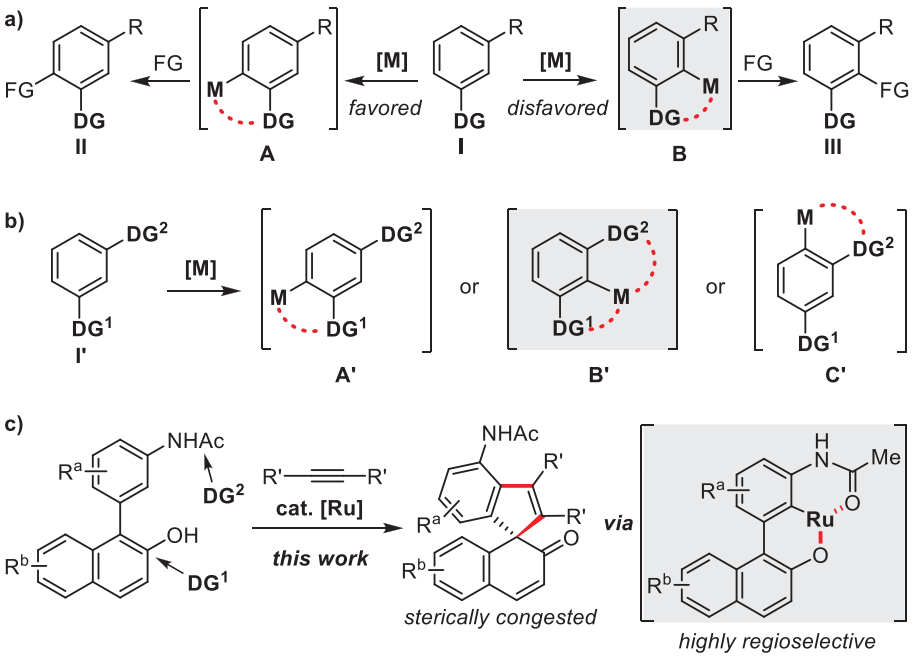
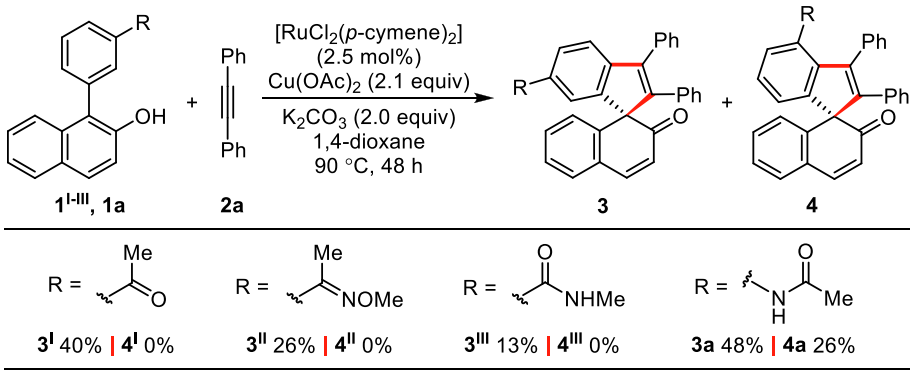


Scheme 1. Reaction development based on the C–H activation of *meta*-substituted arenes.

Table 1
Exploring DG^2 for the Double Directing Group Strategy.[a]



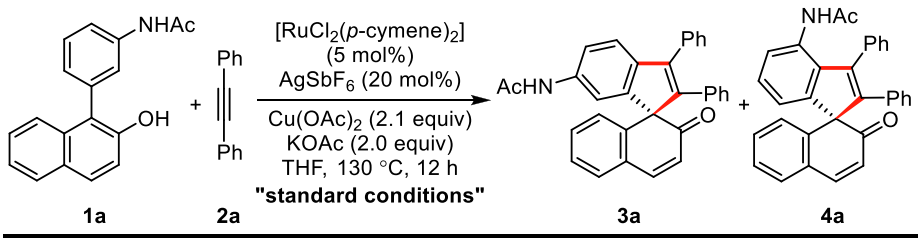
[a] Isolated yields.

Gratifyingly, the desired **4a** could be selectively generated as a single product in 80% yield, with a catalytic system consisting of $[RuCl_2(p\text{-cymene})_2]$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2$ (2.1 equiv), and KOAc (2.1 equiv) in THF at 130 °C for 12 h (entry 1). Control experiments indicated that $Pd(OAc)_2$ and $[Cp^*RhCl_2]_2$ led to poor results in terms of both reactivity and regioselectivity (entries 2–3). Replacing $Cu(OAc)_2$ with oxidants such as Ag_2O and BQ gave inferior performance (entries 4–5). Notably, the runs by using NaOAc, Cs_2CO_3 and K_2CO_3 as the base revealed that both the cation and anion of KOAc was important for maintaining a good reaction performance (entries 6–8). Further studies on the solvent screening showed that THF was crucial for the desired transformation, and no better results were obtained by other solvents (entries 9–13).

With the optimized reaction conditions in hand, the scope with respect to biaryl substrates **1** was first examined (Table 3). The experimental results indicated that many functional groups could be tolerated on both aromatic fragments, thus providing a series of spirocyclic molecules **4b-m** in 63–85% yields with excellent regioselectivity (>19:1 rr for all cases). Specifically, the upper aryl ring could be diversely substituted with electron-neutral methyl group (**4b**), electron-donating methoxy group (**4e**), or an electron-withdrawing group such as fluoro (**4c**), trifluoromethoxy (**4d**), chloro (**4f**) and trifluoromethyl (**4g**) groups, and the C–H bond cleavage regioselectively took place at the more sterically congested site. Moreover, substrates **1h-m**, which were equipped with different substituent at the naphthol ring respectively, were suitable for the desired [3+2] spiroannulation as well. Notably, formyl, ester, and thienyl groups, which might coordinate with the Ru(II)-catalyst in the reaction, didn't affect the efficiency for the formation of their corresponding products **4j-l**.

Having examined the scope of phenolic substrates, we moved to evaluate the performance of alkynes (Table 4). Overall, the titled Ru (II)-catalyzed C–H activation/naphthol dearomatization tandem reaction could proceed smoothly to produce the desired products **4a'-l'** in moderate to good yields. In general, all the products were generated as single regioisomers. Notably, a wide range of functional groups such as methyl (**4a'**), *tert*-butyl (**4b'**), methoxy (**4c'**), fluoro (**4d'j'**), chloro (**4e',i'**), trifluoromethyl (**4f'**) and ester (**4g'**) groups were well accommodated. It should be noted that the use

Table 2
Optimization of the Reaction Conditions.[a]

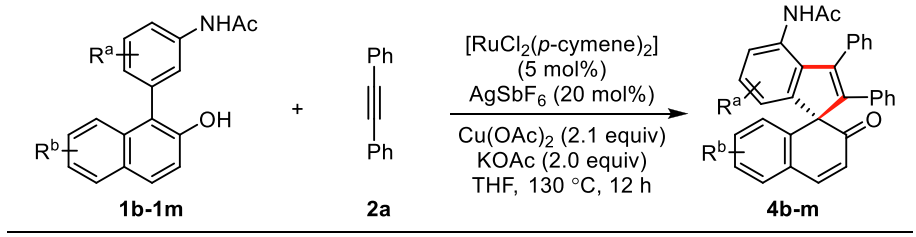


1a 2a 3a 4a

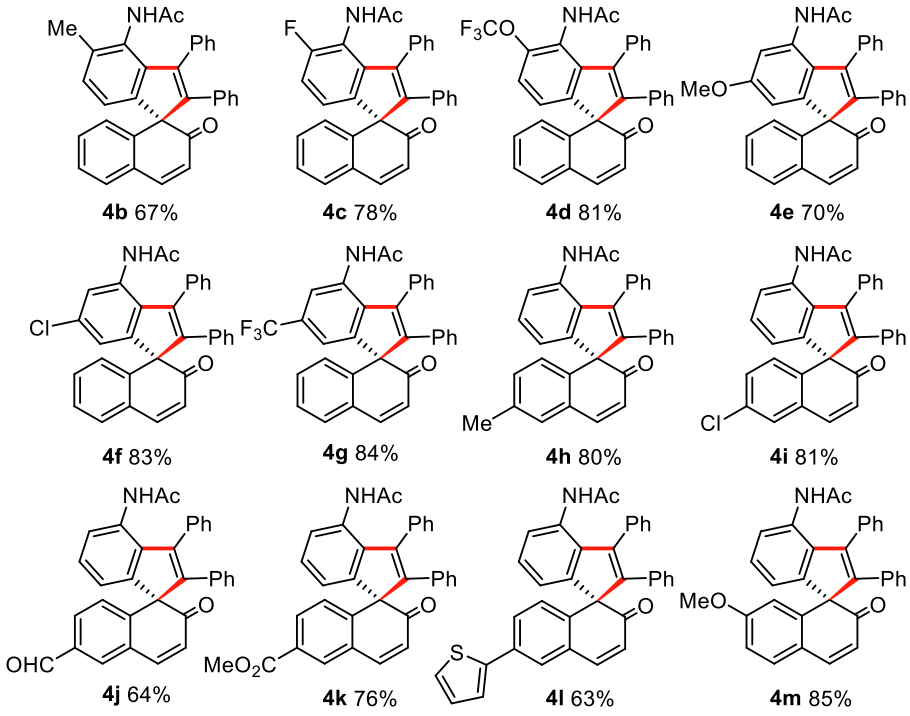
Entry	Variations from standard conditions	**3a**Yield (%)[b]	**4a**Yield (%)[b]
1	none	0	80
2	$Pd(OAc)_2$ instead of $[RuCl_2(p\text{-cymene})_2]$	36	12
3	$[Cp^*RhCl_2]_2$ instead of $[RuCl_2(p\text{-cymene})_2]$	33	18
4	Ag_2O instead of $Cu(OAc)_2$	30	0
5	BQ instead of $Cu(OAc)_2$	16	9
6	NaOAc instead of KOAc	0	54
7	Cs_2CO_3 instead of KOAc	36	14
8	K_2CO_3 instead of KOAc	11	48
9	DMF instead of THF	6	20
10	PhMe instead of THF	5	24
11	1,4-dioxane instead of THF	7	46
12	DCE instead of THF	0	31
13	^{t}AmOH instead of THF	6	66

[a] Performed on 0.2 mmol scale.
[b] Isolated yield.

Table 3
Scope of 1-Aryl-2-naphthols.[a]



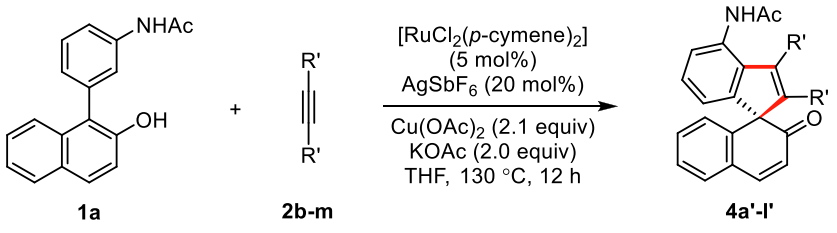
1b-1m 2a 4b-m

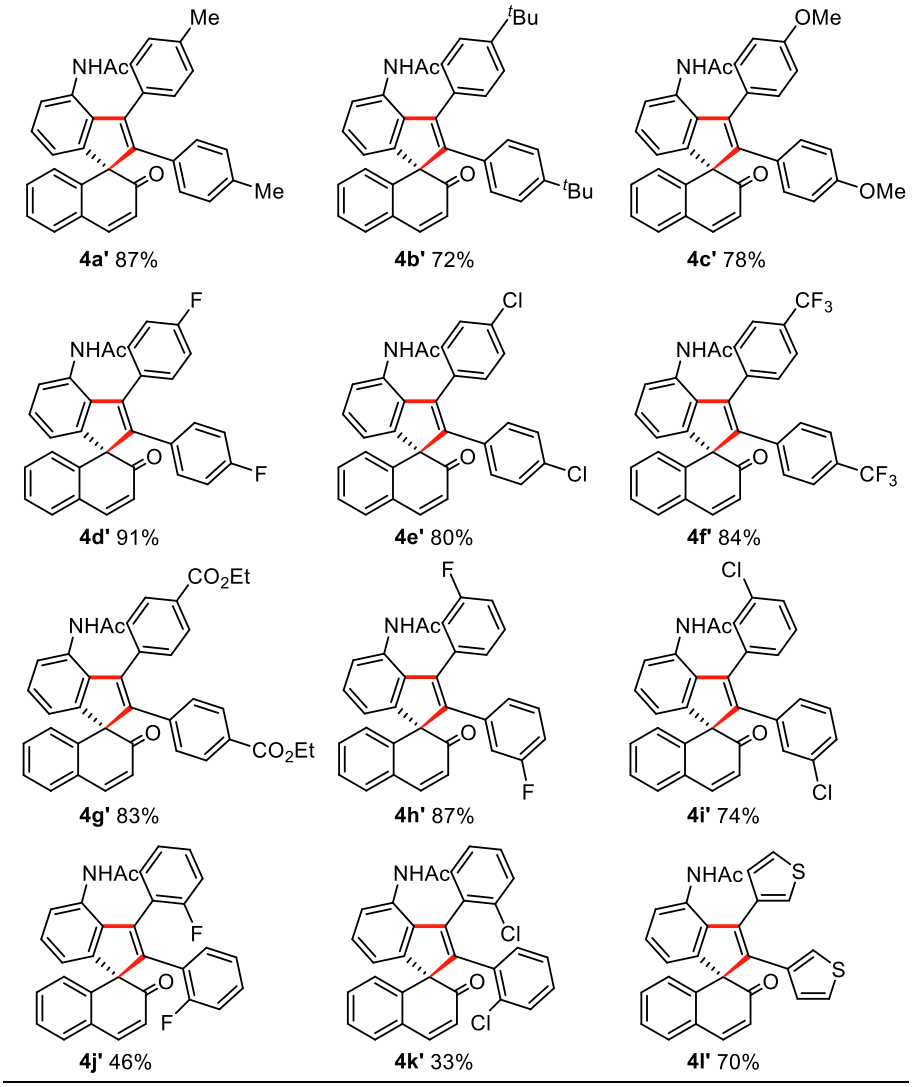


4b 67% **4c** 78% **4d** 81% **4e** 70%
4f 83% **4g** 84% **4h** 80% **4i** 81%
4j 64% **4k** 76% **4l** 63% **4m** 85%

[a] Isolated yields.

Table 4
Scope of Alkynes.[a]



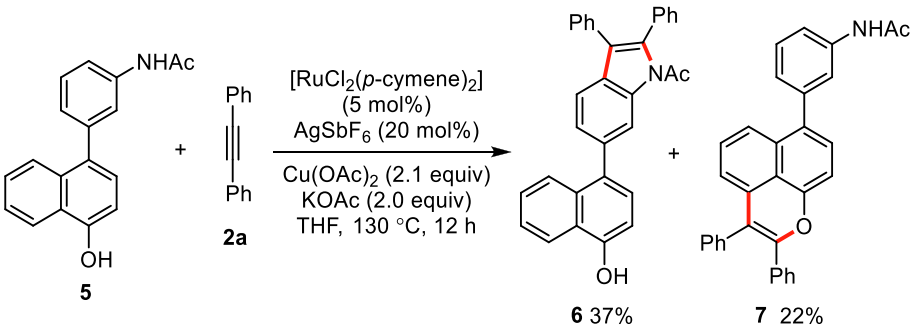


[a] Isolated yields.

of more bulky alkynes didn't shut down the reaction, and sterically more congested products **4j'-k'** could be obtained in acceptable yields. Moreover, the alkyne containing heterocyclic groups behaved well in the [3+2] spiroannulation, affording the desired product **4l'** in 70% yield. In the end, it needed to mention that replacement of aromatic substituents of internal alkynes with either one or two aliphatic groups was unsuccessful, and no anticipated product was not observed.

To demonstrate the importance on the combination of these two DGs for the titled reaction, we studied the process by using a new substrate **5**, which contains the hydroxyl and acetylamino group in the distant positions. As it is shown in the Scheme 2, the [3+2] spiroannulation didn't proceed at all, while two compounds **6** and **7** were isolated in 37% and 22% yield, respectively. These cyclic products were formed by activating different C–H bonds with the assistance of those two directing groups, respectively. The outcome clearly amplified the power of this new double directing strategy for the titled challenging transformation.

In conclusion, we have successfully developed a new Ru(II)-catalyzed [3+2] spiroannulation with a double directing group approach. This current process is featured by the introduction of acetylamino group as a second DG[2], thus reversing conventional regiochemistry of the previously reported [3+2] spiroannulations between 1-aryl-2-naphthols and internal alkynes. Noteworthy, this



Scheme 2. Control Experiment with **5**.

work also represents a rare example of the challenging activation of C–H bond at the more bulky site of *meta*-substituted arenes through the involvement of two directing groups.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153050.

References

[1] a) For reviews, see: Y. Xu, G. Dong Chem. Sci. 9 (2018) 1424–1432;
b) J. Loup, U. Dhawa, F. Pesciaioli, J. Wencel-Delord, L. Ackermann, Angew. Chem. Int. Ed. 58 (2019) 12803–12818;
c) C. Liu, Q. Gu, S. You, Trends Chem. 2 (2020) 737–749;
d) T. Dalton, T. Faber, F. Glorius, A.C.S. Cent, Sci. 7 (2021) 245–761.
[2] a) For reviews, see: G. Rouquet, N. Chatani Angew. Chem. Int. Ed. 52 (2013) 11726–11743;
b) R. He, Z. Huang, Q. Zheng, C. Wang, Tetrahedron Lett. 55 (2014) 5705–5713;
c) W. Ma, P. Gandeepan, J. Li, L. Ackermann, Org. Chem. Front. 4 (2017) 1435–1467;
d) Z. Dong, Z. Ren, S. Thompson, Y. Xu, G. Dong, Chem. Rev. 117 (2017) 9333–9403;
e) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, M. Schnürch, Chem. Soc. Rev. 47 (2018) 6603–6743;
f) Y. Liu, Y. Xia, B. Shi, Chin. J. Chem. 38 (2020) 635–662.
[3] a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, Angew. Chem. Int. Ed. 120 (2008) 4083–4086;
b) B. Li, S. Fang, D. Huang, B. Shi, Org. Lett. 19 (2017) 3950–3953;
c) Q. Wang, S. An, Z. Deng, W. Zhu, Z. Huang, G. He, G. Chen, Nat. Catal. 2 (2019) 793–800;
d) Q. Wang, W. Zhu, Q. Sun, G. He, G. Chen, Chin. J. Chem. 39 (2021) 571–576.
[4] a) G. Zhang, L. Yang, Y. Wang, Y. Xie, H. Huang, J. Am. Chem. Soc. 135 (2013) 8850–8853;
b) S. Luo, F. Luo, X. Zhang, Z. Shi, Angew. Chem. Int. Ed. 52 (2013) 10598–10601;
c) L. Castro, N. Chatani, Chem. Lett. 44 (2015) 410–421;
d) Y. Liang, X. Wang, Y. Yuan, Y. Liang, X. Li, N. Jiao, ACS Catal. 5 (2015) 6148–6152;
e) X. Zhou, J. Xia, G. Zheng, L. Kong, X. Li, Angew. Chem. Int. Ed. 57 (2018) 6681–6685.
[5] a) S. Mochida, K. Hirano, T. Satoh, M. Miura, J. Org. Chem. 76 (2011) 3024–3033;
b) B. Jia, Y. Yang, X. Jin, G. Mao, C. Wang, Org. Lett. 21 (2019) 6259–6263;
c) J. Lin, L. Hu, C. Chen, H. Feng, Y. Yu, Y. Yang, B. Zhou, Org. Lett. 23 (2021) 1194–1198.
[6] a) J. Zhou, X. Li, G. Liao, B. Shi, Chin. J. Chem. 36 (2018) 1143–1146;
b) T. Pinkert, T. Wegner, S. Mondal, F. Glorius, Angew. Chem. Int. Ed. 58 (2019) 15041–15045;
c) C. Ghosh, P. Nagtilak, M. Kapur, Org. Lett. 21 (2019) 3237–3241.
[7] a) J. Huckins, E. Bercot, O. Thiel, T. Hwang, M. Bio, J. Am. Chem. Soc. 135 (2013) 14492–14495;
b) T. Shirai, H. Ito, Y. Yamamoto, Angew. Chem. Int. Ed. 126 (2014) 2696–2699;
c) Y. Yi, H. Lee, C. Jun, Chem. Commun. 52 (2016) 10171–10174.
[8] a) J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, J. Am. Chem. Soc. 135 (2013) 17306–17309;
b) I. Khan, S. Chidipudi, H. Lam, Chem. Commun. 51 (2015) 2613–2616;
c) A. Seoane, N. Casanova, N. Quiñones, J. Mascareñas, M. Gulías, J. Am. Chem. Soc. 136 (2014) 7607–7610;
d) Z. Zuo, X. Yang, J. Liu, J. Nan, L. Bai, Y. Wang, X. Luan, J. Org. Chem. 80 (2015) 3349–3356;
e) J. Zheng, S. Wang, C. Zheng, S. You, J. Am. Chem. Soc. 137 (2015) 4880–4883;
f) L. Han, H. Wang, X. Luan, Org. Chem. Front. 5 (2018) 2453–2457.
[9] a) D. Stuart, M. Bertrand-Laperle, K. Burgess, K. Fagnou, J. Am. Chem. Soc. 130 (2008) 16474–16475;
b) G. Crisenza, O. Sokolova, J. Bower, Angew. Chem. Int. Ed. 127 (2015) 15079–15083.