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Rhodium-Catalyzed C–H Functionalization with *N*-Acylsaccharins

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A rhodium-catalyzed C–H functionalization with activated amides by decarbonylation has been developed. Notably, this is the first C-H arylation by employing *N*-acylsaccharins as coupling partners to give biaryls in good to excellent yield. The highlight of the work is high functional group tolerance such as formyl, ester, vinyl, and the use of a removable directing group.

Carbon–hydrogen bonds are the most common chemical bonds in organic compounds and a ubiquitous structural motif in organic chemistry. In the past decades, great advances have been achieved in transition-metal-catalyzed direct C–H bond functionalization reactions.[1] Site-selective C–H functionalization afforded a direct conversion of carbon– hydrogen (C–H) bonds into new carbon–carbon (C–C) bonds or carbon–heteroatom (C–X) bonds.[2] These C–H activation technologies have been widely utilized in the synthesis of biologically important natural products and advanced functional materials.[3]

In this context, a variety of electrophiles such as aryl halides, tosylates and even aryl sulfonyl chlorides were selected as cross-coupling partners in C–H functionalization.[4, 5] However, the majority of these methods have relatively complicated catalytic systems, and also have limited substrate scope. To extend the substrate scope, organometallic reagents, aryl boronic acids, and arenes were employed as arylation sources in oxidative C–H functionalization.[6] These oxidative approaches have advantages, but there are some drawbacks such as the requirement of large amounts of oxidants (Cu or Ag salt) in these reactions and normally air sensitive.

A significant progress has been made by using acyl chlorides and anhydrides as arylation reagents in C–H functionalization via extrusion of carbon monoxide (Scheme 1a).[7] Both of these protocols can be efficiently worked in the absence of oxidants, and demonstrated high functional group tolerance.

While the progress in the C–H functionalization area was achieved, the difficulty of utilizing amides as coupling partners still exist due to the high activation energy required for an acyl-nitrogen bond cleavage in amides. Recently, Szostak and Shi utilized twisted amides as the coupling partners in the transition-metal-catalyzed system, which demonstrated a novel route in decarbonylation.[8] Inspired by the challenge of employing amides as the arylation precursors, we turned our attention to designing an alternative methodology.

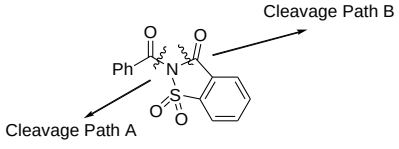
Herein, we report a strategy for C–H functionalization by utilizing *N*-acylsaccharins as coupling partners, which proceeds via C–H/C–N cleavage (Scheme 1b).

N-acylsaccharins provide several advantages: (a) *N*-acylsaccharins can be efficiently synthesized from readily available and low-cost saccharin. (b) In comparison with acyl chlorides and anhydrides, *N*-acylsaccharinsare shelf-stable andeasy to handle white powder.Also, no decomposition was observed when *N*-acylsaccharins suspendedin the water for two weeks. (c) The twisted structure of *N*-acylsaccharins resulted in a chemoselective cleavage of acyl-nitrogen bond (Figure 1).

Also, this protocol tolerated functional groups such as halides, aldehydes, ketones, esters and heterocycles. And notably, this study demonstrates a new model in acyl-nitrogen bond cleavage.

Initially, *N*-benzoylsaccharin **1a** was selected as an electrophile to couple with benzo[h]quinoline **2a** to form 10-phenyl benzo[h]quinoline **3a** in the presence of a rhodium catalyst. For the optimization studies (Table 1). $[Rh(COD)Cl]_2$ was used as the catalyst and toluene as the solvent to investigate the hypothesis. No reaction occurred when this approach was tested at 110 °C (Table 1, entry 1). Inspired by the previous study in the decarbonylation and the preliminary experiment, the

Figure 1. Slective Cleavage of C-N.



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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Scheme 1. Previous Works in C–H Functionalization via Decarbonylation of Carboxylic Acid Derivatives.

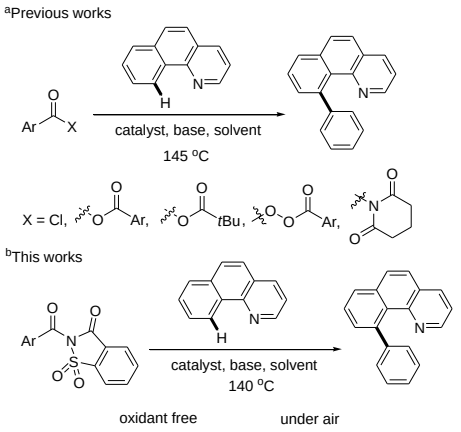
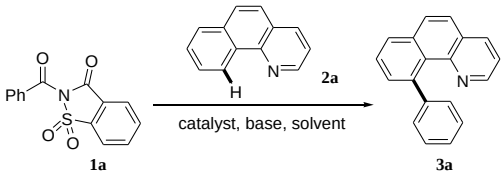


Table 1 Effect of Catalyst, Solvent and Base



entry	catalyst	base[b]	temperature	yield (%)
1	$[Rh(COD)Cl]_2$	none	110 °C	0
2	$[Rh(COD)Cl]_2$	none	140 °C	18
3	$[Rh(COD)Cl]_2$	K_2CO_3	140 °C	47
4	$[Rh(COD)Cl]_2$	Na_2CO_3	140 °C	43
5	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	61
6[c]	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	83
7[d]	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	53
8[e]	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	90
9[f]	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	51
10[g]	$[Rh(COD)Cl]_2$	K_3PO_4	140 °C	38
11	$[Rh(COD)Cl]_2$	K_3PO_4	130 °C	68
12	$[Rh(COD)Cl]_2$	K_3PO_4	150 °C	90
13	$[Rh(CO)_2Cl]_2$	K_3PO_4	140 °C	35
14	$RhCl(PPh_3)_3$	K_3PO_4	140 °C	11

[a]Conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (5 mol %), toluene (0.8 mL). [b]Base (0.3 mmol). [c]xylene. [d]chlorobenzene. [e]*o*-xylene. [f]2.5 mol %. [g]1.0 mol %

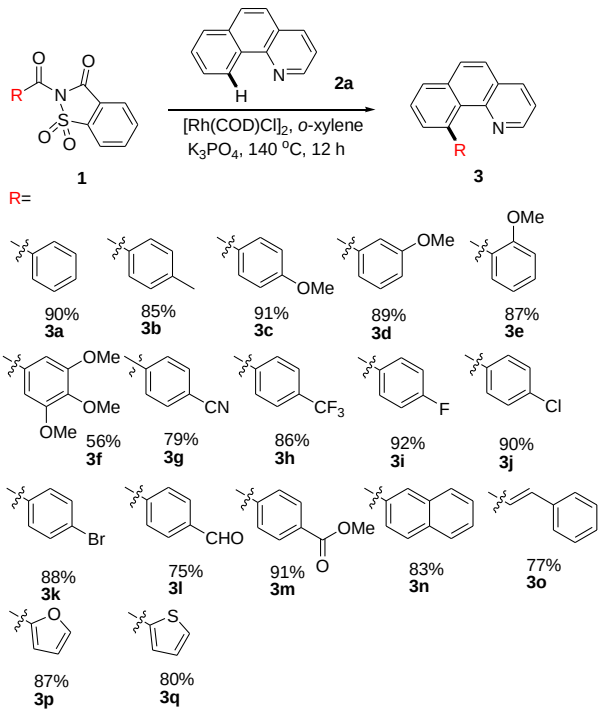
temperature was increased 140 °C, which led to the desired product in 18% yield (Table 1, entry 2). To accelerate the deprotonation process, a variety of bases were selected to examine the protocol. K_3PO_4 display a remarkable result among a series of bases, which led to a 61% yield (Table 1, entries 3-5).

The solvent also plays an important role in determining the yield. *o*-Xylene seems to be the best solvent in this approach since a lower yield was observed when employing toluene, xylene and chlorobenzene (Table 1, entries 5-8) under the same conditions. Also, the loading of rhodium catalyst influenced the yield of the target compound. For example, changing the loading from 5.0 mol % to 1.0 mol % led to a lower yield (Table 1, entries 9-10).

With this condition in hand, the reaction temperature was further optimized. The result of several experiments proved that 140 °C is the best temperature of this protocol (Table 1, entries 11-12). Finally, the optimal conditions of this C–H functionalization with *N*-acylsaccharins were set as 5 mol % $[Rh(COD)Cl]_2$ in the presence of K_3PO_4 (1 equiv) in *o*-xylene at 140 °C for 12 h.

With the optimized reaction conditions in hand, a variety of N-acylsaccharins were employed to probe the scope and limitations of this approach (Scheme 2). To investigate the influence of electronic and steric factors, a range of *N*-acylsaccharins with neutral and electron-donating groups were coupled to benzo[h]quinoline **2a**. This provided corresponding C–H functionalization compounds (**3a-3f**) in good to excellent yields. Amides bearing strong electron-withdrawing groups generated **3g** and **3h** in 79% and 86% yields, respectively. *p*-Fluoro, *p*-chloro and *p*-bromosubstituents all gave excellentyields (**3i-3k**). When *N*-acylsaccharins contained formyl and acetylgroups in the *para*-position, the arylation was accomplished in good yields. The heterocycles furan and thiophene also provided good yields in the typical procedure. Overall, these experiments indicated

Scheme 2. Amide scope in C–H Functionalization.



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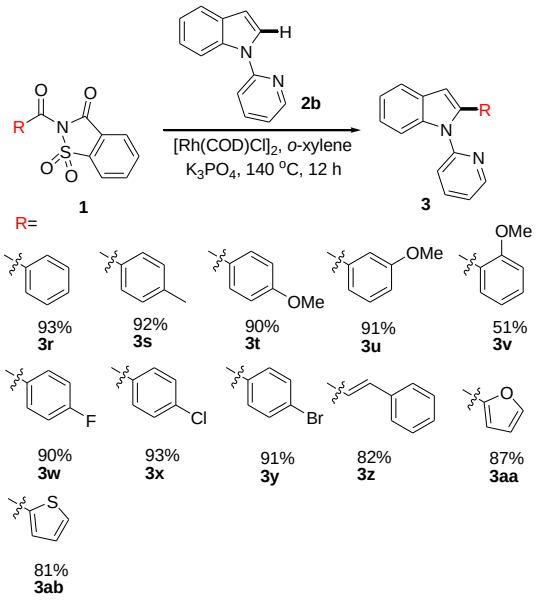
Scheme 3. Amide scope in C2 arylation of N-(2-pyridyl) Indoles.

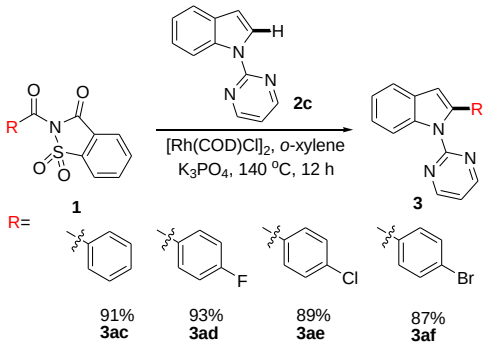


that halides, aldehydes, ketones, esters and heterocycleswere tolerated, even in the case where the *N*-acylsaccharin contained a functional group in the *ortho*-position **3e**.

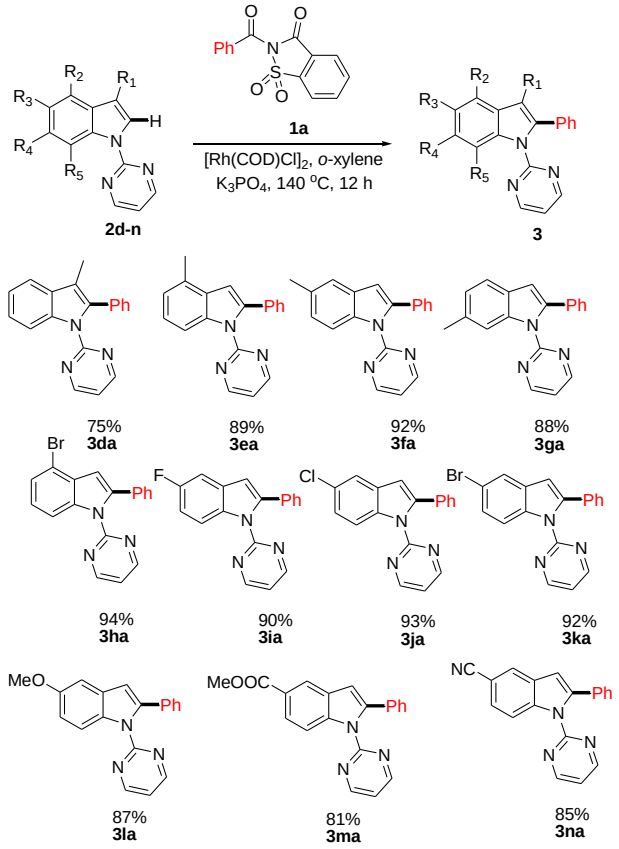
Indoles are among the most investigated heterocycles, widely appearing in natural products and pharmaceuticals.[9] Hence the method was expanded to the direct C2 arylation of indoles via using a removable *N*-pyridyl directing group (Scheme 3). The result demonstrated that utilizing *N*-acylsaccharins containing electron-donating groups in the *para*, *meta*, and *ortho*-positions in the benzene ring, generated the corresponding products (**3r-3v**) in excellent yields. *p*-Fluoro, *p*-chloro and *p*-bromo groups also gave the C2 arylated products in high yields (**3w-3y**). Remarkably, *N*-styrylsaccharin could be utilized in this approach to give the corresponding vinyl product in 82% yield (**3z**). Also, 2-furyl and 2-thienyl amides are compatible with the reaction conditions (**3aa**, **3ab**).

To investigate the influence of N-protecting group, *N*-(2-Pyrimidyl) indole (**2c**) was probed under the same conditions to provide (**3ac-3af**) in excellent yields (Scheme 4). Next, a variety of *N*-(2-Pyrimidyl) indole derivatives were selected to examine

Scheme 4. Amide scope in C2 arylation of N-(2-Pyrimidyl) Indoles.



Scheme 5. Indoles scope in C2 arylation of N-(2-Pyrimidyl) Indoles.



the functional groups tolerance of this protocol. Irrespective of methyl occupied in the C4, C5 and C6 position of the indole, even in C3, corresponding products could be obtained in good to excellent yields (**3ca-3fa**). Also, indoles containing halides were tolerated, particularly bromide (**3ga-3ja**). Notably, the reaction is tolerant to electron-donating and electron-withdrawing substituents on the benzene ring of indole moiety to give desired products in good yields (**3ka-3ma**). The result highlight that, direct access to C-2 arylated indoles via decarbonylation is a viable method in synthetic chemistry (Scheme 5).

Scheme 6. Controlled studies.

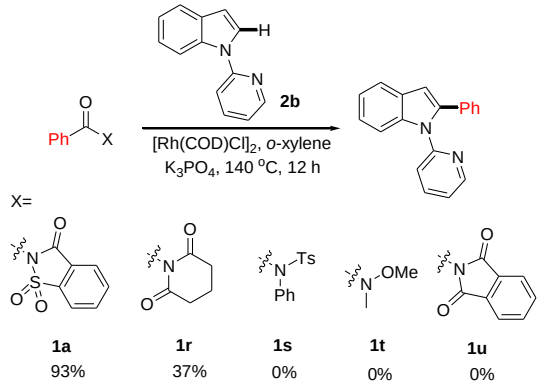
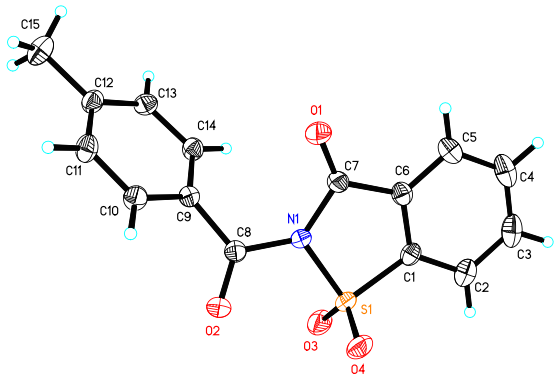


Figure 2. Crystal structure of **1b**.

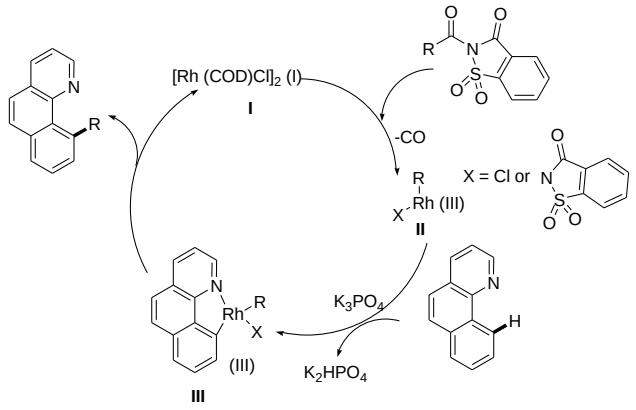


Several amides (**1r**, **1s**, **1t**) were employed in this catalysis systems and a similar amide **1u** were utilized to compare with *N*-benzoyl saccharin under the same conditions. *N*-benzoyl saccharin demonstrated higher reactivity than other amides (Scheme 6).

To further investigate the selective cleavage of *N*-acyl saccharins, the X-ray structure of **1b** (CCDC 1508194) was generated. Compared with amide bond N_1-C_7 (O_1) ($\tau = 5.8^o$, $\chi_N = 11.9^o$, $\chi_C = 2.0^o$), the X-ray structure indicates that amide bond N_1-C_8 (O_2) is highly distorted ($\tau = 21.8^o$, $\chi_N = 12.2^o$, $\chi_C = 1.8^o$). Twisted angle (τ) of amide bond N_1-C_8 (O_2) in *N*-acyl saccharins support ground-state destabilization which could account for its high reactivity and selectivity (Figure 2).[10]

On the basis of rhodium chemistry, a tentative mechanism of the catalytic cycle is proposed (Scheme 7). Oxidative addition of *N*-acylsaccharins to generate an acylrhodium complex, then undergoing extrusion of one molecule of carbon monoxide, generating the complex **II**; then, C–H activation via *ortho*-chelating assistance in the presence of K_3PO_4, which provides the complex **III**. Finally, reductive elimination to form the new C-C bond and regenerate the Rh(I)-species.

Scheme 7. Proposed Mechanism for rhodium-catalyzed C–H Functionalization.



Conclusions

In conclusion, utilization of an activated amide as an electrophilic participant in a decarbonylative catalytic C-H functionalization procedure has been reported. The variety of functional groups tolerated using this approach demonstrated the utilitarian nature of the methodology, allowing efficient access to biaryl compounds. It also provides an alternative route in C–H functionalization and a new activation model of C-N amide bonds

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Notes and references

1 (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.,* 2007, **107**, 174–238; (b) I. J. S. Fairlamb, *Chem. Soc. Rev.,* 2007, **36**, 1036–1045; (c) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.,* 2013, **4**, 886–896; (d) K. Yuan, J.-F. Soulé and H. Doucet, *ACS Catal.,* 2015, **5**, 978–991.

2 (a) T. Newhouse and P. S. Baran, *Angew. Chem. Int. Ed.,* 2011, **50**, 3362–3374; (b) T. Brückl, R. D. Baxter, Y. Ishihara and P. S. Baran, *Acc. Chem. Res.,* 2012, **45**, 788–802; (c) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 826–839; (d) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature,* 2012, **486**, 518–522; (e) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 788–802; (f) G. Shan, X. L. Yang, L. L. Ma and Y. Rao, *Angew. Chem. Int. Ed.,* 2012, **51**, 13070–13074; (g) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.,* 2015, **48**, 1040–1052; (h) H. Wang, M. Moselage, M. J. Gonzalez and L. Ackermann, *ACS Catal.,* 2016, **6**, 2705–2709; (i) J.-T. Yu and C.-D. Pan, *Chem. Commun*., 2016, **52**, 2220–2236; (j) J. Liu, G. Chen and Z. Tan, *Adv. Synth. Catal.,* 2016, **358**, 1174–1194; (k) H. M. L. Davies and D. Morton, *J. Org. Chem.,* 2016, **81**, 343–350.

3 (a) L. G. Mercier and M. Leclerc, *Acc. Chem. Res.,* 2013, **46**, 1597–1605; (b) J. Wencel-Delord and F. Glorius, *Nat. Chem.,* 2013, **5**, 369–375; (c) R. Vanjari and K. N. Singh, *Chem. Soc. Rev.,* 2015, **44**, 8062–8096; (d) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.,* 2016, **45**, 546–676; (e) P. Subramanian, G. C. Rudolf and K. P. Kaliappan, *Chem. Asia. J.,* 2016, **11**, 168–192; (f) L. J. Durak, J. T. Payne and J. C. Lewis, *ACS Catal.,* 2016, **6**, 1451–1454.

4 (a) M. Kim, J. Kwak and S. Chang, *Angew. Chem. Int. Ed.,* 2009, **48**, 8935–8939; (b) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.,* 2010, **46**, 677–685; (c) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.,* 2012, **45**, 814–825.

5 (a) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Angew. Chem. Int. Ed.,* 2010, **49**, 6629–6632; (b) L. Ackermann and A. V. Lygin, *Org. Lett.,* 2011, **13**, 3332–3335; (c) L. Llies, M. Kobayashi, A. Matsumoto, N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.,* 2012, **354**, 593–596; (d) S. Gonell and E Peris, *ACS Catal.,* 2014, **4**, 2811–2817; (e) R. Haridharan, K. Muralirajan and C.-H. Cheng, *Adv. Synth. Catal.,* 2015, **357**, 366–370; (f) L. Ackermann, A. Althammer and R. Born, *Angew. Chem. Int. Ed.,* 2006, **45**, 2619–2622; (g) W. F. Song and L. Ackermann, *Angew. Chem. Int. Ed.,* 2012,

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DOI: 10.1039/C6OB02526A

51, 8251–8254; (h) X. D. Zhao, E. Dimitrijević and V. M. Dong, *J. Am. Chem. Soc.,* 2009, **131**, 3466–3467.

6 (a) J. Norinder, A. Matsumoto, N. Yoshikai and E. Nakamura, *J. Am. Chem. Soc.,* 2008, **130**, 5858–5859; (b) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.,* 2009, **131**, 9651–9653; (c) O. M. Kuzmina and P. Knochel, *Org. Lett.,* 2014, **16**, 5208–5211; (d) R. Shang, L. Llies, S. Asako and E. Nakamura, *J. Am. Chem. Soc.,* 2014, **136**, 14349–14352; (e) C. Sollert, K. Devaraj, A. Orthaber, P. J. Gates and L. T. Pilarski, *Chem. Eur. J.,* 2015, **21**, 5380–5386; (f) V. K. Tiwari, T. N. Kamal and M. Kapur, *Org. Lett.,* 2015, **17**, 1766–1769; (g) J. Hubrich, T. Himmler, L. Rodefeld and L. Ackermann, *Adv. Synth. Catal.,* 2015, **357**, 1229–1236; (h) X. D. Zhao, C. S. Yeung and V. M. Dong, *J. Am. Chem. Soc.,* 2010, **132**, 5837–5844.

7 (a) X. D. Zhao and Z. K. Yu, *J. Am. Chem. Soc.,* 2008, **130**, 8136–8137; (b) W. W. Jin, Z. K. Yu, W. He, W. J. Ye and W. J. Xiao, *Org. Lett.,* 2009, **11**, 1317–1320; (c) W. Y. Yu, W. N. Sit, Z. Y. Zhou and A. S.-C. Chan, *Org. Lett.,* 2009, **11**, 3174–3177; (d) Q. Shuai, L. Yang, X. Y. Guo, O. Baslé and C. J. Li, *J. Am. Chem. Soc.,* 2010, **132**, 12212–12213; (e) F. Pan, Z.-Q. Lei, H. Wang, H. Li, J. Sun and Z.-J. Shi, *Angew. Chem. Int. Ed.,* 2013, **52**, 2063–2067; (f) Z. Q. Lei, F. Pan, H. Li, Y. Li, X. S. Zhang, K. Chen, X. Wang, Y. X. Li, J. Sun and Z. J. Shi, *J. Am. Chem. Soc.,* 2015, **137**, 5012–5020; (g) W. I. Dzik, P. P. Lange and L. J. Gooßen, *Chem. Sci.*, 2012, **3**, 2671-2678.

8 (a) G. R. Meng and M. Szostak, *Org. Lett.,* 2016, **18**, 796–799; (b) J. F. Hu, Y. Zhao, J. J. Liu, Y. M. Zhang, Z. Z. Shi, *Angew. Chem. Int. Ed.,* 2016, **55**, 8718–8722; (c) S. C. Shi, G. R. Meng, M. Szostak, *Angew. Chem. Int. Ed.,* 2016, **55**, 6959–6963.

9 (a) S. Cacchi and G. Fabrizi, *Chem. Rev.,* 2011, **111**, PR215–PR283; (b) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.,* 2012, **41**, 3929–3968; (c) M. Inman and C. J. Moody, *Chem. Sci.,* 2013, **4**, 29–41.

10 (a) A. Greenberg and C. A. Venanzi, *J. Am. Chem. Soc.* 1993, **153**, 6951-6957; (b) M. Szostak and J. Aubé, *Chem. Rev.* 2013, **113**, 5701-5765.