ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c7cc07753j

Received 6th October 2017,
Accepted 15th December 2017

DOI: 10.1039/c7cc07753j

rsc.li/chemcomm

Rhodium(III)-catalyzed chemodivergent annulations between *N*-methoxybenzamides and sulfoxonium ylides *via* C–H activation†

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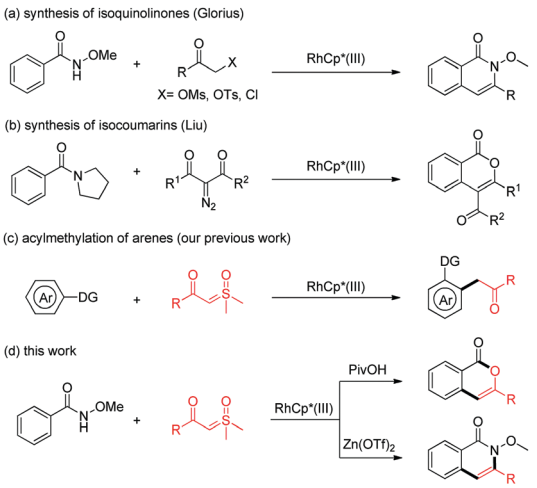
Chemodivergent and redox-neutral annulations between *N*-methoxybenzamides and sulfoxonium ylides have been realized *via* Rh(III)-catalyzed C–H activation. The sulfoxonium ylide acts as a carbene precursor, and coupling occurs under acid-controlled conditions, where $Zn(OTf)_2$ and PivOH promote chemodivergent cyclizations.

In the past decade, transition metal-catalyzed C–H activation of arenes has dramatically improved the efficiency and step-economy of organic syntheses.[1] Among the transition metals, Cp*Rh(III) catalysts have significantly contributed to the arsenal of new heterocycle synthesis.[2] Isoquinolones and isocoumarins are two important classes of heterocycles that are ubiquitously encountered in pharmaceuticals and organics.[3,4] Consequently, the development of efficient approaches to access these heterocycles is of great interest.[5,6] Miura and coworkers pioneered in Rh(III)-catalyzed oxidative coupling of carboxylic acids and internal alkynes for isocoumarin synthesis.[7] We and others achieved isoquinolone *via* coupling of benzamides with alkynes.[8,9] To develop intrinsically unique coupling partners, Glorius and coworkers accomplished the C–H activation of amide for the synthesis of isoquinolones using α-MsO/TsO/Cl ketones as oxidized alkyne equivalents (Scheme 1a),[10] where the amide functions as a nucleophilic directing group (DG). Alternatively, the synthesis of isocoumarins has been accomplished *via* an alkylation–nucleophilic cyclization sequence (Scheme 1b), where the carbonyl of benzamide is attacked by an OH group (Scheme 1b).[11]

As versatile DGs, *N*-methoxy amides have found wide utility in Cp*Rh(III)-catalyzed C–H activation and heterocycle synthesis.[12] Although the *N*-methoxy amide group contains both nucleophilic and electrophilic sites, it is challenging to achieve chemodivergent cyclizations by taking advantage of both sites starting from exactly the same substrates. We and others recently reported the Cp*Rh(III)-catalyzed C–H activation and versatile acylmethylation of arenes



Scheme 1 Synthesis of isoquinolones and isocoumarins *via* annulative C–H activation.

using sulfoxonium ylides as a carbene source (Scheme 1c).[13a,b] However, only one example of cyclization has been reported[13b] and this reagent has been applied in the synthesis of pyrroles *via* a different mechanism.[13c] Given the ambiphilicity of the methylene ketone moiety in the product, we proposed chemodivergent annulations with *N*-methoxybenzamides, which calls for steerable activation of methylene carbonyl and the amide carbonyl groups toward cyclization possibly by Lewis or Brønsted acids.[14] However, challenges remain. First, the homo-coupling of a sulfoxonium ylide may occur because it may act as both an arene and a coupling partner.[15] Second, it is challenging to distinguish between these two functional groups for selective activation. Third, the leaving groups may pose an inhibitory effect. We now report acid-controlled divergent annulations between sulfoxonium ylides and *N*-methoxybenzamide for the synthesis of isoquinolones and isocoumarins (Scheme 1d).

We commenced our investigation with the screening of reaction parameters for the coupling of *N*-methoxybenzamide (**1a**) and sulfoxonium ylide (**2a**). To our delight, the desired

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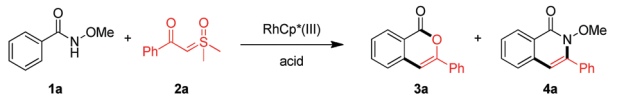
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7cc07753j

Table 1 Optimization of reaction conditions[a]

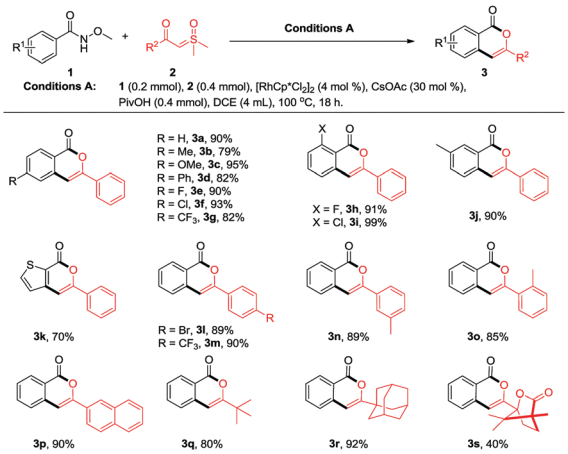


Entry	Additive (equiv.)	Solvent	Yield[b] (%) 3a	4a
1[d]	CsOAc (0.3)/HOPiv (2)	DCE	>95 (90)[c]	<5
2[d]	CsOAc (0.3)	DCE	22	51
3[d]	CsOAc (0.3)	*t*BuOH	15	40
4[d]	CsOAc (0.3)	HFIP	<5	20
5[d]	AgOAc (0.2)	DCE	44	<5
6[d]	$Zn(OTf)_2$ (0.5)	DCE	10	63
7[e]	HOPiv (2)	DCE	38	27
8[e]	CsOAc (0.3)	DCE	52	34
9[e]	$Zn(OTf)_2$ (0.5)	DCE	<5	>95 (95)[c]
10[e]	$Zn(OAc)_2$ (0.5)	DCE	41	45
11[e]	$Zn(NTf)_2$ (0.5)	DCE	<5	50
12[e]	AgOTf (0.5)	DCE	22	19
13[e]	AgOAc (0.5)	DCE	28	18
14[f]	$Zn(OTf)_2$ (0.5)	DCE	19	76

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst, and additives were stirred in the solvent (2 mL) at 100 °C for 16 h. [b] NMR yield of the crude product using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield on a 0.2 mmol scale of **1a**. [d] $[RhCp^*Cl_2]_2$ (4 mol%) was used as a catalyst. [e] $[RhCp^*(MeCN)_3](SbF_6)_2$ (5 mol%) was used as a catalyst. [f] $RhCp^*(OAc)_2$ (8 mol%) was used as a catalyst.

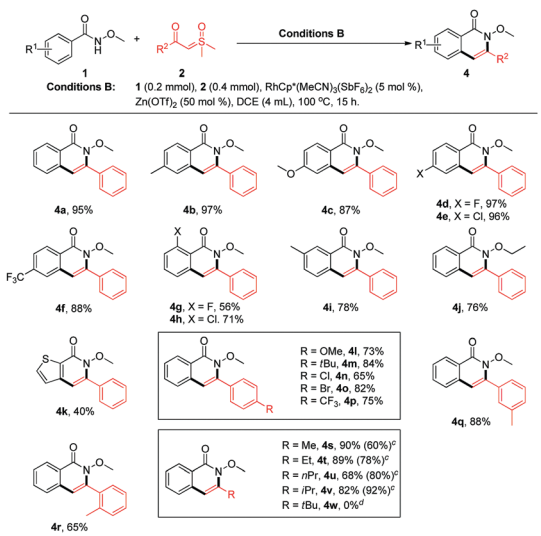
isocoumarin (**3a**) was isolated in 90% yield in the presence of $[RhCp^*Cl_2]_2$, CsOAc, and PivOH (Table 1, entry 1). The PivOH additive proved necessary to ensure high selectivity for isocoumarin. In the absence of PivOH, both isocoumarin **3a** and isoquinolone **4a** were produced (entry 2). Thus, PivOH serves to activate the amide carbonyl group toward oxygen attack. Further screening of the solvent revealed that alcoholic solvents such as *t*BuOH and HFIP both gave inferior results (entries 3 and 4). Significantly, changing the additive to Lewis acid $Zn(OTf)_2$ increased the NMR yield of **4a** (entry 6), and the isolated yield of **4a** was increased to 95% when a cationic catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ was used (entry 9). After extensive screening of the Lewis acid, $Zn(OTf)_2$ was identified as the optimal one (entries 10–13). However, using $RhCp^*(OAc)_2$ (8 mol%) as a catalyst gave a diminished yield of **4a**.[13b] Thus, the conditions in entries 1 (conditions A) and 9 (conditions B) were adopted for subsequent studies.

With the optimal conditions in hand, we first investigated the scope of isocoumarin synthesis (conditions A, Scheme 2). Introduction of electron-donating and -withdrawing groups into the *para* position of the benzene ring was fully tolerated (**3a–3g**). The reaction was also extended to *o*-substituted *N*-methoxybenzamides (**3h**, **3i**), indicating tolerance of steric hindrance. In addition, a *meta*-Me substituted benzamide also reacted smoothly, and the coupling occurred at the less hindered *ortho* site (**3j**). Besides, a thiophene ring also coupled to afforded product **3k** in a moderate yield. The functional group compatibility with respect to the sulfoxonium ylide was also briefly explored, and introduction of electron-donating and -withdrawing groups into the benzene ring was all well tolerated (**3l–3p**, 85–90%). The sulfoxonium ylide was not limited to aryl substitution, and alkyl substituted ylides (**3q–3s**) also coupled in high efficiency.



Scheme 2 Scope of isocoumarin synthesis. [a] See the ESI† for detailed conditions A. [b] Isolated yield.

We then investigated the generality of the synthesis of isoquinolones (conditions B, Scheme 3). A variety of isoquinolones were synthesized in moderate to excellent yields. Electron-donating and -withdrawing groups at different positions of the *N*-methoxybenzamide had a marginal influence on the coupling with a sulfoxonium ylide, and the desired isoquinolones were isolated in consistently high yields (**4a–4i**). In addition, *N*-ethoxybenzamides (**4j**) also coupled to afford the desired product in a good yield. The arenes can also be extended to a thiophene amide (**4k**) in a moderate yield. Sulfoxonium ylides bearing a methoxy (**4l**), alkyl (**4m**, **4q**, **4r**), halogen (**4n** and **4o**), and CF_3 (**4p**) group at different positions all coupled smoothly with *N*-methoxybenzamide, and the corresponding products were isolated in 65–88% yield. Besides, an alkyl-substituted sulfoxonium ylide also showed great reactivity (**4s–4v**). To our surprise, no isocoumarin was generated when alkyl-substituted sulfoxonium ylides were employed under conditions A. Instead, isoquinolones were isolated in good yields



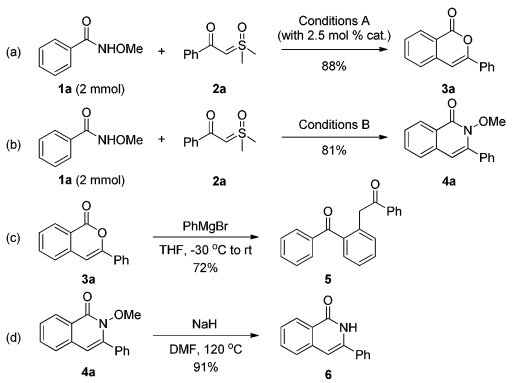
Scheme 3 Scope of isoquinolone synthesis. [a] See the ESI† for detailed conditions B. [b] Isolated yield. [c] Under conditions A. [d] Determined by GC-MS analysis.

(**4s–4v**). In contrast, the sulfoxonium ylide with a sterically hindered group failed to undergo any reaction under conditions B (**4w**).

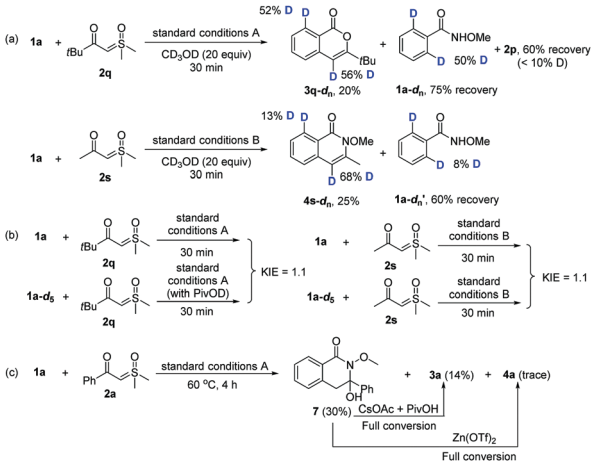
To demonstrate the synthetic utility of the catalytic systems, larger-scale reactions have been performed (Scheme 4). The synthesis of both isocoumarin **3a** and isoquinolone **4a** at a 2 mmol-scale has been realized (Scheme 4a and b). The synthetic utility of the coupled products has been demonstrated in several derivatization reactions. Treatment of **3a** with a phenyl Grignard reagent afforded the corresponding benzophenone **5** in 72% yield (Scheme 4c).[5b] Moreover, *N*-methoxy isoquinolone **4a** was readily reduced to the corresponding NH isoquinolone (**6**) in 91% yield (Scheme 4d).[16]

A series of experiments have been conducted to probe the reaction mechanism. Coupling of **1a** with **2q** under conditions A in CD_3OD provided **3q-d_n** together with the recovery of **1a-d_n**. These data suggest that the C–H activation is reversible. The observed deuterium incorporation at the olefinic position of **3q-d_n** may suggest enolization of the acylmethylated intermediate due to enhanced acidity of the methylene protons. Coupling of **1a** with **2s** under standard conditions B in CD_3OD led to analogous results in terms of H/D exchange. In both coupling systems, coindicant values of KIE = 1.1 were obtained from parallel experiments using **1a** and **1a-d_5** in the coupling with **2q** or **2s** under standard conditions A or B, respectively. These insignificant values suggest that C–H activation is not involved in the turnover-limiting step. When the reaction of **1a** and **2a** was conducted under conditions A at 40 °C, intermediate **7** was isolated in 30% yield along with **3a**.[10] Notably, **7** was fully and selectively converted to **3a** or **4a** in the presence of CsOAc/PivOH or $Zn(OTf)_2$, respectively. This also indicated that the coupling systems likely proceeded *via* initial acylmethylation (Scheme 5).

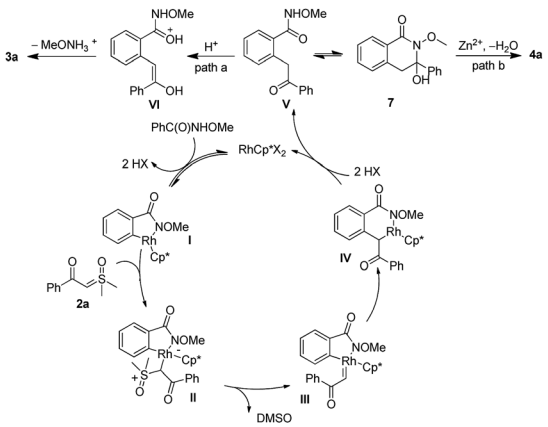
On the basis of literature precedents and our preliminary mechanistic results, a plausible mechanism of coupling of **1a** with **2a** is proposed in Scheme 6. Cyclometalation of *N*-methoxybenzamide gives a rhodacyclic intermediate **I**. Coordination of sulfoxonium ylide generates a Rh(III) alkyl species **II**, and the subsequent α-elimination of DMSO from **II** affords a reactive rhodium α-oxo carbene species **III**, which is then proposed to undergo migratory insertion of the Rh–C bond to give a six-membered rhodacyclic intermediate **IV**. Protonolysis of the



Scheme 4 Larger-scale synthesis and synthetic applications.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

Rh–N and Rh–C bonds releases the acylmethylated intermediate **V** together with the regeneration of the active catalyst. The ketone carbonyl is then nucleophilically attacked by the NH group to reversibly give intermediate **7**.

Following the formation of **V** and **7**, two pathways may be possible. In path a, relatively soft acid PivOH or the neutral Rh(III) catalyst activates the amide group toward nucleophilic attack by the enol oxygen (**VI**), leading to lactonization with the elimination of NH_2OMe in the protonated form. In fact, a related Cp*Rh(III)–HOAc catalytic system has been previously reported by us to promote C–H activation–lactonization.[14a] It is possible that the PivOH also serves to stabilize the NH_2OMe coproduct through protonation. In contrast, a hard Lewis acid $Zn(OTf)_2$ additive together with the more Lewis acidic cationic Rh(III) catalyst selectively activates the ketone carbonyl so that the nucleophilic attack of the amide nitrogen affords the lactamization product upon dehydration.[11]

In summary, we have developed rhodium-catalyzed and acid-controlled chemodivergent annulations between *N*-methoxybenzamides and sulfoxonium ylides, which provide two classes of heterocycles from the same starting materials. This annulation system proceeded in high efficiency and regio- and chemoselectivity.

Other novel transformations of suloxonium ylides in the context of C–H activation are underway in our laboratory and will be reported in due course.

We thank the National Natural Science Foundation of China (21472186 and 21525208) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Selected reviews: (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*c*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*d*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*e*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*f*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281; (*g*) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843; (*h*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107; (*i*) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163; (*j*) L. Ping, D. S. Chung, J. Bouffard and S. G. Lee, *Chem. Soc. Rev.*, 2017, **46**, 4299.

2 (*a*) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212; (*b*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (*c*) N. Kuhl, N. Schroder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443; (*d*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007; (*e*) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308; (*f*) K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040; (*g*) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (*h*) M. Gulías and J. L. Mascareñas, *Angew. Chem., Int. Ed.*, 2016, **55**, 2.

3 (*a*) X. Xiao and M. Cushman, *J. Org. Chem.*, 2005, **70**, 6496; (*b*) A. Padwa and H. Zhang, *J. Org. Chem.*, 2007, **72**, 2570; (*c*) M. Matveenko, O. J. Kokas, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2007, **9**, 3683; (*d*) L. Ingrassia, F. Lefranc, J. Dewelle, L. Pottier, V. Mathieu, S. Spiegl-Kreinecker, S. Sauvage, M. El Yazidi, M. Dehoux, W. Ber-ger, E. Van Quaquebeke and R. Kiss, *J. Med. Chem.*, 2009, **52**, 1100.

4 (*a*) G. Schlingmann, L. Milne and G. T. Carter, *Tetrahedron*, 1998, **54**, 13013; (*b*) R. Rossi, A. Carpita, F. Bellina, P. Stabile and L. Mannina, *Tetrahedron*, 2003, **59**, 2067; (*c*) M. Sakurai, M. Nishio, K. Yama-moto, T. Okuda, K. Kawano and T. Ohnuki, *Org. Lett.*, 2003, **5**, 1083; (*d*) D. Engelmeier, F. Hadacek, O. Hofer, G. Lutz-Kutschera, M. Nagl, G. Wurz and H. Greger, *J. Nat. Prod.*, 2004, **67**, 19; (*e*) A. Saeed, *Eur. J. Med. Chem.*, 2016, **116**, 290.

5 For selected examples on the synthesis of isoquinolones, see: (*a*) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318; (*b*) H. Zhong, D. Yang, S. Wang and J. Huang, *Chem. Commun.*, 2012, **48**, 3236; (*c*) L. Shi, K. Yu and B. Wang, *Chem. Commun.*, 2015, **51**, 17277; (*d*) Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao and A. Lin, *J. Org. Chem.*, 2016, **81**, 2166; (*e*) R. Grigg, E. E. Elboray, S. Akkarasamiyo, N. Chuanopparat, H. A. Dondas, H. H. Abbas-Temirek, C. W. G. Fishwick, M. F. Aly, B. Kongkathip and N. Kongkathip, *Chem. Commun.*, 2016, **52**, 164; (*f*) D. Wang, R. Zhang, R. Deng, S. Lin, S. Guo and Z. Yan, *J. Org. Chem.*, 2016, **81**, 11162; (*g*) L. Qi, K. Hu, S. Yu, J. Zhu, T. Cheng, X. Wang, J. Chen and H. Wu, *Org. Lett.*, 2017, **19**, 218; (*h*) J.-Q. Wu, S.-S. Zhang, H. Gao, Z. Qi, C.-J. Zhou, W.-W. Ji, Y. Liu, Y. Chen, Q. Li, X. Li and H. Wang, *J. Am. Chem. Soc.*, 2017, **139**, 3537; (*i*) D. Ding, T. Mou, J. Xue and X. Jiang, *Chem. Commun.*, 2017, **53**, 5279.

6 For selected examples on the synthesis of isocoumarins, see: (*a*) V. Subramanian, V. R. Batchu, D. Barange and M. Pal, *J. Org. Chem.*, 2005, **70**, 4778; (*b*) P. Zhao, D. Chen, G. Song, K. Han and X. Li, *J. Org. Chem.*, 2012, **77**, 1579; (*c*) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 2030; (*d*) A. Casnati, R. Maggi, G. Maestri, N. D. Ca and E. Motti, *J. Org. Chem.*, 2017, **82**, 8296; (*e*) K. Neog, D. Dutta, B. Das and P. Gogoi, *Org. Lett.*, 2017, **19**, 730; (*f*) C. Yang, X. He, L. Zhang, G. Han, Y. Zou and Y. Shang, *J. Org. Chem.*, 2017, **82**, 2081; (*g*) R. Chen and S. Cui, *Org. Lett.*, 2017, **19**, 4002; (*h*) G. Jiang, J. Li, C. Zhu, W. Wu and H. Jiang, *Org. Lett.*, 2017, **19**, 4440.

7 (*a*) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362; (*b*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407.

8 For selected examples on external oxidant, see: (*a*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565; (*b*) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.*, 2010, **75**, 7487; (*c*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, **39**, 744; (*d*) G. Song and X. Li, *J. Org. Chem.*, 2011, **76**, 7583; (*e*) X.-G. Liu, H. Gao, S.-S. Zhang, Q. Li and H. Wang, *ACS Catal.*, 2017, **7**, 5078.

9 For selected examples on internal oxidants, see: (*a*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (*b*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; (*c*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (*d*) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 9372; (*e*) M. Presset, D. Oehlrich, F. Rombouts and G. A. Molander, *Org. Lett.*, 2013, **15**, 1528; (*f*) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang and M. M. Bio, *J. Am. Chem. Soc.*, 2013, **135**, 14492; (*g*) B. Yu, Y. Chen, M. Hong, P. Duan, S. Gan, H. Chao, Z. Zhao and J. Zhao, *Chem. Commun.*, 2015, **51**, 14365; (*h*) S. Y. Hong, J. Jeong and S. Chang, *Angew. Chem., Int. Ed.*, 2017, **56**, 2408.

10 D.-G. Yu, F. de Azambuja and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 2754.

11 (*a*) X. G. Li, M. Sun, K. Liu, Q. Jin and P. N. Liu, *Chem. Commun.*, 2015, **51**, 2380; (*b*) W. Yang, S. Wang, Q. Zhang, Q. Liu and X. Xu, *Chem. Commun.*, 2015, **51**, 661; (*c*) W. Yang, J. Wang, Z. Wei, Q. Zhang and X. Xu, *J. Org. Chem.*, 2016, **81**, 1675; (*d*) C. Yang, X. He, L. Zhang, G. Han, Y. Zuo and Y. Shang, *J. Org. Chem.*, 2017, **82**, 2081.

12 R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2.

13 (*a*) Y. Xu, X. Zhou, G. Zheng and X. Li, *Org. Lett.*, 2017, **19**, 5256. During the preparation, a similar report on alkylation of arenes was published by the Aïssa's group, see: (*b*) M. Barday, C. Janot, N. R. Halcovitch, J. Muir and C. Aïssa, *Angew. Chem., Int. Ed.*, 2017, **56**, 13117; (*c*) J. Vaitla, A. Bayer and K. H. Hopmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 4277.

14 (*a*) F. Wang, Z. Qi, J. Sun, X. Zhang and X. Li, *Org. Lett.*, 2013, **15**, 6290; (*b*) Q. Wang, F. Wang, X. Yang, X. Zhou and X. Li, *Org. Lett.*, 2016, **18**, 6144; (*c*) G. Zheng, M. Tian, Y. Xu, X. Chen and X. Li, *Org. Chem. Front.*, 2017, DOI: 10.1039/C7QO01033H.

15 Y. Xu, X. Yang, X. Zhou, L. Kong and X. Li, *Org. Lett.*, 2017, **19**, 4307.

16 S. Perveen, Z. Zhao, G. Zhang, J. Liu, M. Anwar and X. Fang, *Org. Lett.*, 2017, **19**, 2470.

