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Rhodium-catalyzed olefination of aryl tetrazoles via direct C-H bond activation

Liang Wang,[a]* Wenting Wu,[a] Qun Chen [a] and Mingyang He [a]*

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Rh(III)-catalyzed direct olefination reaction via aromatic C-H bond activation is described using tetrazole as the directing group. This reaction provides a straightforward way for the synthesis of *ortho*-alkenyl aryl tetrazoles. Various functional groups tolerate the reaction conditions and afford the corresponding products in moderate to excellent yields.

Over the past decades, catalytic C-H functionalization has emerged as a powerful and atom-economic strategy for the elaboration of useful organic molecules.[1] Particularly, the utilization of transition metal catalysts together with directing groups provides an efficient way to facilitate the C-H bond cleavage and the C-C bond formation.[2] As for the alkenylation of C-H bond, namely the Fujiwara−Moritani reaction,[3] a large number of examples have been reported in recent years by using diverse directing groups such as imino,[4] hydroxyl,[5] imidazolyl,[6] carbonyl,[7] oxazolyl,[8] amido,[9] pyridyl,[10] oxime ether,[11] carboxyl,[12] carbamate,[13] pyrazole,[14] guanidine,[15] and N-nitroso etc.[16]

Meanwhile, tetrazoles have received considerable attention owing to their widely applications in synthetic organic chemistry,[17] medicinal and pharmaceutical field,[18] as well as material science.[19] For example, biphenyl tetrazoles are well known intermediates for the synthesis of sartan family drugs such as Losartan and Valsartan. Shuman reported the direct *ortho*-lithiation of a phenyltetrazole followed by an electrophilic reaction to afford the 2-aryl substituted carbapenems (Figure 1, A).[20] Yasuda described the synthesis of this angiotensin II antagonist via palladium-catalyzed coupling of a enol triflate with aryl boronic acids.[21] However, the prefunctionalization of the substrates as well as long steps limited their applications, especially in the large-scale synthetic process.

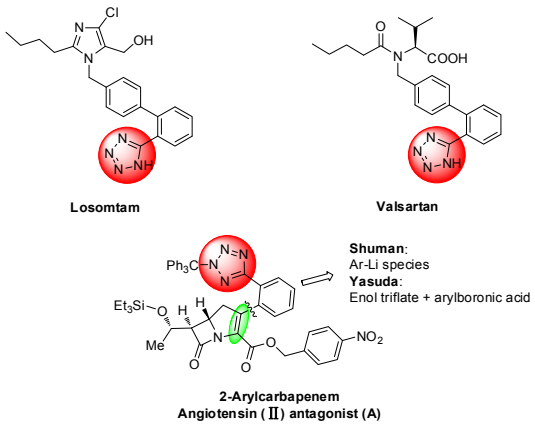
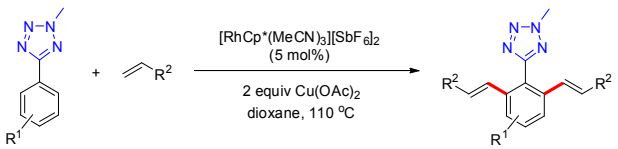


Figure 1 Bioactivated compounds with tetrazole moiety.

To the best of our knowledge, the tetrazole moiety chelating-assisted C-H functionalization of aromatics has not been fully explored.[22] Seki reported the arylation of aryl tetrazoles in $RuCl_3/PPh_3$ system and this procedure was successfully applied to a practical synthesis of angiotensin II receptor blockers.[22a-c] Similarly, Ackermann developed a Ru(II)-catalyzed C-H arylation of 5-benzyl substituted aryl tetrazoles, which provided a step-economical access to Valsartan.[22d] Based on these, we believed that the tetrazole moiety is not only important in lots of organic intermediates but also an useful directing group for further functionalization, which could afford compounds with potential bioactivities. Herein, we wish to report a rhodium-catalyzed direct *ortho* C-H olefination reactions between aryl tetrazoles and alkenes (Scheme 1).



Scheme 1 Rhodium-catalyzed direct C-H olefination of aryl tetrazoles.

The reaction conditions were first explored by employing 2-methyl substituted aryl tetrazole (**1a**, 1.0 equiv) and methyl acrylate (**2a**, 2.0 equiv) as the substrates. The reaction did not proceed in the absence of catalyst. Other catalysts such as $RhCl_3$, $Rh(CF_3COO)_2$ and $[RhCp^*Cl_2]_2$ were also ineffective for this

[a] *School of Petrochemical Engineering and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou, 213164, P. R. China. E-mail: lwcczu@126.com and hemingyangjpu@yahoo.com; Fax: +86-519-86330251.*

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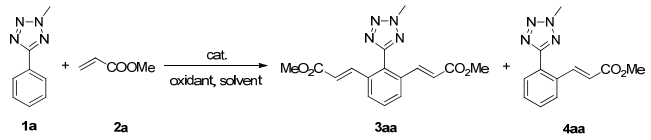
transformation. Treatment of **1a** and **2a** using $[RuCl_2(p\text{-Cymene})]_2$ as catalyst and $Cu(OAc)_2$ as oxidant in dichloroethane gave the product of **3aa** and **4aa** in 46% and 31% yield, respectively (Table 1, entry 3). Good yields were obtained (**3aa**, 84%; **4aa**, 7%) when the reaction was carried out using $[RhCp^*Cl_2]_2$ as catalyst and $AgSbF_6$ as additive (Table 1, entry 5). To our delight, switching the catalyst to $[RhCp^*(MeCN)_3][SbF_6]_2$ afforded the diolefinated product **3aa** in 90% yield and only trace amount of **4aa** was detected (Table 1, entry 7).

Table 1. Optimization of reaction conditions[a]



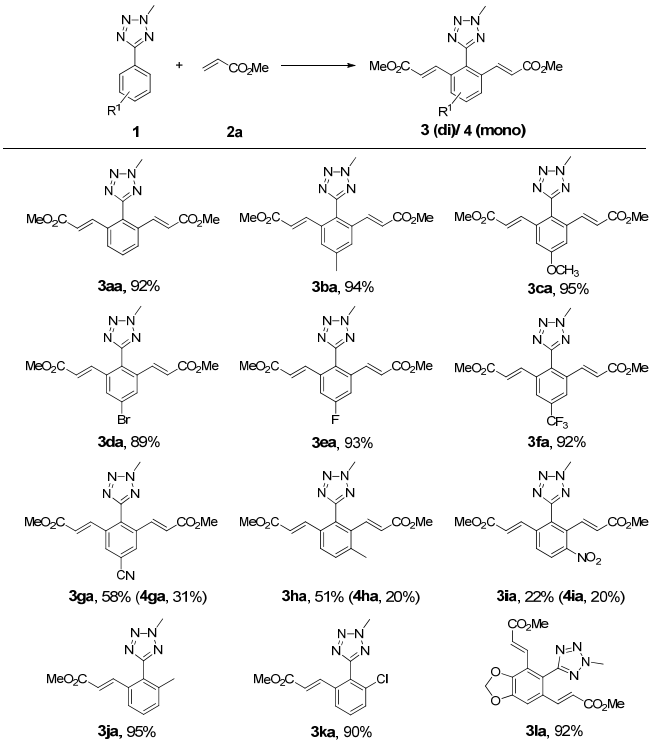
Entry	Catalyst	Oxidant	Solvent	Yield(%)[b]	
				3aa	**4aa**
1	$RhCl_3$	$Cu(OAc)_2$	DCE	0	0
2	$Rh(OOCCF_3)_2$	$Cu(OAc)_2$	DCE	0	0
3	$[RuCl_2(p\text{-Cymene})]_2$	$Cu(OAc)_2$	DCE	46	31
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	15	18
5[c]	$[RhCp^*Cl_2]_2/AgSbF_6$	$Cu(OAc)_2$	DCE	84	7
6	None	$Cu(OAc)_2$	DCE	0	0
7	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	DCE	90	trace
8	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	DMF	Trace	16
9	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	benzene	52	34
10	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	92	trace
11	$RhCp^*L_3(SbF_6)_2$	-	dioxane	13	27
12	$RhCp^*L_3(SbF_6)_2$	Ag_2CO_3	dioxane	68	15
13	$RhCp^*L_3(SbF_6)_2$	B.Q.	dioxane	55	19
14	$RhCp^*L_3(SbF_6)_2$	$PhI(OAc)_2$	dioxane	51	22
15[d]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	85	trace
16[e]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	62	23
17[f]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	92	trace
18[g]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	88	trace
19[h]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	72	16
20[i]	$RhCp^*L_3(SbF_6)_2$	$Cu(OAc)_2$	dioxane	44	30

[a] Conditions : **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (5 mol%), oxidant (2 equiv), solvent (1.5 mL), 110 °C, air, 12 h. For entries 6~18, L = CH_3CN. [b] Isolated Yield. [c] $AgSbF_6$ (4 equiv) was added. [d] $Cu(OAc)_2$ (1.5 equiv). [e] 2.5 mol% catalyst was used. [f] Under O_2. [g] Under N_2. [h] 100 °C. [i] 1 equivalent of **2a** was used.

With the promising preliminary result in hand, different solvents including DMF, dioxane and benzene were then evaluated (Table 1, entries 7-10). The reaction was sluggish in DMF, providing **4aa** as major product in 16% yield. A total 86% yield was observed using benzene as solvent, albeit the di/mono selectivity was not satisfactory. Changing the solvent to dioxane gave the highest yield (92%) and selectivity (Table 1, entry 10). The substitution of $Cu(OAc)_2$ with other oxidants was investigated using dioxane as solvent, although all modifications resulted in either a reduced yield or selectivity (Table 1, entries 11-14). Decreasing the amount of catalyst as well as oxidant also led to a lower yield and selectivity (Table 1, entries 15 and 16). The reactions under either O_2 or N_2 gave similar results as that under air, while a lower reaction temperature slightly decreased the yields (Table 1, entries 17~19). Finally, decreasing the the amount of **2a** to 1 equivalent led to a lower conversion, together with a mixture of *mono*- and *di*-olefinated products (Table 1, entry 20). Thus, the optimized reaction conditions were ultimately identified as 5 mol% of $[RhCp^*(MeCN)_3][SbF_6]_2$ and 2 equiv of $Cu(OAc)_2$ in dioxane at 110 °C.

Various substituted tetrazoles were then subjected to the standard conditions to determine the scope and limitations of the present method as summarized in Table 2.

Table 2. Reaction scope for substituted tetrazoles.[a]



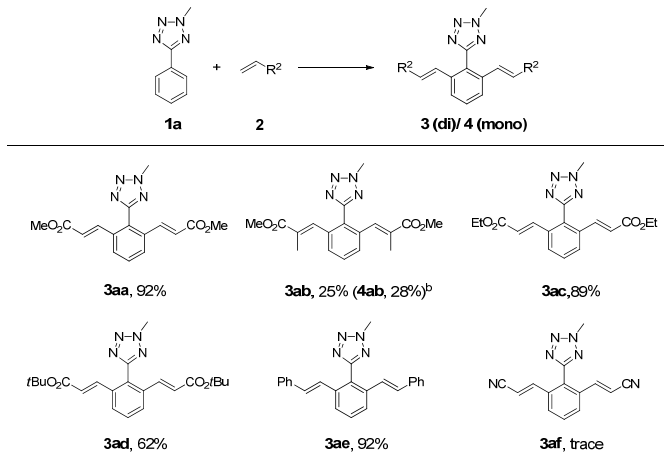
[a] Reaction conditions: **1** (0.1 mmol), methyl acrylate **2a** (0.2 mmol), $[RhCp^*(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv), dioxane (1.5 mL), 110 °C, air, 12 h.

Generally, all the cases were *ortho*-selective and gave the desired products in moderate to excellent yields. For the *para*-substituted tetrazoles, a series of functional groups such as methyl, methoxy, bromo, fluoro, trifluomethyl and cyano tolorate the reaction conditions, affording the corresponding products in high yields (**3aa**~**3ga**, 89~95%). Notably, nearly all the reactions gave *di*-olefinated products except cyano-substituted tetrazoles which delivered a *mono*-olefinated product **4ga** in 31% yield. The steric hindrance had a little influence on the reaction. Interestingly, *meta*-substituted tetrazoles gave *di*-olefinated products **3ha** and **3ia** in 51% and 20% yield, respectively. The corresponding *mono*-olefinated products **4ha** and **4ia**, however, were only obtained in 20% yields (the structures for **4ha** and **4ia** were provided in support information). The *ortho*-substituted tetrazoles worked well to provide the *mono*-olefinated product in excellent yields (**3ja**, 95%; **3ka**, 90%). Moreover, reactions of tetrazoles **3l** also proceeded smoothly to give the products **3la** in 92% yield.

Next, we examined the substrate scope of alkene derivatives. As shown in Table 3, a series of olefins including methyl acrylate, methyl methacrylate, ethyl acrylate, *tert*-butyl acrylate and styrene readily participated in this transformation, providing the

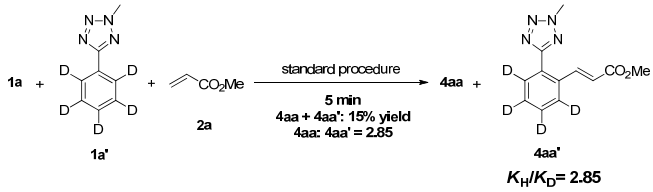
corresponding products in moderate to excellent yields (53~92%). All these reactions gave *di*-olefinated tetrazoles except methyl methacrylate, which afforded a mixture of *di*- and*mono*-olefinated tetrazoles in 25% and 28% yield, respectively. For acrylonitrile and other aliphatic alkenes, however, only trace amount of product was observed.

Table 3. Olefination of **1a** with alkene derivatives.[a]



[a] Reaction Conditions: **1a** (0.1 mmol), alkene **2** (0.2 mmol), $[RhCp^*(MeCN)_3][SbF_6]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv), dioxane (1.5 mL), 110 °C, air, 12 h. [b] Methyl methacrylate amount was 0.3 mmol.

To gain more detailed information about the mechanism of the present reaction, the following experiment was conducted. A mixture of **1a** and **1a'** in a 1:1 ratio was used to determine the intermolecular kinetic isotope effect and significant kinetic isotope effect (k_H/k_D = 2.85) for the *mono*-olefinated product **4aa**/**4aa'** was observed (Scheme 2). This result revealed that the C-H bond cleavage was the rate-determining step.



Scheme 2 Kinetic Isotope effect study.

On the basis of above results and literature information,[23-25] a plausible mechanism is proposed in Scheme 3. The first step involves the coordination of the tetrazole nitrogen of **1a** to the rhodium complex, which is followed by insertion of the metal into the *ortho* C−H bond. Then, coordination of **2a** to intermediate **A** gives the intermediate **B**, which is transformed into seven-membered rhodacycle **C** by migratory insertion of olefin. Subsequently, *β*-hydride elimination and reductive elimination take place to release the monoolefinated product **4aa** and $Rh(I)Cp^*$, and reoxidation of Rh(I) to Rh(III) by $Cu(OAc)_2$ to finish the first catalytic cycle. Since nitrogen atoms at 2 and 5 position of tetrazole can form rhodium complex with the catalyst, the *di*-olefinated product **3aa** is then obtained via a second same catalytic cycle.

Conclusions

In summary, we have developed an efficient Rh(III)-catalyzed C-H olefination reaction between aryl tetrazoles and alkenes. This procedure afforded the olefinated aryl tetrazoles in moderate to excellent yields. Various functional groups such as methyl, methoxy, bromo, fluoro, trifluomethyl and cyano survived the reaction conditions. Importantly, this reaction provided a straightforward way for the synthesis of olefinated tetrazole derivatives which may be having some potential bioactivities.

Acknowledgments

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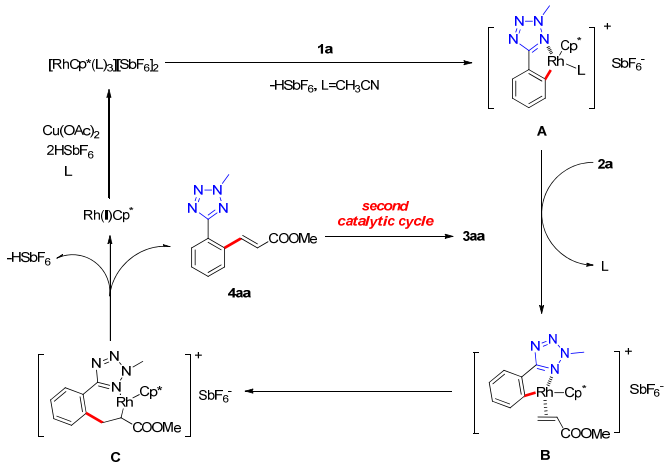

Scheme 3 Proposed reaction mechanism.

Notes and references

1 a) M. C. White, *Science* 2012, **335**, 807; b) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* 2012, **45**, 826.

2 a) A. J. Hickman, M. S. Sanford, *Nature* 2012, **484**, 177-; b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* 2010, **110**, 890; c) J. A. Labinger, J. E. Bercaw, *Nature* 2002, **417**, 507; d) H. M. L. Davies, J. R. Manning, *Nature* 2008, **451**, 417; e) J. F. Hartwig, *Nature* 2008, **455**, 314; f) X. Chen, K. M. Engle, D.-H. Wang, J.-Q.Yu, *Angew. Chem. Int. Ed.* 2009, **48**, 5094; g) L. Ackermann, *Chem. Rev.* 2011, **111**, 1315; h) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* 2011, **40**, 4740; i) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* 2012, **112**, 5879; j) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* 2012, **45**, 788; k) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* 2012, **45**, 814.

3 a) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* 1969, **91**, 7166; b) Y. Fujiwara, I. Moritani, M. Matsuda, *Tetrahedron* 1968, **24**, 4819; c) I. Moritani, Y. Fujiwara, *Tetrahedron Lett.* 1967, **8**, 1119.

4 a) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* 2002, **4**, 1783; b) L. Ackermann, *Org. Lett.* 2005, **7**, 2229.

5 a) R. B. Bedford, S. J. Coles, M. B. Hursthouse, M. E. Limmert, *Angew. Chem. Int. Ed.* 2003, **42**, 112; b) R. B. Bedford, M. E. Limmert, *J. Org. Chem.* 2003, **68**, 8669; c) T. Satoh, M. Miura, *Chem. Eur. J.* 2010, **16**, 11212.

6 S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* 2005, **70**, 3113.

7 a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* 2003, **125**, 1698; b) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* 2005, **127**, 5936.

8 X. Chen, J. J. Li, X. S. Hao, C. E. Goodhue, J. -Q. Yu, *J. Am. Chem. Soc.* 2006, **128**, 78.

9 Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem. Int. Ed.* 2007, **46**, 5554.

10 L. V. Desai, K. J. Stower, M. S. Sanford, *J. Am. Chem. Soc.* 2008, **130**, 13285.

11 V. S. Thirunavukkarasu, K. Parthasarathy, C. H. Cheng, *Chem. Eur. J.* 2010, **16**, 1436.

12 a) D. H. Wang, K. M. Engle, B. F. Shi, J. -Q. Yu, *Science* 2010, **327**, 315; b) B. F. Shi, Y. H. Zhang, J. K. Lam, D. H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* 2010, **132**, 460; c) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* 2007, **72**, 5362; d) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* 2007, **9**, 1407; e) N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* 2009, **74**, 7094; f) T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* 2011, **13**, 706.

13 F. Chao, T. P. Loh, *Chem. Commun.* 2011, **47**, 10458.

14 L. Ackermann, J. Pospech, H. K. Potukuchi, *Org. Lett.* 2012, **14**, 2146.

15 J. Shao, W. Chen, M. A. Giulianotti, R. A. Houghten, Y. Yu, *Org. Lett.* 2012, **14**, 5452.

16 B. Liu, Y. Fan, Y. Gao, C. Sun, C. Xu, J. Zhu, *J. Am. Chem. Soc.* 2013, **135**, 468.

17 R. C. Larock, Comprehensive Organic Transformations. A Guide to Functional Group Preparations; VCH Publishers: New York, 1989.

18 a) M. I. Fernandez-Bachiller, C. Perez, L. Monjas, J. Rademann, M. I. Rodríguez-Franco, *J. Med. Chem.* 2012, **55**, 1303; b) S. G. Das, B. Srinivasan, D. L. Hermanson, N. P. Bleeker, J. M. Doshi, R. Tang, W. T. Beck, C. Xing, *J. Med. Chem.* 2011, **54**, 5937.

19 G. Aromí, L. A. Barrios, O. Roubeau, P. Gamez, *Coord. Chem. Rev.* 2011, **255**, 485.

20 R. F. Shuman, A. O. King, R. K. Anderson, US 5039814, 1991.

21 N. Yasuda, L. Xavier, D. L. Rieger, Y. Li, A. E. DeCamp, U. H. Dolling, *Tetrahedron Lett.* 1993, **34**, 3211.

22 a) M. Seki, *ACS Catal.* 2011, **1**, 607; b) M. Seki, M. Nagahama, *J. Org. Chem.* 2011, **76**, 10198; c) M. Seki, *Synthesis* 2012, 3231; d) E. Diers, N. Y. P. Kumar, T. Mejuch, I. Marek, L. Ackermann, *Tetrahedron* 2013, **69**, 4445.

23 H. Wang, R. Hu, H. Zhang, A. Zhou, S. Yang, *Org. Lett.* 2013, **15**, 5302.

24 T. Iitsuka, P. Schaal, K. Hirano, T. Satoh, C. Bolm, M. Miura, *J. Org. Chem.* 2013, **78**, 7216.

25 K. Parthasarathy, A. R. Azcargorta, Y. Cheng, C. Bolm, *Org. Lett.* 2014, **16**, 2538.