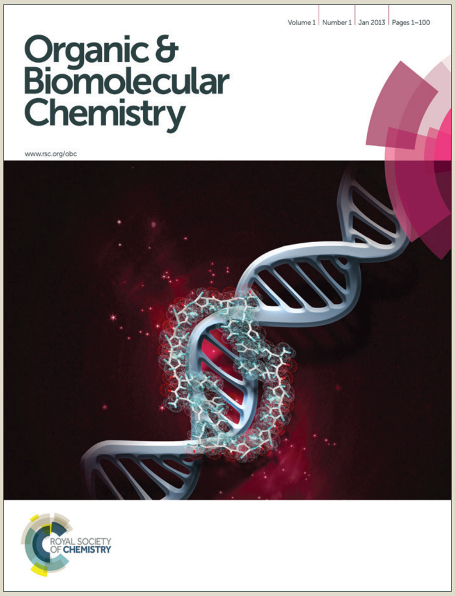
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

COMMUNICATION

Gold-catalyzed α-Furanylations of Quinoline *N*-Oxides with Alkenyldiazo Carbonyl Species

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Vinayak Vishnu Pagar and Rai-Shung Liu*

Gold-catalyzed α-furanylations of 8-alkylquinoline *N*-oxides has been achieved using alkenyldiazo carbonyl species as nucleophiles. The reactions are applicable to a reasonable range of alkenyldiazo species and 8-alkylquinoline *N*-oxides. The reaction mechanism is postulated to involve an initial nucleophilic of diazocarbonyl species at 8-alkylquinoline *N*-oxides, followed by diazo decompositions.

Quinoline cores are widely found in natural products, pharmaceutics and common synthetic building blocks in organic synthesis.[1] The reactions of quinoline compounds generally follow those of pyridine derivatives. α-Arylations of pyridines are generally performed with Pd-catalyzed coupling reactions[2-4] using α-halo- or metallated pyridyl reagents. Direct C-H functionalizations of pyridine derivatives can avoid an extra "prefunctionalization" of a pyridine core.[5-6] Although there are literature reports on the addition of Grignard reagents to pyridine *N*-oxides to obtain α-aryl substituted pyridines, satisfactory yields can be obtained only in the presence of electrophiles such as acetic anhydride in a large proportion (1.2 equiv, eq 1).[7] Although α-functionalizations of pyridine *N*-oxide can be achieved with alkenes and alkynes catalyzed by Ni, Pd or Rh complexes,[5-6] no corresponding arylation reactions are reported yet. Herein, we report new gold-catalyzed heteroarylations of 8-alkylquinoline *N*-oxide **2** with alkenyldiazo carbonyl species with its reaction protocol depicted in eq 3. The mechanism of this non-oxidation process has been elucidated with suitable experiments.

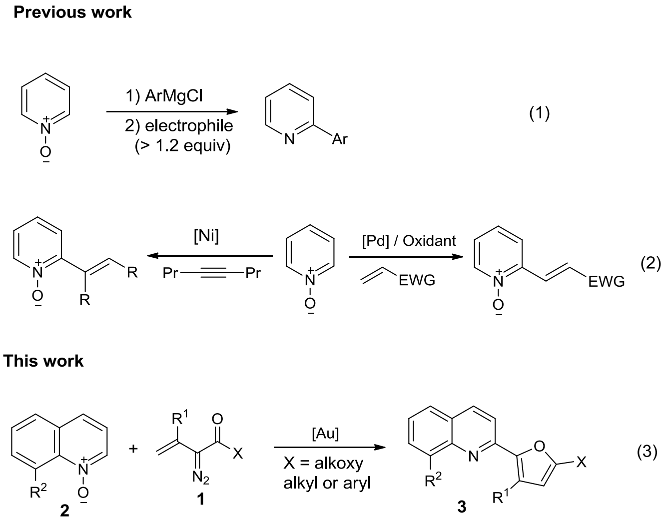


Table 1 shows the optimization of the reactions between ethenyldiazo acetate **1a** and 8-methylquinoline *N*-oxide **2a** using various acid catalysts. In a typical operation, diazo species **1a** (1.0 equiv) and **2a** (1.5 equiv) were mixed together in 1,2-dichloroethane (DCE) before an addition of a DCE solution of catalyst at 25 °C. The resulting mixture was then stirred at 55 °C for 2-3 h to consume initial diazo reagents completely. With LAuCl/AgNTf$_2$ (L= P(t-Bu)$_2$(o-biphenyl) (5 mol %), its reaction in dichloroethane at mild conditions (25 °C, 6 h) gave the desired product, 2-(5-ethoxyfuran-2-yl)-8-methylquinoline **3a** in 25% yield (Table 1, entry 1). The product yield was improved significantly to 60% if the reaction was operated at 55 °C for 2.5 h (entry 2). An alteration of silver salt as in LAuCl/ AgSbF$_6$ increased the yield of furan **3a** in 64% (entry 3). Other gold catalysts IPrAuCl/AgSbF$_6$ (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) and PPh$_3$AuCl/AgSbF$_6$ appeared to be less efficient to obtain furan **3a** in 30-40 % yields respectively (entries 4-5). In a control experiment, P(t-Bu)$_2$(o-biphenyl)AuCl alone gave only 20 % furan product in 4 h (entry 6). We also tested the reaction with LAuCl (5 mol %)/AgSbF$_6$ (20 mol%), and its reaction was complete within 2 h to give the desired product **3a** in 52 % (entry 7). The data in entries 6-7 suggest that silver enhances the addition of vinyldiazo acetate to 8-methylquinoline *N*-oxide to accelerate the reaction, but the diazo decomposition is activated by cationic gold species. In the absence

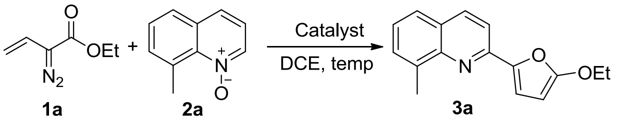
---

Department of Chemistry, National Tsing-Hua University, Hsinchu, Taiwan 30013 ROC. E-mail: rsliu@mx.nthu.edu.tw

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

of catalyst, the reaction gave a complicated mixture of products due to decomposition of starting reagents (entry 8). Silver catalysts including AgNTf$_2$ and AgSbF$_6$ gave desired **3a** in low yields (7-10 %, entries 9-10). We tested the reaction with Rh$_2$(OAc)$_4$ (2.5 mol %) and Cu(OTf)$_2$ (5 mol %); both cases gave complicated mixture of products (entries 11-12). Among these tests, self-cyclization of vinyldiazo acetates did occur but to a less extent, and resulting ethyl 1*H*-pyrazole-3-carboxylate was produced in small proportions (<20 %).[8]

Table1. Reactions over various metal catalysts

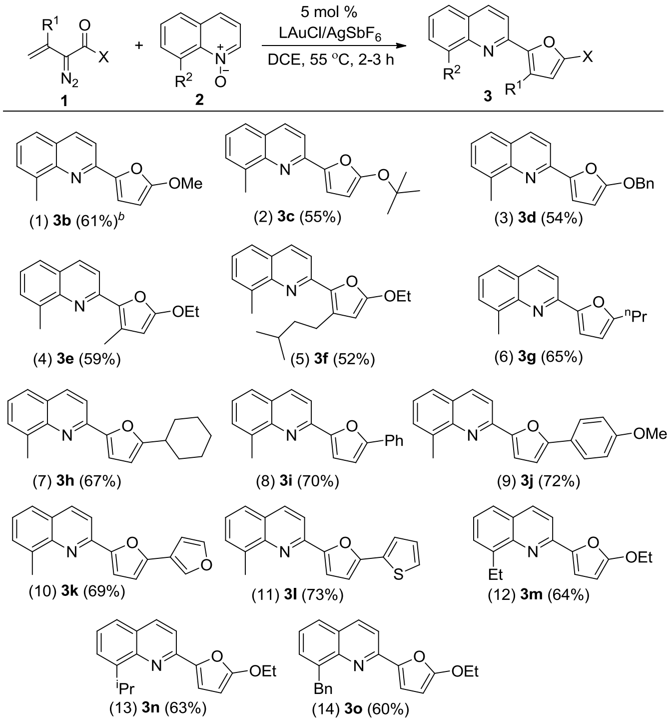


Entry	Catalyst^b (5 mol %)	temp (°C)	time (h)	**3a** (Yield%)^c
1	LAuCl/AgNTf$_2$	rt	6	25
2	LAuCl/AgNTf$_2$	55	2.5	60
3	**LAuCl/AgSbF$_6$**	**55**	**2.5**	**64**
4	IPrAuCl/AgSbF$_6$	55	3	30
5	PPh$_3$AuCl/AgSbF$_6$	55	2.5	40
6	LAuCl	55	4	20
7	LAuCl/AgSbF$_6$^{d}	55	2	52
8	—	55	4	Decompose
9	AgNTf$_2$	55	3	7
10	AgSbF$_6$	55	3	10
11	Rh$_2$(OAc)$_4$	55	3	-
12	Cu(OTf)$_2$	55	3	-

[a] **1a** (0.24 M, 1 equiv), **2a** (1.5 equiv), [b] L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr = 1,3-bis(diisopropylphenyl) imidazol-2-ylidene. [c] Product yields are given after purification from a silica column. [d] LAuCl (5 mol%) and AgSbF$_6$ (20 mol%).

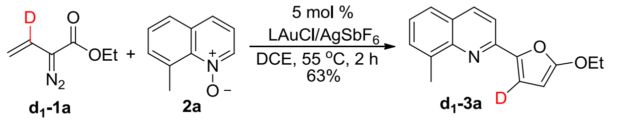
We examined the reactions using various alkenyldiazo carbonyl compounds and 8-alkylquinoline *N*-oxides. In a typical operation, initial alkenyldiazo reagents were treated with 8-alkylquinoline *N*-oxides and LAuCl/AgSbF$_6$ (L = P(*t*-Bu)$_2$(o-biphenyl), 5 mol %) in DCE (55 °C) for 2-3 h, leading to a complete consumption of starting vinyldiazo to yield α-arylated quinoline derivatives **3b**-**3o** in moderate to good yields. Entries 1-3 shows the compatibility of this arylation with diazo species **1b-1d** bearing various esters (X = OMe, O^{t}Bu, OBn), providing desired products **3b**-**3d** in 54-61% yields. We examined also the reactions of diazo species **1e** and **1f** bearing variable substituents at the alkenyl C(2)-carbon (R^1= methyl and isopentyl), yielding desired products **3e** and **3f** in 59-52% yields respectively (entries 4 and 5). Herein, the molecular structure of furan product **3e** was determined by X-ray diffraction study to confirm its structure.[9] We also tested the arylation reactions using the diazo ketones **1g**-**1h** (X = *n*-propyl and cyclohexyl); the corresponding products were obtained in **3g**-**3h** in 65% and 67% yields respectively (entries 6-7). In entries 8-9 we examined the reactions of alkenyldiazo arylketones **1i** and **1j** (X = phenyl, 4-methoxyphenyl) that afforded expected products **3i** and **3j** with satisfactory yields (70-72%). The reactions were also suitable for the heteroaryl vinyldiazo ketones (X=3-furanyl, 2-thienyl) to afford desired compounds **3k** and **3l** in 69-73% yields, respectively (entries 10 and 11). To expand the reaction scope, we also prepared other 8-substituted quinoline *N*-oxide **2b**-**2d** (R^2 = ethyl, isopropyl and benzyl); their reaction with ethenyldiazo ester **1a** afforded furan products **3m**-**3o** in moderate yields (60-64%, entries 12-14). We also tested the reaction on 2-arylsubstituted pyridine oxides, but the reactions were unsuccessful.

Table 2 Reaction scopes for the formation of furan

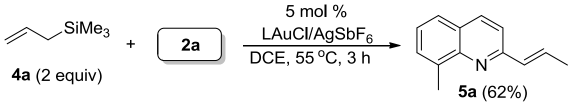


[a] **1** (0.24 M, 1 equiv), **2** (1.5 equiv). [b] Product yields are given after purification from a silica column.

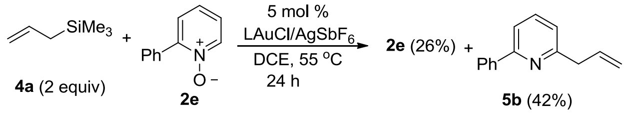
Shown in equation (4) is a deuterium labeling experiment to elucidate the reaction mechanism. We prepared deuterated diazo species **d$_1$-1a** in which its alkenyl C(2)-proton was fully deuterated; its resulting product **d$_1$-3a** contained a fully deuterium at its C(3)-furyl carbon. We envisage that the success of 8-alkylquinoline oxides is due to their better electrophilicity than a monomeric pyridine oxide like species **2e**; we test this hypothesis with two separate experiments as depicted in eqs 5 and 6. Indeed, gold catalyzed allylation of 8-methylquinoline oxide worked well to yield addition product **5a** in 62% yield at a brief period (3 h) whereas 2-phenylpyridine oxide **2e** gave unreacted **2e** and addition product **5b** in 26% and 42% yields respectively after a prolonged period (24 h). 8-methylqunoline oxide is obviously more reactive than 2-phenylpyridine oxide in the gold-catalyzed electrophilic additions.



(4)

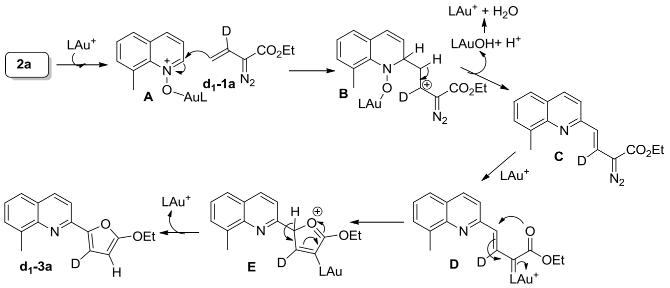


(5)



(6)

Scheme 1 depicts a plausible mechanism to rationalize this α-hetereoarylation reaction, involving a prior addition of alkenyldiazo esters at 8-methylquinoline oxide before a diazo decomposition; such a nucleophilic addition/diazo decomposition route has several literature precedents.[10,11] The feasibility of a prior nucleophilic addition is supported by a control experiment in eq 5. We envisage that gold complex coordinates to the oxygen of 8-methylquinoline *N*-oxide to increase its C(α)-carbon electrophilicity. A subsequent nucleophilic attack of alkenyldiazo ester at this Au(I)-bound oxide complex generates an addition product **B**, which undergoes a loss of water to form species **C.** At this stage, gold complexes activates the diazo decomposition of species **C** to yield gold carbenes **D** that undergo an oxa-Nazarov [12] cyclization to yield furanylium cation **E,** ultimately affording observed compound **d$_1$-3a** via a protodeauration**.** This proposed mechanism also rationalizes our deuterium labeling experiment that no loss of deuterium is observed for resulting **d$_1$-3a**. This mechanism is highly speculative and additional work is required for its confirmation.



Scheme 1 Plausible mechanism

Conclusions

We report here a new gold-catalyzed reaction between vinyldiazo carbonyl compounds and 8-alkylquinoline *N*-oxides to yield 2-furanyl-quinoline products.[13] The reactions are operable with a reasonable range of alkenyldiazo species and quinoline oxides but inapplicable to monomeric pyridine *N*-oxides. We postulate a mechanism involving an initial nucleophilic addition of diazocarbonyl esters at 8-alkylquiniline *N*-oxides, followed by gold-induced diazo decomposition. This instance provides an additional example for a nucleophilic addition/diazo decomposition cascade of alkenyldiazo carbonyl reagents.

Experimental section

General catalytic procedure for the synthesis of furan (3a)

A dichloroethane (1 mL) solution of P(*t*-Bu)$_2$(*o*-biphenyl)AuCl (18.9 mg, 0.035 mmol) and AgSbF$_6$ (12.2 mg, 0.035 mmol) was stirred under argon atmosphere at 25°C for 10 min. To this solution was added dropwise a dichloroethane (2 mL) solution of ethyldiazoacetate (**1a**) (100 mg, 0.71 mmol) and 8-methylquinoline *N*-oxide (**2a**) (170 mg, 1.07 mmol) over 5 minute. The resulting solution was stirred at 55 °C for additional 2.5 h before it was filtered over a short silica bed. The filtrate was concentrated and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate (9:1) as eluent to give 2-(5-ethoxyfuran-2-yl)-8-methylquinoline (**3a)** as yellow oil (115 mg, 0.45 mmol, 64% yield).

Acknowledgment

The authors wish to thank the Ministry of Science and technology, Taiwan, for supporting this work.

Notes and references

1 (a) L. A. Mitscher, *Chem. Rev.*, 2005, **105**, 559; (b) J. L. McCormick, T. C. McKee, J. H. Cardellina and M. R. Boyd, *J. Nat. Prod*., 1996, **59**, 469; (c) S. Madapa, Z. Tusi and S. Batra, *Curr. Org. Chem.*, 2008, **12**, 1116; (d) Y. L. George, J. F. Ernest, D. G. Monte and H. B. John, *J. Med. Chem.*, 1962, **5**, 1063; (e) K. C. Fang, Y. L. Chen, J. Y. Sheu, T. C. Wang and C. C. Tzeng, *J. Med. Chem.*, 2000, **43**, 3809; (f) S. Y. Ablordeppey, P. Fan, S. Li, A. M. Clark and C. D. Hufford, *Bioorg. Med. Chem.*, 2002, **10**, 1337; (g) M. L. Vargas, M. V. Castelli, V. V. Kouznetsov, G. J. Urbina, S. N. Lo´pez and M. Sortino, *Bioorg. Med. Chem.*, 2003, **11**, 1531; (h) O. Bilker, V. Lindo, M. Panico, A. E. Etiene, T. Paxton, A. Dell, M. Rogers, R. E. Sinden and H. R. Morris, *Nature*, 1998, **392**, 289; (i) T. Deng, Y. Chen and N. Belzile, *Anal. Chim. Acta,* 2001, **432**, 293; (j) J. P. Michael, *Nat. Prod. Rep*., 2008, **25**, 166.

2 (a) M. R. Kumar, K. Park and S. Lee, *Adv. Synth. Catal.,* 2010, **352**, 3255; (b) Y. Zou, G. Yue, J. Xu and J. Zhou, *Eur. J. Org.*

Chem., 2014, 5901; (c) X. Rao, C. Liu, J. Qiu and Z. Jin, *Org. Biomol. Chem.*, 2012, **10**, 7875; (d) M. L. N. Rao and R. J. Dhanorkar, *Eur. J. Org. Chem.,* 2014, 5214; (e) S. Goggins, E. Rosevere, C. Bellini, J. C. Allen, B. J. Marsh, M. F. Mahon and C. G. Frost, *Org. Biomol. Chem.*, 2014, **12**, 47.

3 (a) K. Godula, B. Sezen and D. Sames, *J. Am. Chem. Soc*., 2005, **127**, 3648; (b) R. Gerber and C. M. Frech, *Chem. Eur. J.,* 2011, **17**, 11893; (c) V. P. W. Bohm, T. Weskamp, C. W. K. Gstottmayr and W. A. Herrmann, *Angew. Chem. Int. Ed*., 2000, **39**, 1602; (d) O. M. Kuzmina, A. K. Steib, D. Flubacher and P. Knochel, *Org. Lett.,* 2012, **14**, 4818; (e) P. P. Singh, S. K. Aithagani, M. Yadav, V. P. Singh and R. A. Vishwakarma, *J. Org. Chem.,* 2013, **78**, 2639; (f) J. Wen, S. Qin, L.-F. Ma, L. Dong, J. Zhang, S.-S. Liu, Y.-S. Duan, S.-Y. Chen, C.-W. Hu and X.-Q. Yu, *Org. Lett.,* 2010, **12**, 2694.

4 (a) S. Verbeeck, C. Meyers, P. Franck, A. Jutand and B. U. W. Maes, *Chem. Eur. J.,* 2010, **16**, 12831; (b) H. Malmberg and M. Nilsson, *Tetrahedron*, 1986, **42**, 3981; (c) S. Gronowitz, P. Bjork, J. Malm and A.-B. Hornfeldt, *J. Organometallic chem.,* 1993, **450**, 127. (d) M. R. Luzung, J. S. Patel and J. Yin, *J. Org. Chem.,* 2010, **75**, 8330.

5 (a) K. S. Kanyiva, Y. Nakao and T. Hiyama, *Angew. Chem. Int. Ed*., 2007, **46**, 8872; (b) J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc*., 2007, **129**, 5332; (c) L.-C. Campeau, S. Rousseaux and K. Fagnou, *J. Am. Chem. Soc*., 2005, **127**, 18020; (d) Y. Tan, F. B. Landeros and J. F. Hartwig, *J. Am. Chem. Soc*., 2012, **134**, 3683; (e) L. Acermann and S. Fenner, *Chem. Commun.,* 2011, **47**, 430; (f) H.-Y. Sun, S. I. Gorelsky, D. R. Stuart, L.-C. Campeau and K. Fagnou, *J. Org. Chem.,* 2010, **75**, 8180.

6 S. H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc*., 2008, **130**, 9254; (b) J. Ryu, S. H. Cho and S. Chang, *Angew. Chem. Int. Ed*., 2012, **51**, 3677; (c) Y. Shen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *Chem. Commun.,* 2014, **50**, 4292; (d) J. Wu, X. Cui, L. Chen, G. Jiang and Y. Wu, *J. Am. Chem. Soc*., 2009, **131**, 13888; (e) B. Xiao, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc*., 2013, **135**, 616; (f) G. Li, C. Jia, K. Sun, *Org. Lett.* **2013**, *15*, 5198.

7 (a) H. Andersson, T. S.-L. Banchelin, S. Das, R. Olsson and F. Almqvist, *Chem. Commun.,* 2010, **46**, 3384; (b) H. Andersson, M. Gustafsson, D. Bostrom, R. Olsson and F. Almqvist, *Angew. Chem. Int. Ed*., 2009, **48**, 3288; (c) H. Andersson, F. Almqvist and R. Olsson, *Org. Lett.,* 2007, **9**, 1335; (d) T. J. V. Bergen and R. M. Kellogg, *J. Org. Chem.,* 1971, **36**, 1705; (e) M. Hussain, T. S.-L. Banchelin, H. Andersson, R. Olsson and F. Almqvist, *Org. Lett.,* 2013, **15**, 54; (f) H. Andersson, S. Das, M. Gustafsson, R. Olsson and F. Almqvist, *Tetrahedron Lett.,* 2010*,* **51***,* 4218. (g) M. A. Fakhfakh, A. Fournet, E. Prina, J.-F. Mouscadet, X. Franck, R. Hocquemiller and B. Figadere, *Bioorg. Med. Chem*., 2003, **11**, 5013; (h) T. R. Webb, *Tetrahedron Lett.*, 1985, **26**, 3191.

8 (a) M. B. Supurgibekov, D. Cantillo, C. O. Kappe, G. K. Suryaprakash and V. A. Nikolaev, *Org. Biomol. Chem.*, 2014, **12**, 682; (b) M. B. Supurgibekov, V. M. Zakharova, J. Sieler and V. A. Nikolaev, *Tetrahedron Lett.*, 2011, **52**, 341; (c) A. Padwa, Y. S. Kulkarni and Z. Zhang, *J. Org. Chem.,* 1990, **55**, 4144.

9 The crystallographic data of compounds **3e** was provided in Supporting Information; these data were also deposited in Cambridge crystallographic center (**3e** CCDC 1057272).

10 (a) M. P. Doyle, K. Kundu and A. E. Russel, *Org. Lett.,* 2005, **7**, 5171; (b) Y. Liu, Y. Zhang, N. Jee and M. P. Doyle, *Org. Lett.* 2008, **10**, 1605; (c) G. Deng, J. Wang, Z. Qu and J. Wang, *Angew. Chem. Int. Ed.,* 2002, **41**, 2773; (d) M. A. Calter, P. M. Sugathapala and C. Zhu, *Tetrahedron Lett.* 1997, **38**, 3837; (e) Y. Liu, K. Bakshi, P. Zavalij and M. P. Doyle, *Org. Lett.* 2010, **12**, 4304; (f) L. Zhou and M. P. Doyle, *J. Org. Chem*. 2009, **74***,* 9222; (g) M. P. Doyle, M. Yan, W. Hu and L. Gronenberg, *J. Am. Chem. Soc*. 2003, **125***,* 4692.

11 (a) A. M. Jadhav, V. V. Pagar and R.-S. Liu, *Angew. Chem. Int. Ed.* 2012, **51**, 11809; (b) V. V. Pagar, A. M. Jadhav and R.-S. Liu, *J. Org. Chem.,* 2013, **78**, 5711; (c) V. V. Pagar and R.-S. Liu, *Angew. Chem. Int. Ed.,* 2015, **54**, 4923.

12 (a) R. B. Dateer, K. Pati and R.-S. Liu, *Chem. Commun.,* 2012, **48**, 11522; (b) X. Xu, P.Y. Zavalij, W. Hu and M. P. Doyle, *Chem. Commun.,* 2012, **48**, 11522; (c) L. Lu, P. Lu and S. Ma, *Eur. J. Org. Chem.*, 2007, 676; (d) M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliott, J. W. Hoekstra and M. Oppenhuizen, *J. Org. Chem.,* 1980, **45**, 3657.

13. (a) M. Hoffmann, S. Miaskiewicz, J.-M. Weibel, P. Pale and A. Blanc, Beilstein *J. Org. Chem.*, 2013, **9**, 1774; (b) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076; (c) S. Kramer, J. L. H. Madsen, M. Rottlander and T. Skrydstrup, *Org. Lett.* 2010, **12**, 758;(d) A. Blanc, A. Alix, J.-M. Weibel and P. Pale, *Eur. J. Org. Chem.*, 2010, 1644; (e) M. H. Suhre, M. Reif and S. F. Kirsch, *Org. Lett.* 2005, **7**, 3925; (f) T. Yao, X. Zhang and R. C. Larock, *J. Org. Chem.,* 2005, **70**, 7679.