

# ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

## COMMUNICATION

## Triazole-Gold Promoted Intermolecular Propargyl Alcohol Addition to Alkyne: Reaction Cascade Toward Substituted Allenes

Cite this: DOI: 10.1039/x0xx00000x

Seyedmorteza Hosseyini,<sup>a</sup> Shengtao Ding,<sup>a</sup> Yijin Su,<sup>b</sup> Novruz G. Akhmedov,<sup>b</sup> Xiaodong Shi<sup>a\*</sup>

Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

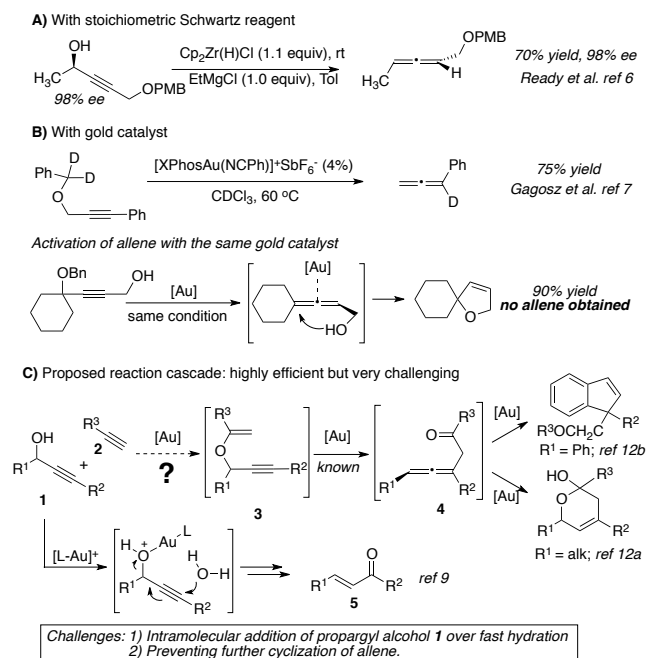
www.rsc.org/

Gold-catalyzed intermolecular propargyl alcohol addition to alkyne was achieved. Reaction of propargyl alcohol with typical gold catalyst gave almost exclusively hydration product. Triazole gold catalyst (TA-Au) successfully prevented the hydration, giving the vinyl ether followed by 3,3-rearrangement. Synthetically useful substituted allenes were formed with high efficiency, substrate tolerability and chemoselectivity. Also more than 95% chirality transfer from propargyl alcohol to allene was obtained.

In the last decade, there has been a rapid growth of homogeneous gold catalysis.<sup>1</sup> Triggered by the breakthrough example of ambient alkyne hydration (Teles hydration),<sup>2</sup> the predominant reactivity of gold catalysts was identified as a highly effective  $\pi$ -acid toward alkyne, alkene and allene activation.<sup>3</sup> In general, compared to intramolecular functional group rearrangements, transformations that enable reactions between multiple components (intermolecular) is of greater interest because it allows rapid increase of structural complexity through the accumulation of functionalities. However, like other catalytic systems, gold catalysis encountered unbalanced development between the intramolecular transformations (far more advanced) and their intermolecular counterparts (much less developed). For example, while the gold catalyzed intramolecular Conia-ene reaction was originally reported in 2004, the similar intermolecular Nakamura reaction was not achieved until 2014.<sup>4</sup> Thus, developing new catalytic systems that can facilitate the challenging intermolecular transformations will provide new opportunity to further advance the synthetic

versatility of gold catalysis.<sup>5</sup> Herein, we report successful intermolecular propargyl alcohol addition to alkyne using the triazole-gold catalyst (TA-Au) to form allene.

We sought to enlist propargyl alcohols as a precursor for allene synthesis due to its general availability and ease of synthesis. However, there were very few examples reported in the literature using this approach due to A) derivatization or Lewis acid was usually required to convert OH to a good leaving group and B) formation of propargyl cation intermediates might cause various side reactions. One recent successful example was the stereospecific reduction of propargyl alcohol using 1.1 equivalent of [Cp<sub>2</sub>Zr(H)Cl], reported by Ready and co-workers (Scheme 1A).<sup>6</sup>



**Scheme 1.** Synthesis of allenes from propargyl alcohols.

Although a stoichiometric amount of Schwartz reagent was required, this reaction provided the first example of asymmetric

<sup>a</sup> Department of Chemistry, University of South Florida, Tampa, FL 33620, USA,

E-mail: xms@usf.edu

<sup>b</sup> C. Eugene Bennett Department of Chemistry, West Virginia University, West Virginia 26506, United States.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

allene synthesis from readily available enantiomerically enriched propargyl alcohols.

[Rh(COD)Cl<sub>2</sub>]<sub>2</sub>, AgOTf, RuCl<sub>3</sub>, all gave no allene.

Another interesting example was the gold catalyzed propargyl benzyl ether rearrangement reported by Gagosz and co-workers.<sup>7</sup> Using [XPhosAu(NCPh)]<sup>+</sup> (Echavarren catalyst) at 60 °C, the desired allenes were prepared in modest to good yields through a proposed 1,5-H shift. While this transformation was very interesting, it suffered from the allene activation by the same gold catalyst, especially when nucleophile was presented in the same molecule. With the presence of nucleophilic hydroxyl group, cyclization occurred through gold catalyzed allene activation (formation of dihydro furan) with no allene isolated (**Scheme 1B**).

Our proposed strategy was the intermolecular addition of propargyl alcohol to terminal alkynes. Besides the clear kinetic difference between inter- and intra-molecular reactions, the existence of competitive reaction paths is the key challenge that hindered the success of intermolecular transformations.

Gold catalyzed propargyl alcohol derivative rearrangements (intramolecular reactions) have been well studied.<sup>8</sup> However, the propargyl alcohol has not been used as a nucleophile in gold catalysis due to the rapid hydration (formation of enone) promoted by the same gold catalyst.<sup>9</sup> Once the first step of the proposed mechanism takes place, the second step, which is the gold-catalyzed propargyl vinyl ether Saucy-Marbet rearrangement is well known to occur.<sup>10</sup> Notably, the synthesis of propargyl vinyl ether is problematic, which we propose to generate in situ. So far, the most practical approach in preparing propargyl vinyl ether was the vinyl ether exchange promoted by stoichiometric amount of Hg(OAc)<sub>2</sub>.<sup>11</sup> The other challenge of the proposed reaction was the chemoselectivity, because it is well known that the resulting allenone can easily undergo further cyclization.<sup>12</sup> So, the choice of the catalyst is very critical to be reactive for the intermolecular addition of propargyl alcohol to alkyne while remaining inert toward intermolecular allenone cyclization. Thus, our proposed intermolecular propargyl alcohol addition to alkyne will be very attractive as a practical new route to allene synthesis from simple starting materials, if proper conditions are revealed.

Our group have recently reported 1,2,3-triazole-gold (TA-Au) complexes as effective catalysts to activate alkyne **3** over allene **4**, giving the desired allene ketone/aldehyde **4** without further cyclization.<sup>13</sup> This process was highly efficient (with 1% loading providing, up to 95% yield at rt). To explore the possibility of intermolecular propargyl alcohol addition to alkyne, mixture of **1a** and alkyne **2a** were employed to react with various gold catalysts. The summarized screening conditions are shown in **Table 1** (see details in ESI).

First, rapid decomposition of the gold catalyst was observed with the mixture of gold and silver salts and only 50% conversion of **1a** was obtained with 5% catalyst loading (PPh<sub>3</sub>AuCl/AgOTf). Silver-free gold catalyst PPh<sub>3</sub>AuNTf<sub>2</sub> gave a slower decomposition rate, reaching a higher conversion of **1a**. However, as discussed above, significant gold-catalyzed **1a** hydration was observed (formation of

enone **5a**) with no desired intermolecular addition product obtained. Solvent screening (CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN, dioxane, toluene, etc.) revealed toluene as the optimal choice because it gave less hydration of **1a**. Notably, furan **6a** was observed under this condition with a very low yield (7%). Screening of primary ligand revealed that XPhos bound gold cation produced more furan **6a** (27%), suggesting that the desired intermolecular addition occurred.

**Table 1.** Screening of gold catalysts.<sup>a</sup>

[Au] cat.	solv (wet)	time	convn of <b>1a</b> (%)	<b>4a</b>	<b>6a</b>	<b>5a</b>	<b>7a</b>
PPh <sub>3</sub> AuCl/AgOTf (5%)	dioxane	6 h	50	0	0	41	39
PPh <sub>3</sub> AuNTf <sub>2</sub> (5%)	dioxane	6 h	83	0	0	72	48
PPh <sub>3</sub> AuNTf <sub>2</sub> (5%)	toluene	12 h	66	0	7	28	65
IPrAuNTf <sub>2</sub> (5%)	toluene	12 h	67	0	6	18	65
XPhosAuNTf <sub>2</sub> (5%)	toluene	12 h	76	0	27	16	85
(ArO) <sub>3</sub> PAuNTf <sub>2</sub> (5%)	toluene	12h	77	0	6	24	60
[(Ph <sub>3</sub> PAu) <sub>3</sub> O] <sup>+</sup> SbF <sub>6</sub> <sup>-</sup> (5%)	toluene	14 h	25	12	trace	<5	<5
[XPhosAu(MeCN)] <sup>+</sup> TfO <sup>-</sup> (5%)	toluene	14 h	70	25	20	25	25
[XPhosAu(TA-H)] <sup>+</sup> TfO <sup>-</sup> (5%)	toluene	14 h	100	55	18	<5	<5
[XPhosAu(TA-Me)] <sup>+</sup> TfO <sup>-</sup> (5%)	toluene	14 h	82	77	0	0	25
[XPhosAu(TA-Me)] <sup>+</sup> TfO <sup>-</sup> (1% ( <b>2a</b> , 1.8 equiv) (45 °C))	toluene	8 h	100	<b>94</b>	0	0	22
other tested metal catalysts (5%), including Pd(OAc) <sub>2</sub> , CuI, Cu(OTf) <sub>2</sub> , PtCl <sub>2</sub> , [Rh(COD)Cl <sub>2</sub> ] <sub>2</sub> , AgOTf, RuCl <sub>3</sub> , all gave no allene.							

<sup>a</sup> Reaction condition: **2a** (0.6 mmol) and catalyst (0.025 mmol) in toluene (0.7 mL) was added to a solution of **1a** (0.5 mmol). See detailed screening conditions in the Electronic Supplementary Information. <sup>1</sup>H-NMR yields by 1,3,5-trimethoxybenzene as internal standard are shown.

The optimal result was obtained using TA-Me modified TA-Au catalyst, although hydration of alkyne **2a** caused the incomplete conversion of **1a**. Increasing the amount of **2a** to 1.8 equivalents led to the complete consumption of **1a**. Finally, with 1% gold loading at 45 °C, the desired allene **4a** was obtained in 94% isolated yield (1.8 equiv of alkyne **4** was generally needed).

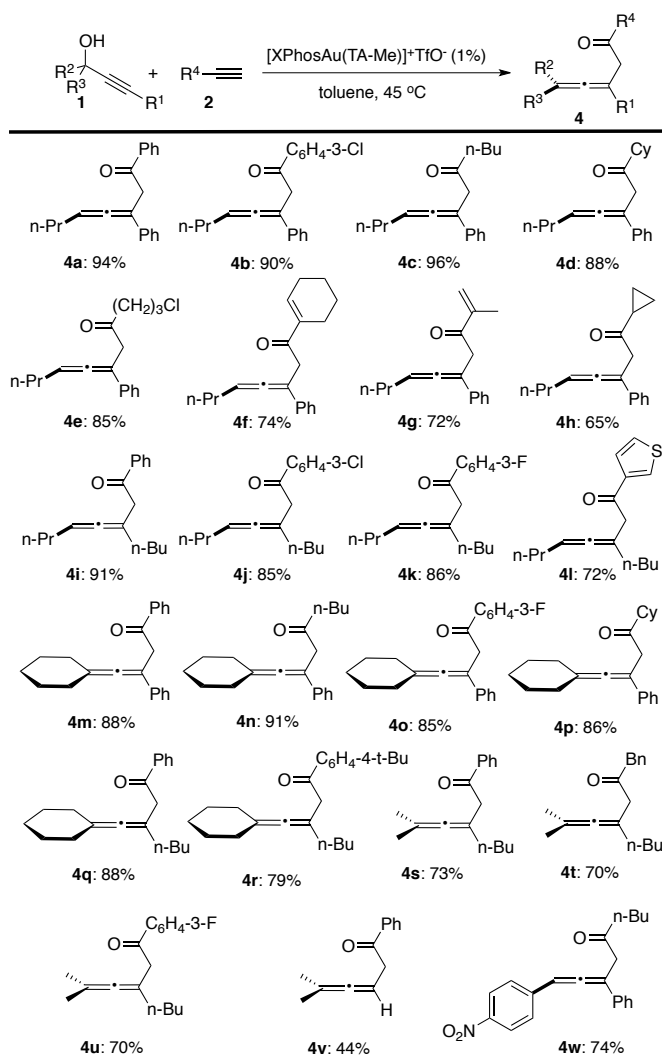
Other metal catalysts have also been tested, such as Pd(II), Ag(I), Cu(I/II), Rh(I) and Ru(III) as well as propionic acid. Allene formation was not observed in those cases (see ESI), which highlighted the superior reactivity of the gold cation toward alkyne activation. With the optimal conditions revealed, we explored the substrate scope. The results are summarized in **Table 2**.

With TA-Au as the catalyst, this new transformation tolerated a large group of substrates. First, the reaction worked well with aromatic alkynes (**4a** and **4b**), aliphatic alkynes (**4c** and **4d**), conjugated 1,3-enyne (**4f** and **4g**) and heteroaromatic alkynes (**4i**), giving the desired allenes in good to excellent yields. Both electron rich (**4r**) and electron deficient (**4k**) aromatic alkynes were suitable substrates. Linear (**4c**) and branched (**4d**) aliphatic alkynes also worked well under this catalytic system even with primary alkyl chloride (a good leaving group, **4e**) worked well. In addition, the reaction tolerated conjugated enynes, giving the highly reactive allenones, which are very challenging building blocks to be synthesized using other methods. Both cases demonstrated good functional group tolerability under mild reaction

condition of this new approach. However, internal alkynes did not give the desired reactions due to the poor reactivity of the alkyne. Applications of harsher conditions (such as higher temperature) lead to the formation of a complex reaction mixture likely caused by the similar reactivity of the two alkynes (hard to differentiate by catalyst).

The reaction scope of propargyl alcohol was also investigated and functional group tolerability was observed.

Table 2. Allene synthesis substrate scope.<sup>a</sup>



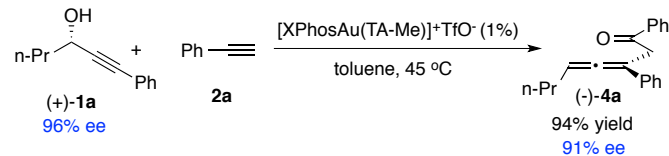
<sup>a</sup> General reaction condition (see detailed in ESI): **2a** (0.9 mmol) and catalyst (0.005 mmol) in toluene (0.7 mL) was added to a solution of **1a** (0.5 mmol) and stirred at 45 °C. Isolated yields are shown.

First, with an aliphatic group at the R<sup>1</sup> position, both secondary (**4i**) and tertiary (**4m**) propargyl alcohols worked well under the standard condition. At the R<sup>2</sup> position, both aliphatic alkyne and aromatic alkyne were suitable. Terminal propargyl alkyne (**4v**) gave lower yield due to the increasing amount of **1v** hydration. Substrates with electron deficient aromatic groups at R<sup>1</sup> position worked well for this transformation (**4w**). However, with phenyl or electron-rich aryl group at the R<sup>2</sup>/R<sup>3</sup> position, complex reaction mixtures are

received with very low yield of allene observed (<15%). This is likely due to the formation of benzylic carbocation, which led to various side reactions. Overall, as successful example of intermolecular propargyl alcohol addition for the one-pot synthesis of allenones, this new method tolerates a good scope of propargyl alcohols and alkynes.

We have previously demonstrated that TA-Au could serve as chemoselective catalyst in promoting propargyl vinyl ether chirality transfer.<sup>14</sup> To validate whether chirality transfer could be achieved under this more challenging intermolecular condition, we prepared (+)-**1a** (96% ee) and submitted it to the reaction condition. To our excitement, more than 95% chirality transfer was achieved (**scheme 2**), which highlighted the enhanced selectivity of TA-Au in this challenging intermolecular reaction cascade.

Scheme 2. Effective chirality transfer with TA-Au.



In conclusion, we report herein the first successful example of intermolecular propargyl alcohol addition to alkyne as a general approach for the synthesis of substituted allenones. This method used simple starting materials and was carried out under mild conditions (1% gold loading) with more than 95% chirality transfer. In contrast, other tested catalysts (gold or other metals) gave almost no desired allene products due to the lack of chemoselectivity and inevitable gold-catalyzed propargyl alcohol hydration side reaction.

We thank the NSF (CHE-1362057) and NSFC (21228204) for financial support.

- (a) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877; (b) A. S. K. Hashmi, *Acc. Chem. Res.*, 2014, **47**, 864; (c) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.*, 2014, **47**, 902; (d) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.*, 2012, **41**, 2448; (e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (f) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (g) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (h) R. A. Widenhoefer, *Chem. Eur. J.*, 2008, **14**, 5382; (i) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (j) A. Fürstner; P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410; (k) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.*, 2007, **46**, 3410. (l) C-F. Xu, M. Xu, L-Q. Yang, C-Y. Li, *J. Org. Chem.*, 2012, **77**, 3010.
- J. H. Teles, S. Brode, M. Chabanas, *Angew Chem. Int. Ed.*, 1998, **37**, 1415.
- (a) C. -Y. Wu, T. Horibe, C. B. Jacobsen, F. D. Toste, *Nature*, 2015, **517**, 449; (b) A. Homs, M. E. Muratore, A. M. Echavarren, *Org. Lett.*, 2015, **17**, 461. (c) K. Ji, Z. Zheng, Z. Wang, L. Zhang, *Angew. Chem. Int. Ed.*, 2015, **54**, 1245; (d) Y. He, H. Wu, F. D. Toste, *Chem. Sci.*, 2015, **6**, 1194; (e) N. V. Borrero, L. G. DeRatt, K. A. Abboud, A. Aponick, *Org. Lett.*, 2015, **17**, 1754; (f) K. Speck, K. Karaghiosoff, T. Magauer, *Org. Lett.*, 2015, **17**, 1982; (g) Z. Wang, Y. Wang, L. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 8887; (h) S. N. Karad, R. -S. Liu, *Angew. Chem. Int. Ed.*, 2014, **53**, 5444; (i) D. Malhotra, M. S. Mashuta, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed.*, 2014, **53**, 4456; (j) J. Carreras, M. Livendahl, P. R. McGonigal, A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2014, **53**,

- 4896; (k) Y. Wang, P. R. McGonigal, B. Herlé, M. Besora, A. M. Echavarren, *J. Am. Chem. Soc.*, 2014, **136**, 801; (l) Malhotra, D.; Mashuta, M. S.; Hammond, G. B.; Xu, B. *Angew. Chem. Int. Ed.*, 2014, **126**, 4545. (m) A. Ghosh, A. Basak, K. Chakrabarty, B. Ghosh, G. Kanti Das, *J. Org. Chem.*, 2014, **79**, 5652; (n) S. Dong, Z. Yao, L. Feng,; P. Daka, H. Wang, Z. Xu, *Org Lett.*, 2014, **16**, 22; (o) M. Kumar, G. B. Mommand, B. Xu, *Org. Lett.*, 2014, **16**, 3452; (p) M. V. Vita, P. Mieville, J. Waser, *Org Lett.*, 2014, **16**, 5768; (q) F. Schroder, T. Coralie, E. Salanouve, H. Clavier, L. Giordano, D. Moraleda, Y. Gimbert, V. Mourise- Mansuy, J- P. Goddard, L. Fensterbank, *Organometallics*, 2014, **33**, 4051; (r) D. Weber, M. R. Gagné, *Chem. Sci.*, 2013, **4**, 335; (s) J. M. Ketcham, B. Biannic, A. Aponick, *Chem. Commun.*, 2013, **49**, 4157; (t) X. Wang, Z. Yao, S. Dong, L. Feng, H. Wang, Z. Xu, *Org Lett.*, 2013, **16**, 2234; (u) W. Rao, M. J. Koh, P. W. H. Chan, *J. Org. Chem.*, 2013, **78**, 3183; (v) J. P. Reeds, A. C. Whitwood, M. P. Healy, I. J. S. Fairlamb, *Organometallics*, 2013, **32**, 3108; (w) D. M. Barber, H. J. Sanganee, D. J. Dixon, *Org. Lett.*, 2012, **14**, 5290; (x) A. Ariafard, E. Asadollah, M. Ostadebrahim, N. A. Rajabi, B. F. Yates, *J. Am. Chem. Soc.*, 2012, **134**, 16882; (y) D. V. Partyka, M. Zeller, A. D. Hunter, T. J. Gray, *Inorg. Chem.*, 2012, **51**, 8394; (z) T. J. Brown, D. Weber, M. R. Gagné, R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2012, **134**, 9134.
4. (a) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 4526; (b) R. L. LaLonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.*, 2007, **129**, 2452; (c) Y. Xi, D. Wang,; X. Ye, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett.*, 2014, **16**, 306.
5. For gold catalyzed hydroxylation see: (a) N. Huguet, A. M. Echavarren, *Top. Organomet. Chem.*, 2013, **43**, 291; (b) C. Obradors, A. M. Echavarren, *Chem. Eur. J.*, 2013, **19**, 3547; (c) L. Adriaenssens, A. Escribano-Cuesta, A. Homs, A. M. Echavarren, P. Ballester, *Eur. J. Org. Chem.*, 2013, **8**, 1494; (d) Y. Xi, B. Dong, X. Shi, *Beilstein J. Org. Chem.*, 2013, **9**, 2537; (e) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (f) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.*, 2004, **126**, 8654.
6. X. Pu, , J. M. Ready, *J. Am. Chem. Soc.*, 2008, **130**, 10874.
7. B. Bolte,; Y. Odabachian, F. Gagosz, *J. Am. Chem. Soc.*, 2010, **132**, 7294.
8. (a) N. Li, T- Y. Wang, L- Z. Gong, L. Zhang, *Chem. Eur. J.*, 2015, **21**, 3585; (b) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.*, 2011, **47**, 6536; (c) A. S. K. Hashmi, T. Wang, S. Shi, M. Rudolph, *J. Org. Chem.*, 2012, **77**, 7761.
9. (a) D. Wang, Y. Zhang, A. Harris, L. N. S. Gautam, X. Shi, *Adv. Synth. Catal.*, 2011, **353**, 2584; (b) R. S. Ramón, S. Gaillard, A. M. Z. Slawin, A. Porta, A. D'Alfonso, G. Zanoni, S. P. Nolan, *Organometallics*, 2010, **29**, 3665; (c) M. N. Pennell, M. G. Unthank, P. Turner, T. D. Sheppard, *J. Org. Chem.*, 2011, **76**, 1479.
10. (a) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 15978; (b) D. V. Vidhani, M. E. Krafft, I. V. Alabugin, *Org. Lett.*, 2013, **15**, 4462. (c) D. Tejedor, G. Méndez-Abt, L. Cotos, F. García-Tellado, *Chem. Soc. Rev.*, 2013, **42**, 458. (d) Z-B Zhu, S. F. Kirsch, *Chem. Commun.*, 2013, **49**, 2272. (e) Q. Wang, S. Aparaj, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett.*, 2012, **14**, 1334.
11. J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, M. A. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 1330.
12. (a) W. Zi, H. Wu, F. D. Toste, *J. Am. Chem. Soc.*, 2015, **137**, 3225; (b) P. Nun, S. Gaillard, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.*, 2010, **46**, 9113; (c) D. Wang, Y. Zhang, R. Cai, X. Shi, *Beilstein J. Org. Chem.*, 2011, **7**, 1014.
13. (a) S. E. Motika, Q. Wang, X. Ye, X. Shi, *Org. Lett.*, 2015, **17**, 290; (b) Y. Xi, Q. Wang, Y. Su, M. Li, X. Shi, *Chem. Commun.*, 2014, **50**, 2158; (c) Y. Su, Y. Zhang, N. G. Akhmedov, J. L. Petersen, X. Shi, *Org. Lett.*, 2014, **16**, 2478; (d) Y. Xi, B. Dong, E. J. McClain, Q. Wang, T. L. Gregg, N. G. Akhmedov, J. L. Petersen, X. Shi, *Angew. Chem. Int. Ed.*, 2014, **53**, 4657; (e) D. Wang, X. Ye, X. Shi, *Org. Lett.*, 2010, **12**, 2088.
14. D. Wang, L. N. S. Gautam, C. Bollinger, A. Harris, M. Li, X. Shi, *Org. Lett.*, 2011, **13**, 2618.