

# 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.

## Ni(II)-catalyzed dehydrative alkyneylation of unactivated (hetero)aryl C–H bonds using oxygen: an user-friendly approach

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

Yan-Hua Liu, Yue-Jin Liu, Sheng-Yi Yan and Bing-Feng Shi

DOI: 10.1039/x0xx00000x

www.rsc.org/

A Ni(II)-catalyzed dehydrative alkyneylation of unactivated C(sp<sup>2</sup>)-H bonds with terminal alkynes under atmospheric pressure of oxygen was developed. This reaction features the use of catalytic amount of nickel as catalyst and O<sub>2</sub> as the sole oxidant, providing an user-friendly approach to the synthesis of aryl alkynes.

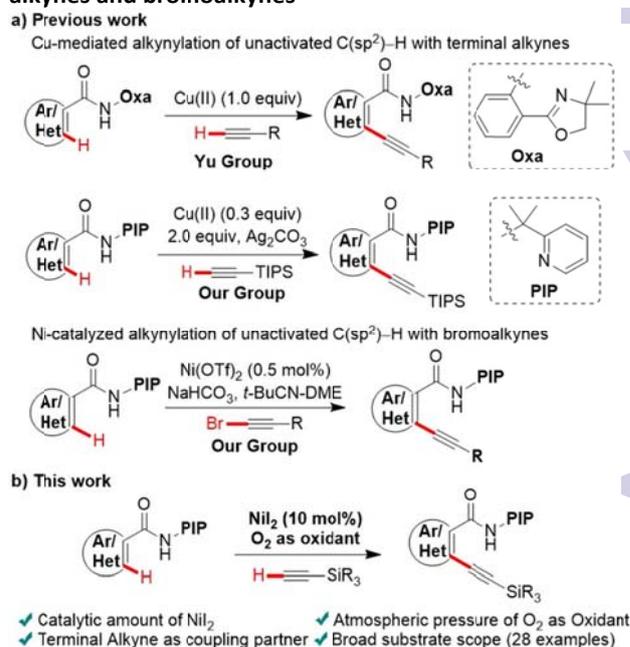
Aryl alkynes represent an important class of structural motifs because of their innate functional significance in biochemistry, material sciences and their versatility as key building blocks in organic synthesis.<sup>1</sup> Consequently, the development of efficient methods for the synthesis of aryl alkynes is of particular interest. The Sonogashira cross-coupling reaction between aryl halides/pseudohalides with terminal alkynes has proven to be one of the most valuable transformations for the synthesis of these compounds.<sup>2</sup> Over the past few years, the “inverse Sonogashira coupling” of C(sp<sup>2</sup>)-H bonds with alkynyl halides or hypervalent iodine reagents has witnessed a rapid development.<sup>3,4</sup> Although efficient and powerful, these alkyneylation protocols still required the prefunctionalization of at least one coupling partners. From the viewpoint of atom- and step-economy, the direct dehydrogenative alkyneylation of (hetero)arenes with terminal alkynes would be more desirable and straightforward.<sup>5</sup> Since 2009, Au(I),<sup>6</sup> Cu(II),<sup>7</sup> Pd(II)<sup>8</sup> and Ni(II)<sup>9</sup>-mediated oxidative alkyneylation of electronically activated arenes with terminal alkynes have been disclosed by Nevado, Li, Su, Muria and Chang. However, these transformations are limited to the use of electron biased arenes that containing acidic C–H bonds or electron-rich heteroarenes. Moreover, the catalytic systems are complicated with the use of excess of additives, expensive ligands or metallic oxidants.

More recently, Yu<sup>10</sup> and our group<sup>11</sup> demonstrated Cu(II)-promoted alkyneylation of unactivated C(sp<sup>2</sup>)-H with terminal alkynes assisted by amide-oxazoline and PIP (2-pyridinyl isopropyl) directing groups independently (Scheme 1a).<sup>12,13</sup>

Department of Chemistry, Zhejiang University, Hangzhou, 310027, China

† Electronic Supplementary Information (ESI) available: Experimental details, X-ray for **3a**, and characterization data for new compounds. See DOI: 10.1039/x0xx00000x

### Scheme 1. Cheap-metal-catalyzed dehydrative alkyneylation of unactivated C(sp<sup>2</sup>)-H bonds with terminal alkynes and bromoalkynes



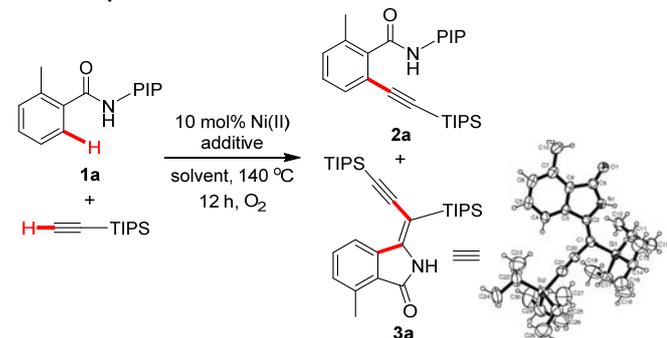
However, stoichiometric amount of transition-metals (silver or copper salt), acting either as co-oxidants or co-catalysts, were required in both cases to enhance the reactivity and inhibit the formation of undesired Hay/Glaser-type alkyne homocoupling products. Considering the prevalent, inexpensive, environmentally benign attributes of O<sub>2</sub>, it would be highly desirable to use atmospheric pressure of molecular oxygen as the sole oxidant and H-acceptor.<sup>14</sup> However, dehydrative alkyneylation of C–H bonds with terminal alkynes using oxygen remains elusive, because several fundamental challenges, such as the homocoupling of alkynes,<sup>15</sup> the tandem annulation and the intramolecular aminoalkynylation of the alkynylated products<sup>17</sup> ought to be overcome.

Inspired by our recent work on Ni(II)-catalyzed alkyneylation of (hetero)arenes with bromoalkynes under a sustainable

simple catalytic system (Scheme 1a)<sup>4a</sup> along with previous successes on other type of oxidative coupling reactions using oxygen,<sup>14</sup> we anticipated that Ni(II) possesses the potential to catalyze the dehydrogenative alkylation using O<sub>2</sub> as the sole oxidant.<sup>18,19</sup> Herein, we communicate these results; and it is worth noting that a broad range of substrates including heterocycle substrates, are compatible with this protocol.

We initiated our investigation with applying the modified conditions previously established for Ni-catalyzed C–H alkylation with bromoalkynes.<sup>4a</sup> However, the alkylnated product **2a** was only obtained in 10% yield (Table 1, entry 1). Subsequent evaluation of Ni(II) catalysts revealed that NiI<sub>2</sub> was the best providing **2a** in 37% yield (entry 4).<sup>17</sup> When *t*-BuCN was used as solvent, the overall conversion was improved to 44%, however, with the formation of 6% of **3a** (entry 5).<sup>20</sup> Compound **3a** was derived from **2a** by a domino the intramolecular aminoalkynylation of **2a** followed by the cleavage of the tertiary N–C bond to release the PIP group.<sup>17</sup> Further optimization study indicated the use of weak bases, such as KH<sub>2</sub>PO<sub>4</sub> and NaHCO<sub>3</sub>, can improved the conversion; nevertheless, the yield of **3a** was promoted simultaneously (entries 6 and 7). We found that the use of less equivalent of alkyne could significantly suppress the side reaction (entry 8). To our surprise, the alkylation proceeded well without any ligand and base additives (entries 9 and 10), rendering this protocol more appealing and user-friendly. We were pleased

**Table 1. Optimization of the reaction conditions<sup>a</sup>**

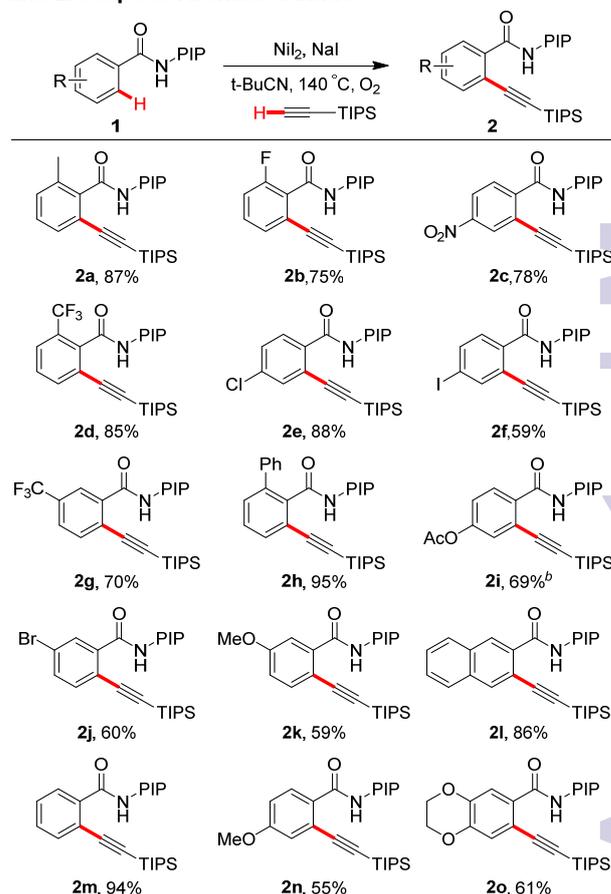


entry	Ni(II)	<b>1a</b> (equiv)	alkyne (equiv)	solvent	additive	yield(%) <sup>b</sup> <b>2a/3a</b>
1 <sup>c</sup>	Ni(OTf) <sub>2</sub>	1.0	1.5	<i>n</i> -PrCN	Na <sub>2</sub> CO <sub>3</sub>	10/0
2 <sup>c</sup>	Ni(acac) <sub>2</sub>	1.0	1.5	<i>n</i> -PrCN	Na <sub>2</sub> CO <sub>3</sub>	18/0
3 <sup>c</sup>	Ni(OAc) <sub>2</sub>	1.0	1.5	<i>n</i> -PrCN	Na <sub>2</sub> CO <sub>3</sub>	19/0
4 <sup>c</sup>	NiI <sub>2</sub>	1.0	1.5	<i>n</i> -PrCN	Na <sub>2</sub> CO <sub>3</sub>	37/0
5 <sup>c</sup>	NiI <sub>2</sub>	1.0	1.5	<i>t</i> -BuCN	Na <sub>2</sub> CO <sub>3</sub>	38/6
6 <sup>c</sup>	NiI <sub>2</sub>	1.0	1.5	<i>t</i> -BuCN	KH <sub>2</sub> PO <sub>4</sub>	47/20
7 <sup>c</sup>	NiI <sub>2</sub>	1.0	1.5	<i>t</i> -BuCN	NaHCO <sub>3</sub>	41/17
8 <sup>c</sup>	NiI <sub>2</sub>	1.0	1.0	<i>t</i> -BuCN	NaHCO <sub>3</sub>	38/4
9	NiI <sub>2</sub>	1.0	1.0	<i>t</i> -BuCN	NaHCO <sub>3</sub>	53/6
10	NiI <sub>2</sub>	1.0	1.0	<i>t</i> -BuCN	---	52/6
11	NiI <sub>2</sub>	1.5	1.0	<i>t</i> -BuCN	---	73/6
12 <sup>d</sup>	NiI <sub>2</sub>	1.5	1.0	<i>t</i> -BuCN	Nal	87 <sup>e</sup> /trace

<sup>a</sup>Reaction conditions: Ni(II) (10 mol%), additive (2.0 equiv), 1 atm O<sub>2</sub> in 0.5 mL solvent at 140 °C for 12 h. <sup>b</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixtures using CH<sub>2</sub>Br<sub>2</sub> as internal standard. <sup>c</sup>With 0.2 equiv DME. <sup>d</sup>With 1.0 equiv Nal. <sup>e</sup>Isolated yield. TIPS = triisopropylsilyl.

to find that lowering the amount of alkyne could suppress the undesired reactions as reported previously (entry 11).<sup>21,7a,8e</sup> The yield of **2a** was further improved to 87% with trace of **3a** when 1 equivalent of Nal was used as additive (entry 14). It is worth mentioning that PIP directing group was the optimal under the optimized reaction conditions. Other commonly used amide-type directing groups failed to give the desired alkylation product, while 8-aminoquinolyl only gave product

**Table 2. Scope of Aromatic Amides<sup>a</sup>**



<sup>a</sup>Reaction conditions: **1** (0.15 mmol), alkyne (0.1 mmol), NiI<sub>2</sub> (0.01 mmol), Nal (0.1 mmol), *t*-BuCN (0.5 mL), 140 °C, O<sub>2</sub>, 12 h. Isolated yield. <sup>b</sup>*n*-PrCN as solvent.

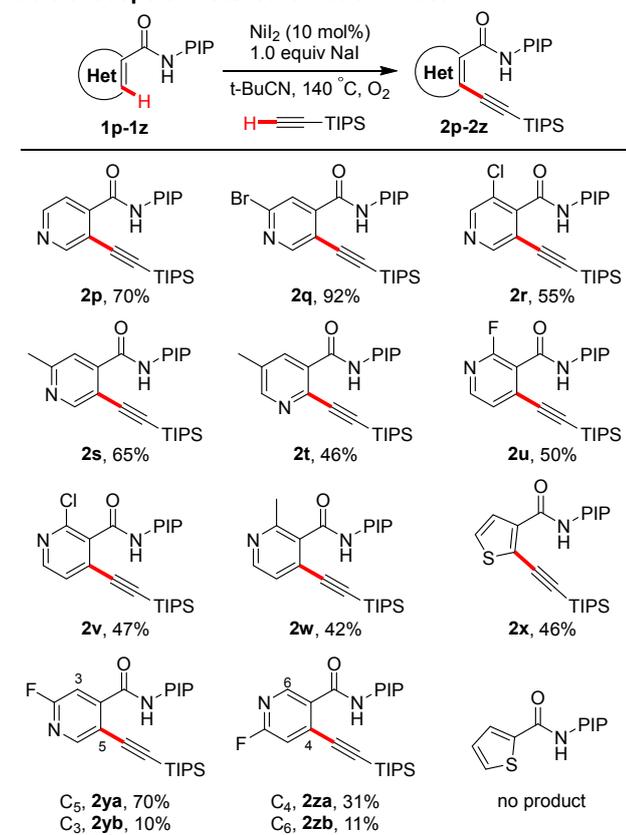
**5** in 37% isolated yield (see the ESI† for details).

With the optimized reaction conditions in hand, we first investigated the scope of benzamides. As shown in Table 2, a wide variety of functionalized benzamides bearing both electron-donating (**2a**, **2h**, **2i**, **2k**, **2n** and **2o**) or electron-withdrawing (**2b-2g** and **2j**) groups were tolerated, furnishing the desired products in moderate to high yields. Gratifyingly, the iodine atom attached to the *para*-position remains intact during the alkylation (**2f**) and no *para*-alkynylated product was detected.

Encouragingly, this catalytic system can also be applied to the heteroaromatic amides, providing the corresponding alkylnated products in synthetically acceptable yields (Table 3). Generally, isonicotinamides (**1p-1s** and **1y**) exhibited superior reactivity than nicotinamides (**1u-1w**, **1z**). For 2-fluoronicotinamide **1z**, the *para*-C–H bond was more reactive than the *ortho*-C–H bond relative to the nitrogen atom (**2za**, 51%

and **2zb**, 11%, respectively). Moreover, thiophene-3-carboxamide **1x** reacted smoothly to give the desired product

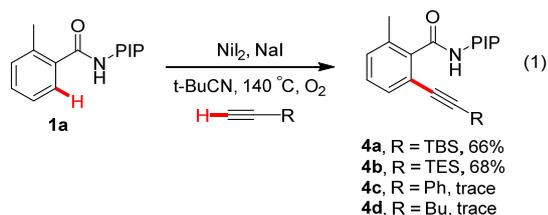
**Table 3. Scope of Heteroaromatic Amides<sup>a</sup>**



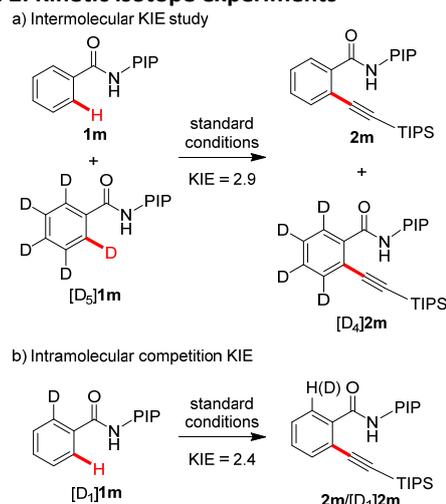
<sup>a</sup>Reaction conditions: alkyne (0.1 mmol), **1** (0.15 mmol), NiI<sub>2</sub> (0.01 mmol), NaI (0.1 mmol), t-BuCN (0.5 mL), 140 °C, O<sub>2</sub>, 18 h. Isolated yield.

**2x** in 46% yield; while thiophene-2-carboxamide turned out to be unreactive under this reaction conditions, probably due to the potential coordination of sulfur atom with nickel catalyst to act as a tridentate ligand.

We also tested the scope of terminal alkynes. As shown in eq 1, the bulky silyl groups are crucial for the success of this reaction. Both TBS-alkyne and TES-alkyne reacted smoothly with benzamide **1a** to give the desired products **4a** and **4b** in moderate yields; while ethynylbenzene and 1-hexyne only gave trace amount of alkynylated products. Although the silyl group is essential for this protocol, we have demonstrated that the PIP and TIPS groups could be successfully removed under mild conditions previously.<sup>11</sup> Given the readily removal of the silyl group and the versatility of the resulting terminal alkynes, we anticipated that synthetic applications via a desilylation/metal-mediated coupling sequence would be feasible.



**Scheme 2. Kinetic isotope experiments**



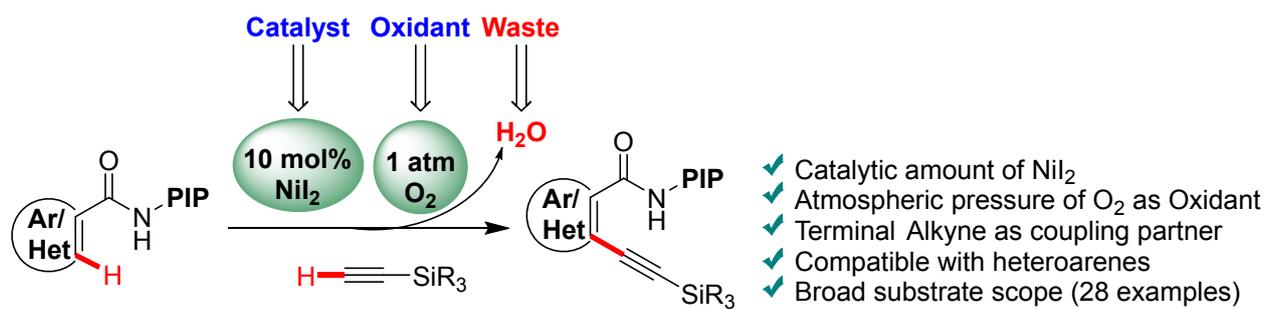
Finally, both inter- and intramolecular kinetic isotope experiments were conducted to elucidate the mechanism, and the KIE values of 2.9 and 2.4 was obtained respectively, indicating that the C–H cleavage might be involved in the rate-determining step (Scheme 2).

In conclusion, we have developed a Ni(II)-catalyzed dehydrogenative alkynylation of unactivated C(sp<sup>2</sup>)–H with terminal alkynes under atmospheric pressure of oxygen. This protocol features the use of catalytic amount of nickel as catalyst and O<sub>2</sub> as the sole oxidant, representing a more straightforward and environment-friendly method to the synthesis of aryl alkynes. Further investigations to expand this catalytic system to other Ni-catalyzed C–H functionalization reactions are currently underway in our laboratory.

## Notes and references

- a) F. Diederich, P. J. Stang, R. R. Tykwinski, *Acetylenes in Chemistry: Chemistry, Biology and Material Science*; Wiley-VCH: Weinheim, 2005; b) L. Anastasia and E. Negishi, *Chem. Rev.*, 2003, **103**, 1979; c) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079; d) C. Liu, H. Zhang, W. S. Li and A.-W. Lei, *Chem. Rev.*, 2011, **111**, 1780; e) J. P. Brand and J. Waser, *Chem. Soc. Rev.*, 2012, **41**, 4165; f) B. Godoi, R. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937; g) C. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783.
- a) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46; b) C. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; c) H. Doucet and J. Cyrille Hierso, *Angew. Chem. Int. Ed.*, 2007, **46**, 834.
- a) Z. Shao and F. Peng, *Angew. Chem. Int. Ed.* 2010, **49**, 9566; b) A. S. Dudnik and V. Gevorgyan, *Angew. Chem. Int. Ed.* 2011, **49**, 2096; c) J. P. Brand and J. Waser, *Chem. Soc. Rev.*, 2012, **41**, 4165.
- For selected examples, see: a) Y.-J. Liu, Y.-H. Liu, S.-Y. Yan and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 6388; b) F. Xie, Z.-S. Qi, S.-J. Yu and X.-W. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780; c) C. Feng and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2011, **50**, 2722; d) C. Feng, D. Feng and T.-P. Loh, *Chem. Commun.*, 2011, 2722.

- 2014, **50**, 9865; e) G. L. Tolnai, S. Ganss, J. P. Brand and J. Waser, *Org. Lett.*, 2013, **15**, 112; f) Y. Ano, M. Tobisu and N. Chatani, *Org. Lett.*, 2012, **14**, 354; g) J. P. Brand and J. Waser, *Org. Lett.*, 2012, **14**, 744; h) T. Kawano, N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2010, **75**, 1764; i) N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 4156; j) M. Tobisu, Y. Ano and N. Chatani, *Org. Lett.*, 2009, **11**, 3250; k) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem. Int. Ed.*, 2009, **48**, 9346; l) I. V. Seregin, V. Ryabova and V. Gevorgyan, *J. Am. Chem. Soc.*, 2007, **129**, 7742.
- 5 For selected reviews, see: a) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* 2014, **53**, 74; b) F. Jia and Z. Li, *Org. Chem. Front.* 2014, **1**, 194; c) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.* 2012, **41**, 3464; d) L. Yang and H. Huang, *Catal. Sci. Technol.* 2012, **2**, 1099; e) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; f) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; For selected examples, see: g) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* 2004, **126**, 11810; h) Z. Li and C.-J. Li, *Org. Lett.* 2004, **6**, 4997; i) M. Chen, X. Zheng, W. Li, J. He and A. Lei, *J. Am. Chem. Soc.* 2010, **132**, 4101; j) C. He, S. Guo, J. Ke, J. Hao, H. Chen and A. Lei, *J. Am. Chem. Soc.* 2012, **134**, 5766; k) J. Ke, C. He, H. Liu, M. Li and A. Lei, *Chem. Commun.* 2013, **49**, 7549; l) M. Gao, C. He, H. Chen, R. Bai, B. Cheng and A. Lei, *Angew. Chem. Int. Ed.* 2013, **52**, 6958.
- 6 T. de-Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512.
- 7 a) Y. Wei, H.-Q. Zhao, J. Kan, W.-P. Su and M.-C. Hong, *J. Am. Chem. Soc.*, 2010, **132**, 2522; b) M. Kitahara, K. Hirano, H. Tsurugi, T. Satoh and M. Miura, *Chem. Eur. J.*, 2010, **16**, 1772.
- 8 a) L. Yang, L. Zhao and C.-J. Li, *Chem. Commun.*, 2010, **46**, 4184; b) S. H. Kim, J. Yoon and S. Chang, *Org. Lett.*, 2011, **13**, 1474; c) F. Shibahara, Y. Dohke and T. Murai, *J. Org. Chem.*, 2012, **77**, 5381; d) S.H. Kim, S. H. Park, S. Chang, *Tetrahedron*, 2012, **68**, 5162; e) X.-M. Jie, Y.-P. Shang, P. Hu and W.-P. Su, *Angew. Chem. Int. Ed.*, 2013, **52**, 3630.
- 9 N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh, and M. Miura, *Org. Lett.*, 2010, **12**, 2358.
- 10 M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 11590.
- 11 Y.-J. Liu, Y.-H. Liu, X.-S. Yin, W.-J. Gu and B.-F. Shi, *Chem. Eur. J.*, 2015, **21**, 205.
- 12 For reviews on metal-catalyzed C–H activation with bidentate auxiliary, see: a) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.* 2013, **52**, 11726; b) B. Zhang, H.-X. Guan, B. Liu and B.-F. Shi, *Chin. J. Org. Chem.* 2014, **34**, 1487; c) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.* 2015, **48**, 1053; d) R. K. Rit, M. R. Yadav, K. Ghosh, A. K. Sahoo, *Tetrahedron*, 2015, DOI: 10.1016/j.tet.2015.03.085; For pioneering study, see: V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* 2005, **127**, 13154.
- 13 a) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang, E. F. Shi, *Chem. Sci.* 2013, **4**, 4187; b) Q. Zhang, K. Chen, W.-H. Rao, Y.-J. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.* 2013, **52**, 13588.
- 14 a) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3381; b) A. N. Campbell and S. S. Stahl, *Acc. Chem. Res.* 2012, **45**, 851; c) W.-Q. Wu and H.-F. Jiang, *Acc. Chem. Res.* 2012, **45**, 1736; d) L. Jin and A. Lei, *Science China Chemistry* 2012, **55**, 2027; e) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329.
- 15 a) W. Yin, C. He, M. Chen, H. Zhang and A. Lei, *Org. Lett.*, 2009, **11**, 709; b) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.
- 16 a) S. Ding, Y. Yan and N. Jiao, *Chem. Commun.* 2013, **49**, 4250; b) J. Dong, F. Wang and J. You, *Org. Lett.*, 2014, **16**, 2884.
- 17 a) J. He, M. Wasa, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 3387; b) S. Nicolai, S. Erard, D. F. González and J. Waser, *Org. Lett.*, 2010, **12**, 384; c) S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem. Int. Ed.*, 2011, **50**, 4680.
- 18 a) Y.-J. Liu, Z.-Z. Zhang, S.-Y. Yan, Y.-H. Liu and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 7899; b) S.-Y. Yan, Y.-J. Liu, B. Liu, Y.-H. Liu, Z.-Z. Zhang and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 7341; c) S.-Y. Yan, Y.-J. Liu, B. Liu, Y.-H. Liu, Z.-Z. Zhang and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 4069.
- 19 For selected recent examples of Ni(II)-catalyzed C–H functionalization, see: a) C. Lin, D.-Y. Li, B.-J. Wang, J.-Z. Yao and Y.H. Zhang, *Org. Lett.*, 2015, **17**, 1328; b) X. Wang, R.-H. Qiu, C.-Y. Yan, V. P. Reddy, L.-Z. Zhu, X.-H. Xu and S.-F. Yin, *Org. Lett.*, 2015, **17**, 1970; c) X.-H. Ye, J. L. Petersen and X.-D. Shi, *Chem. Commun.*, 2015, **51**, 7863; d) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 15509; e) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952; f) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2013, **135**, 5308; g) W.-F. Song, S. Lackner and L. Ackermann, *Angew. Chem. Int. Ed.*, 2014, **53**, 1; h) X.-S. Wu, Y. Zhao and H.-B. Ge, *J. Am. Chem. Soc.*, 2014, **136**, 1789; i) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898. For a representative review, see: j) L. C. M. Castro and N. Chatani, *Chem. Lett.* 2015, **44**, 410.
- 20 CCDC 1062939 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- 21 C. Theunissen and G. Evano, *Org. Lett.*, 2014, **16**, 4488.



A Ni(II)-catalyzed dehydrative alkyne coupling of unactivated C(sp<sup>2</sup>)-H bonds with terminal alkynes under atmospheric pressure of oxygen is described.