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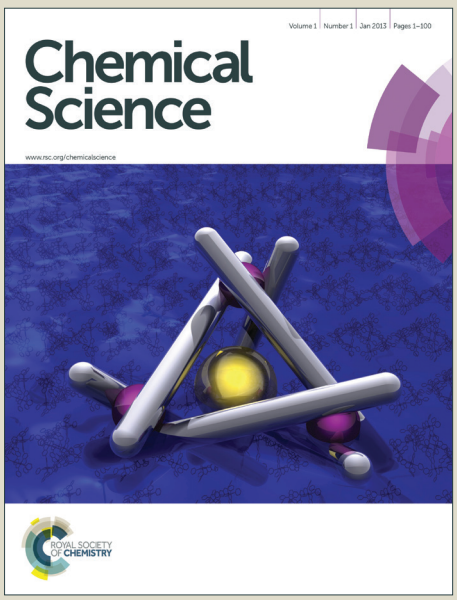

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Modular synthesis of dihydro-isoquinolines: Palladium-catalyzed sequential C(sp^2)–H and C(sp^3)–H bonds activation

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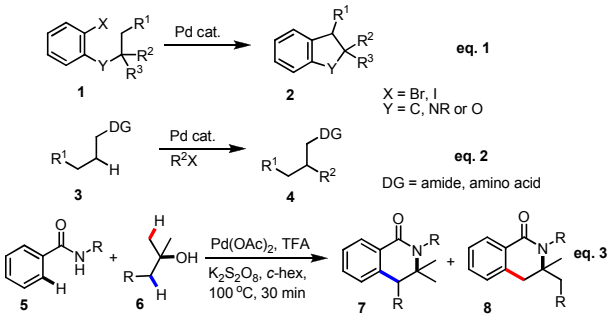
An efficient synthesis of dihydro-isoquinolines *via* Pd–catalyzed double C–H bonds [a C(sp^2)–H and a C(sp^3)–H bond] activation/annulation (CHAA) reaction is presented. This methodology features short reaction time, high atom economy (loss of H_2O only) and the formation of steric less favoured tertiary C–N bond. This fast (30 min) and environmentally benign radical C–H activation approach has demonstrated the potential direction for the future design/development of fast and efficient C–H direct functionalization processes.

Transition metal catalyzed C–H bond activation has become one of the most studied research areas in the last 15 years.[1] The activation of C(sp^2)–H bonds for the syntheses of fuctionalized arenes and alkenes have been further applied in material science and pharmaceutical sciences.[2] However, the reactions on the less reactive C(sp^3)–H bond are still the challenge for synthetic organic chemists. Pioneers like Yu, Guant, Kündig, Baudoin, Shi and Rao *et. al.* in this area mainly have focused on two typical strategies, 1. Pd-induced oxidative addition onto aryl halide followed by intramolecular C(sp^3)–H bond activation to give cyclized product **2** see in **Scheme 1-eq. 1**;[3] 2. Directed C(sp^3)–H bond activation of alkane **3** followed by oxidative addition of aryl or alkyl halide and reductive elimination for the introduction of alkyl or aryl substituents to the system. (**Scheme 1-eq. 2**)[4]



Scheme 1. Direct functionalization of C(sp^3)–H bond.

However, in both of the strategies (**Scheme 1, eq. 1 and eq. 2**), aryl halides or alkyl halides have to be utilized for the direct functionalization of C(sp^3)–H bond. Herein, we report our latest discovery on the first direct double activations of C(sp^2)–H and C(sp^3)–H bonds for the synthesis of dihydro-isoquinolines under radical processes. (**Scheme 1-eq. 3**)

Previously, we have demonstrated a type of C-H activation/annulation reaction for the synthesis of hydroxyl isoindolone *via* Pd(III) or Pd(IV)-catalyzed radical processes.[5] The possible Pd(III) intermediate **9** and Pd(IV) species **10** may be formed during the processes.

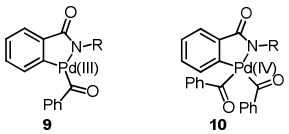


Figure 1. Proposed Pd(III) and Pd(IV) intermediates

Inspired by the proposed reactive intermediates, we envisaged a new pathway for the direct C(sp^2)–C(sp^3) bond construction *via* a sequential C(sp^2)–H and C(sp^3)–H bonds activation. As described in **Scheme 2**, an arene bearing a directing group undergoes a directed C(sp^2)–H activation to give a Pd(II) intermediate **12**, upon the radical addition, one or two aliphatic chain(s) (depends on the oxidation state on Pd centre) could be introduced for the further C(sp^3)–H bond activation analoguous to

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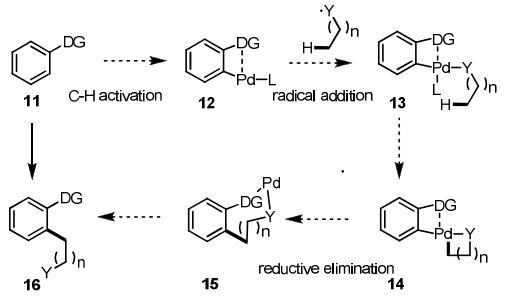
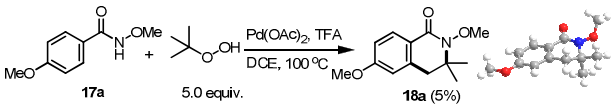
the initial step under CMD processes. After the formation of the bicyclic system the highly reactive Pd(III/IV) species undergoes a reductive elimination to give a medium Pd ring followed by a further reductive elimination or work up to give the final product **16**.



Scheme 2. Proposal on the sequential C(sp^2)–H and C(sp^3)–H bonds activation

With regard to the proof of concept, N-substituted benzamides, acetanilides as well as 2-phenyl pyridines were examined with a variety of radical synthons (possibly formed amide, aldehyde or alcohol radicals) in the combination of radical initiators (AIBN, TBHP *et. al.*), in all cases, either unreacted starting material was recovered or hydrolysis was observed for reactions with benzamides. Even under our reaction conditions we have previously reported for the synthesis hydroxyisoindolones, we did not observe any of the proposed products (either direct coupled product or CHAA product). Interesting, however, when N-methoxyl benzamide **17a**[6] was treated with 5.0 equivalents of tertiary butyl hydrogen peroxide (TBHP) in the presence of $Pd(OAc)_2$ (10 mol%) and 10.0 equivalents of TFA in DCE at 100 °C, our proposed product **18a** was isolated in 5%. The product structure was unambiguously confirmed by the X-ray crystallography. With the proof of concept, we have carried out our preliminary studies using non-substituted benzamide **17b** as the model for the reaction condition evaluations.

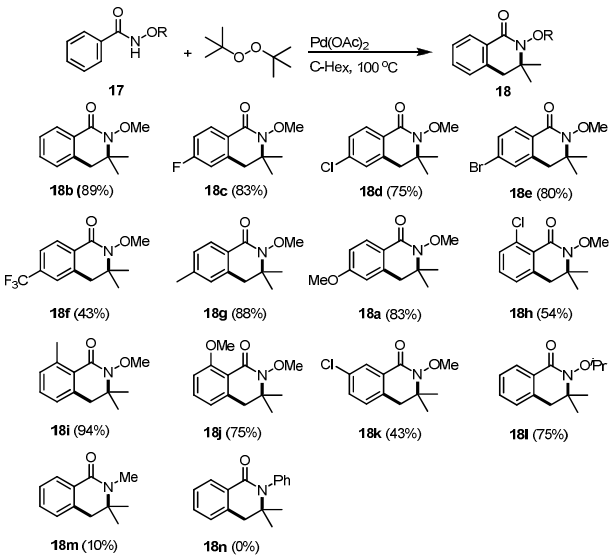


Scheme 3. The synthesis of dihydro-isoquinoline and x-ray structure of **18a**

Based on the preliminary studies, we found that di-*tert*-butyl peroxide (DTBP) was an excellent source for the C–H activations. TFA seemed to be crutial for this type of transfermation in order to make the C(sp^3)–H activation to proceed while other acid or base additives did not provide any of our desired product **18b** during our studies. The reaction condition screening focused on the stoichiometry of acid as well as the screening of the solvents. We found that acid additive is crucial for this transformation, as demonstrated in supporting information **Table 1**, in the presence of 20.0 equivalents of TFA, reactions using AcOH and cyclohexane as the solvents gave the corresponding dihydro-isoquinoline **18b** in 69% and 75% respectively (see supporting information, **Table 1, entries 3 and 4**), prior to DCE which gave rather disappointingly low yield. When THF was chosen as the solvent, no product was isolated. Further increase of the amount of TFA used gave rise to a much high yield and the product was then isolated in 89% yield. The stoichiometry of TFA as the additive was also evaluated and 25 equivalents seemed to be an optimal condition for this transformation (SI, **Table 1, entry 6**). In addition, hexfluorobutyric acid (HFBA) has also shown a good reactivity for the reaction and the desired dihydro-isoquinoline was synthesised in 85% yield (SI, **Table 1, entry 7**).

With the optimal conditions in hands, we have started to evaluate the scope and limitations of this methodology. Both electronic and steric effects on the substituents on the aromatic ring did not affect the reactivity. The corresponding dihydro-isoquinolines were successfully prepared. For the synthesis of dihydro-isoquinoline **18b**, we pleased to find that even under our optimal conditions, the introduction of 3.0 equivalents of benzaldehyde (similar conditions which had been reported previously for the synthesis of hydroxyl isoindolones), our desired product **18b** was isolated in 55% yield together with benzoic acid (27%) and methyl benzoate (18%). Superingly, no hydroxyl isodolone was detected form the ^{1}H NMR of the crude reaction mixture which indicates that our desired reaction is favored than the hydroxyl isoindolone formation processes. Benzamide bearing electron deficient substituents at the *para*-position are good substrates and the corresponding dihydro-isoquinolines **18c**-**18f** were synthesized in good yields. Electron rich benzamides are also tolerated; the products **18g** and **18a** were also facilitated in good yields. Either electron rich or electron deficient substituents at the *ortho*-position would both provide dihydro-isoquinolines **18h**-**18j** in 54-94% yields. Reaction of *meta*-substituted benzamide would give rise to the corresponding product **18k** exclusively in 43% yield which has consistently agreed with the selectivity we have reported previously.[7] In addition, the reaction with *N*-isopropoxy benzamide was also examined isoquinoline **18l** was obtained in 75% yield. The reaction of N-methyl benzamide is also working and the corresponding product **18m** was successfully synthesized albeit with low yield (10%). The low yielding reaction is due to the low reaction conversion as most of the starting material left without being converted onto the dihydro-isoquinoline. Unfortunately, the attempts on the synthesis of N-phenyl dihydro-isoquinoline **18n** failed to provide the desired product.

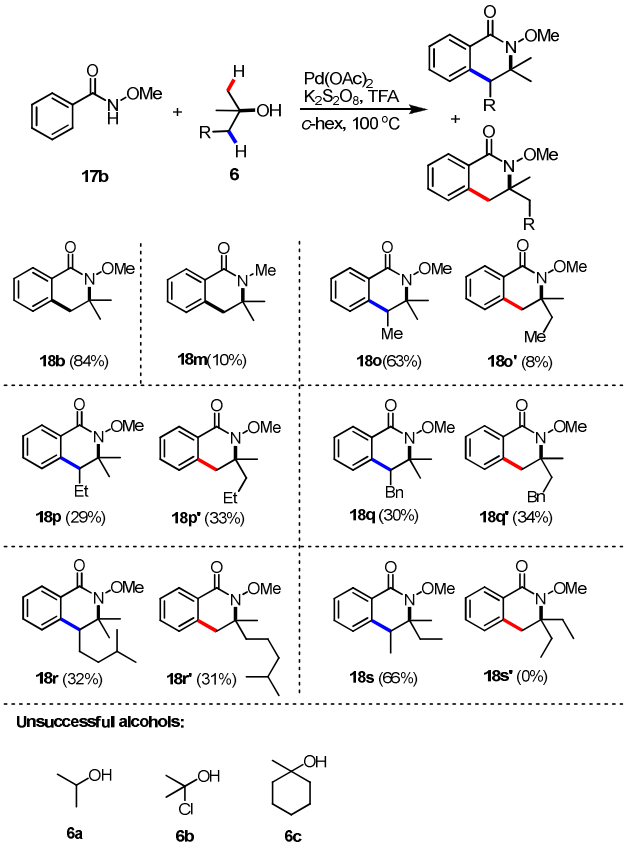
Table 1. Reaction scope on benzamides[a]



[a] Reaction conditions: Benzamide **17** (0.2 mmol), DTBP (0.8 mmol), $Pd(OAc)_2$ (10 mol%), with TFA (25.0 equiv.) at 100 °C in cyclohexane (0.2 M), 30 min.

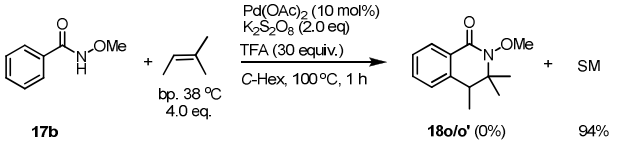
Not only peroxides are efficient coupling partner, we were pleased to find that when inorganic salt $K_2S_2O_8$ was employed as the oxidant for the reaction, product **18b** could be synthesised in similar good yield (84%) comparing to the corresponding reaction with DTBP. The reaction with N-methyl benzamide was also working while the desired N-methyl dihydro-isoquinoline **18m** was isolated in 10% yield together with 88% unreacted starting material. Unsymmetrical tertiary alcohols are also tolerated in the reaction, while the reaction of 1,1-dimethyl propanol with benzamide **17b** gave the two regio-isomers **18o** and **18o'** in 63% and 8% respectively. However, the regioselectivity for the syntheses of **18p** and **18q** seemed very low and the isomers **18p** and **18p'** were isolated in 29% and 33% respectively. Similarly, dihydro-isoquinolines **18o** and **18o'** were formed in a nearly 1:1 ratio. The low regio-selectivity in **18p** and **18q** may due to the steric hindrance balanced with the electronic effect, which had predominantly played crucial role in the good selectivity for the preparation of **18o** and **18o'**. Similar trend was observed when a more hindered alcohol was utilized the corresponding dihydro-isoquinolines **18r** and **18r'** were isolated in 32% and 31% yields. Interestingly, when 3-methylpentan-3-ol was employed, only single regioisomer **18s** was isolated in 66% yield. These results may indicate the later C–H activation if alcohol is more likely to be proceeded at the more substituted carbon centre. Unfortunately, alcohols **6a**-**6c** failed to give the corresponding dihydro-isoquinolines, only background radical hydrolysis product benzoic acid and/or methyl benzoate formation were observed.

Table 2. Reaction scope on the tertiary alcohols[a]



[a] Reaction conditions: Benzamide **17** (0.2 mmol), tertiary alcohol (0.8 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.) with TFA (10 equiv.) at 100 °C in cyclohexane (0.2 M), 30 min.

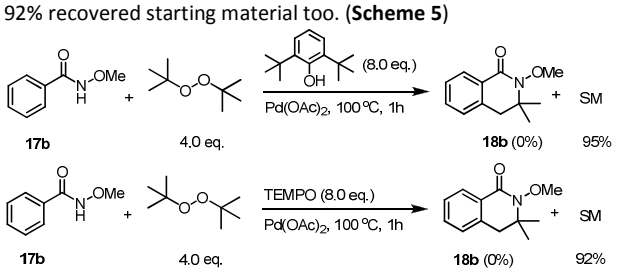
Early this year, Yang has reported the Pd-catalyzed intramolecular tandem aminoalkylation for the activation of C(sp^3)-H bond. An intramolecular cyclization reaction of alkenes for the formation of five membered-lactams have been described.[8] A concern of the product formation could be due to the simple elimination of tertiary alcohol for the generation of alkene which would be further reacted with benzamide in the presence of Pd catalyst. However, under our standard conditions, when alkene was subjected into the reaction, no desired product **18p** was observed, instead only unreacted starting material was recovered in 94% yield after column chromatography. (**Scheme 3**)



Scheme 4. The reaction of benzamide **17b** with alkene

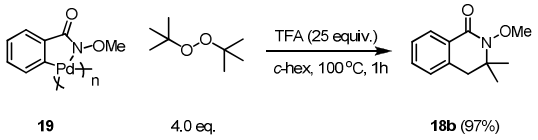
The use of radical scavenger for the reaction was tested; we found that the introduction of 8.0 equivalents of butylated hydroxytoluene (BHT) totally shut down the reactivity. After heating the reaction mixture under standard conditions for one hour, no desired product was observed and only 95% of unreacted starting material was recovered. Unfortunately, the trapping reaction using

TEMPO only gave us a complicated reaction mixture together with 92% recovered starting material too. (**Scheme 5**)



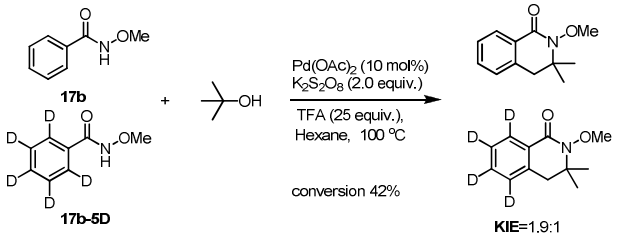
Scheme 5. The reaction with radical scavengers

The reaction using the pre-C–H activated palladacycle **19** was also successful which may indicate that this reaction may undergo C–H activation of directed arene first followed by the second C–H activation of the alkyl group after the addition of the radical to the Pd centre.



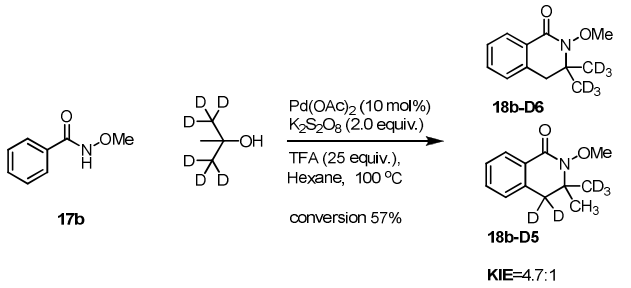
Scheme 6. The control experiment with palladacycle **19**

To have a better understanding of the reaction mechanism, we have set up a competitional KIE studies. The 1:1 mixture of benzamide **17b** with **17b-D5** under our standard conditions give a 1.9:1 mixture of **18b** and **18b-D5** which showed a primary isotope effect which indicates that the C(sp^2)–H activation processes may be involved in the selectivity determining step .



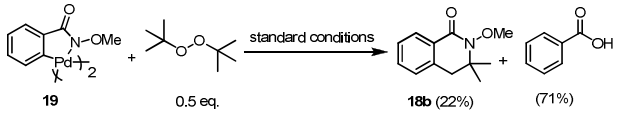
Scheme 7. The intermolecular KIE on the C(sp^2)–H activation processes

Similarly, an intramolecular KIE studies using tert-butanol-D6 were also carried out. A much higher KIE value of 4.7:1 comparing to the KIE value 1.9:1 for *ortho*-C(sp^2)–H activation (**Scheme 7**) was observed which may imply that the C(sp^3)–H activation processes may be involved in the rate determining step.[9] Our KIE value for the C(sp^3)–H activation is comparable with the KIE value of 5.8:1 obtained by Baudoin[10] and Shi's KIE value of 6.2:1[4c] during their studies of C(sp^3)-H activation reactions. Both H/D exchange experiments on benzamide **17b-5D** and *tert*-butanol-D6 did not show H/D scrambling under Pd-catalyzed conditions (see in Supporting Information) unlike Rh- and Ru-catalyzed C–H activation processes which are similar to the discoveries had been discussed previously in our isoquinolone syntheses.[11] The large KIE value has also proved that the activation of *tert*-butanol is likely to be involved in the reaction pathway instead of the reaction with the possible formed alkene during the reaction which has been discussed in **Scheme 4**.



Scheme 8. The intramolecular KIE on the C(sp^3)–H activation

According to our initial proposal as well as the evidences we have collected during the mechanistic studies. We have proposed a plausible reaction mechanism based on the Pd(II)-Pd(IV) cycle for the reaction pathway. The reaction of palladacycle **19** with 1.0 equivalent of tertiary butoxide radical (0.5 equiv. of DTBP) did not provide our desired product in greater than 50% yield (**Scheme 9**) which may indicate the reaction need more radical for the oxidation of Pd(II) species ultimately onto Pd(IV) which may involve in the key reaction mechanism instead of Pd(III) intermediate.



Scheme 9. The reaction of palladacycle **19** with limited radical source

As we have discussed in **Figure 2**, starting from benzamide **17b** for instance, the C(sp^2)–H activation occurred first under acidic conditions to give a palladacycle **A**, (**Figure 2**) Under radical conditions, Pd(IV) species B may form which would give the active precursor **C** after ligand exchange on the *tert*-butanol with trifluoroacetate. The further reaction involved in a CMD process for the activation of a C(sp^3)–H bond to form a bicyclic intermediate **D**. The final product was then formed after a reductive elimination as well as a further elimination of PdO which had also been proposed by Daves during their studies of *syn*-elimination of PdO.[12] The ligand exchange would be beneficial for the regeneration of active Pd(II) species for the next catalytic cycle.

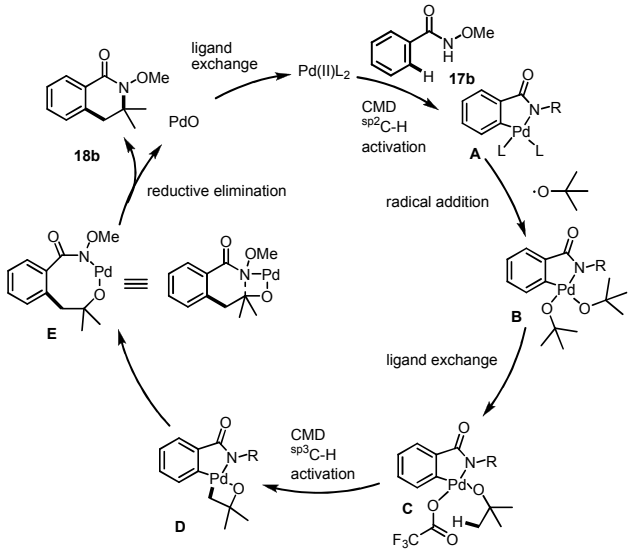


Figure 2. Plausible reaction mechanism

In conclusion, we have reported a novel approach for the synthesis of a series of useful dihydro-isoquinolines *via* sequential C(sp^2)–H and C(sp^3)–H bonds activation of benzamides reacting with tertiary alcohols. These novel radical processes featured 1. *high reactivity*–two intermolecular unactivated C–H bonds were directly functionalized together with a challengeable tertiary amide bond formation; 2. *highly efficiency*–reactions were generally fast, in most of the cases, reactions were completed within 30 minutes; 3. modular synthesis–the heterocyclic ring system were constructed in a clickable fashion. The detailed mechanistic studies are still in progress.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 For selected reviews on C-H activations, see: a) R. H. Crabtree, *Chem. Rev.*， 1985, **85**, 245; b) R. G. Bergman, Nature, 2007, 446, 391-393.c) M. Brookhart, M. L. H. Green, G. Parkin, *Proc. Natl. Acad. Sci. USA*, 2007, 104, 6908-6914;
2 For selected reviews, see: a) N. Kuhl, M. H. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.,* 2012, **51**, 10236-10254; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed*., 2005, **44**, 4442.
3 a) W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, J. Am. Chem. Soc., 2014, 136, 16940-16946; b) K. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.*, 2014, **53**, 11950; c) G. Shan, X. Yang, Y. Zong, Y. Rao, *Angew. Chem*., 2013, **125**, 13851; d) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc*., 2008, **130**, 7190.
4 a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature*, 2014, **510**, 129; b) D. Katayev, E. Larionov, M. Nakanishi, C. Besnard, E. P. Kündig, *Chem. Eur. J*., 2014, **20**, 15021; c) S. Janody, R. Jazzar, A. Comte, P. M. Holstein, J.-P. Vors, M. J. Ford, O. Baudoin, *Chem. Eur. J*., 2014, **20**, 11084; d) J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang, Z.-J. Shi, *Angew. Chem. Int. Ed*., 2014, **53**, 4945; e) T. Saget, N. Cramer, *Angew. Chem. Int. Ed*., 2012, **51**, 12842.
5 Q. Yu, N. Zhang, J. Huang, S. Lu, Y. Zhu, X. Yu, K. Zhao, *Chem. Eur. J*., 2013, **19**, 11184.
6 D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.,* 2008, **130**, 7190.
7 H. Zhong, D. Yang, S. Wang, J. Huang, *Chem. Commun*., 2012, **48**, 3236.
8 W. Du, Q. Gu, Z. Li, D. Yang, *J. Am. Chem. Soc.,* 2015, **137**, 1130.
9 E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed*., 2012, **51**, 3066.
10 M. Chaumontet, R. Piccardi, N. Audic, J. Hitce,J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc*., 2008, **130**, 15157.
11 N. Zhang, B. Li, H. Zhong, J. Huang, *Org. Biomol. Chem*., 2012, **10**, 9429.
12 U. Hacksell, G. D. Daves, *Organometallics*, 1983, **2**, 772.