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

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An efficient synthesis of dihydro-isoquinolines via a Pd-catalyzed double C–H bond (a C(sp\(^2\))–H and a C(sp\(^3\))–H bond) activation/annulation (CHAA) reaction is presented. This methodology features a short reaction time, high atom economy (loss of H\(_2\)O only) and the formation of a sterically 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. The activation of C(sp\(^3\))–H bonds for the syntheses of functionalized arenes and alkynes has been further applied in material science and pharmaceutical sciences. However, the reactions on the less reactive C(sp\(^3\))–H bond are still a challenge for synthetic organic chemists. Pioneers like Yu, Gaunt, Kündig, Baudoin, Shi and Rao et al. in this area have mainly focused on two typical strategies: (1) Pd-induced oxidative addition onto an aryl halide followed by intramolecular C(sp\(^3\))–H bond activation to give cyclized product 2, see Scheme 1-eqn (1); (2) directed C(sp\(^3\))–H bond activation of alkane 3 followed by the oxidative addition of an aryl or alkyl halide and reductive elimination for the introduction of alkyl or aryl substituents into the system (Scheme 1-eqn (2)).

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

Previously, we have demonstrated a type of C–H activation/annulation reaction for the synthesis of hydroxyl isindolones via Pd(II) or Pd(IV)-catalyzed radical processes. The possible Pd(III) intermediate 9 and Pd(IV) species 10 may be formed during the processes (Fig. 1).

Inspired by the proposed reactive intermediates, we envisaged a new pathway for the direct C(sp\(^3\))–C(sp\(^3\)) bond construction via a sequential C(sp\(^3\))–H and C(sp\(^3\))–H bond activation. As described in Scheme 2, an arene bearing a directing group undergoes a directed C(sp\(^3\))–H activation to give a Pd(II) intermediate 12, upon the radical addition, one or two aliphatic chain(s) (depends on the oxidation state of the Pd centre) could be introduced for the further C(sp\(^3\))–H bond activation, analogous to 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 an intermediate Pd ring followed by further reductive elimination or work up to give the final product 16.

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 a combination of radical
cyclohexane as the solvents gave the corresponding dihydro-
transformation, as demonstrated in ESI Table S1. 

focused on the stoichiometry of the acid as well as the screening 
18b acid or base additives did not provide any of our desired product 
in order to make the C(sp3) –H activation proceed while other 
acid or base additives did not provide any of our desired product 
under our optimal conditions, the introduction of 3.0 equiva-
TFA seemed to be crucial for this type of transformation 

Based on the preliminary studies, we found that di-tert-butyl 
peroxide (DTBP) was an excellent source for the C–H ac-
tivations. TFA seemed to be crucial for this type of transformation 
in order to make the C(sp3)–H activation proceed while other 
acid or base additives did not provide any of our desired product 
18b during our studies. The reaction condition screening 
focuses on the stoichiometry of the acid as well as the screening 
of the solvents. We found that the acid additive is crucial for this 
transformation, as demonstrated in ESI Table S1.† In the 
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 ESI, Table 
S1,† entries 3 and 4), prior to DCE which gave a rather disappoin-
tingly low yield. When THF was chosen as the solvent, no 
product was isolated. Further increasing the amount of TFA 
used gave rise to a much higher 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 (ESI, Table S1, entry 6†). In 
addition, hexafluorobutyric acid (HFBA) has also shown a good 
reactivity for the reaction and the desired dihydro-isoquinoline 
was synthesised in 85% yield (ESI, Table S1, entry 7†).

With the optimal conditions in hand, we have started to 
evaluate the scope and limitations of this methodology. Neither 
the electronic nor the steric effects of the substituents on the 

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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 nearly 1 : 1 ratio. The low regioselectivity in 18p and 18q may due to steric hindrance balanced with electronic effects, which had predominantly played crucial roles in the good selectivity for the preparation of 18o and 18o'. A similar trend was observed when a more hindered alcohol was utilized and the corresponding dihydro-isoquinolines 18r and 18r' were isolated in 32% and 31% yields. Interestingly, when 3-methylpentan-3-ol was employed, only a single regioisomer 18s was isolated as a 3 : 2 mixture of 2 diastereoisomers (the relative stereochemistry was not determined). These results may indicate that the later C–H activation of an alcohol is more likely to proceed at the more substituted carbon centre. Unfortunately, alcohols 6a–6c failed to give the corresponding dihydro-isoquinolines, only the background radical hydrolysis products benzoic acid and/or methyl benzoate were formed.

Early this year, Yang has reported the Pd-catalyzed intramolecular tandem aminoalkylation for the activation of C(sp3)–H bonds. An intramolecular cyclization reaction of alkenes for the formation of five-membered-lactams has been described. A concern for the product formation could be the simple elimination of a tertiary alcohol for the generation of an alkene, which would be further reacted with benzamide in the presence of the Pd catalyst. However, under our standard conditions, when an alkene was subjected to the reaction, no desired product 18p was observed, instead only unreacted starting material was recovered in 94% yield after column chromatography (Scheme 4).

The use of a 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 the unreacted starting material was recovered. Unfortunately, the

### Table 1 Reaction scope of the benzamides

| Benzamide | 17 | DTBP (0.8 mmol), Pd(OAc)₂ (10 mol%), with TFA (25.0 equiv.) at 100 °C in cyclohexane (0.2 M), 30 min. |
|-----------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18b (69%) | 18c (83%)       | 18d (75%)                                                                                                                                         |
| 18f (43%) | 18g (88%)       | 18h (83%)                                                                                                                                         |
| 18i (94%) | 18j (75%)       | 18k (43%)                                                                                                                                         |
| 18m (10%) | 18n (0%)        | 18o (80%)                                                                                                                                         |

### Table 2 Reaction scope of the tertiary alcohols

| Tertiary Alcohol | Benzamide 17 (0.2 mmol), TFA (10 equiv.) at 100 °C in cyclohexane (0.2 M), 30 min. |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| 18b (84%)       | 18m(10%)                                                                                                                                         |
| 18o (53%)       | 18r (8%)                                                                                                                                          |
| 18s (32%)       | 18r (31%)                                                                                                                                         |
| 18t (66%)       | 18r (0%)                                                                                                                                          |

### Scheme 4 The reaction of benzamide 17b with an alkene.

### Scheme 5 The reactions with radical scavengers.
trapping reaction using TEMPO gave us a complicated reaction mixture with 92% of the starting material recovered (Scheme 5). 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 the directed arene first followed by a second C–H activation of the alkyl group after the addition of the radical to the Pd centre (Scheme 6).

To have a better understanding of the reaction mechanism, we set up competitive KIE studies. A 1:1 mixture of benzamide 17b with 17b-5D under our standard conditions gave a 1.9:1 mixture of 18b and 18b-D5 which showed a primary isotope effect which indicates that the C(sp2)–H activation processes may be involved in the selectivity determining step.

Similarly, intramolecular KIE studies using tert-butanol-D6 were also carried out. A much higher KIE value of 4.7:1 compared to the KIE value 1.9:1 for ortho-C(sp2)–H activation (Scheme 7) was observed which may imply that the C(sp3)–H activation processes may be involved in the rate determining step.4 Our KIE value for the C(sp3)–H activation is comparable with the KIE value of 5.8:1 obtained by Baudoin10 and Shi’s KIE value of 6.2:1 (ref. 4d) during their studies of C(sp3)–H activation reactions (Scheme 8). 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 the ESI†), unlike in Rh- and Ru-catalyzed C–H activation processes which are similar to the discoveries that have been discussed previously in our isoquinolone syntheses.11 The large KIE value has also proven 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 is shown in Scheme 4.

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(n)–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 that the reaction needs more radicals for the oxidation of the Pd(n) species ultimately into Pd(IV), which may be involved in the key reaction mechanism instead of Pd(III) intermediate.

As we have shown in Fig. 2, starting from benzamide 17b for instance, the C(sp3)–H activation occurred first under acidic conditions to give a palladacycle A, (Fig. 2). Under radical conditions, the Pd(IV) species B may form, which would give the active precursor C after ligand exchange of the tert-butanol with trifluoroacetate. The further reaction is involved in a CMD process for the activation of a C(sp3)–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. The ligand exchange would be beneficial for the regeneration of the active Pd(II) species for the next catalytic cycle.

In conclusion, we have reported a novel approach for the synthesis of a series of useful dihydro-isoquinolines via sequential C(sp²)–H and C(sp³)–H bond 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) high efficiency – reactions were generally fast, in most of the cases reactions were completed within 30 minutes; (3) modular synthesis – the heterocyclic ring systems were constructed in a clickable fashion. Detailed mechanistic studies are still in progress.

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