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Ruthenium-catalyzed, site-selective C–H activation: access to C5-substituted azaflavanone†

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A site-selective ruthenium-catalyzed keto group assisted C–H bond activation of 2-aryl tetrahydroquinoline (azaflavanone) derivatives has been achieved with a variety of alkenes for the first time. A wide range of substrates was utilized for the synthesis of a wide variety of alkenylated azaflavanones. This simple and efficient protocol provides the C5-substituted azaflavanone derivatives in high yields with a broad range of functional group tolerance. Further, the C5-alkenylated products were converted into substituted 2-aryl quinoline derivatives in good yields.

Introduction

The activation and functionalization of the inert C–H bond by metals has been one of the active research thrust areas among organic chemists¹ in recent years. Notably, the directing group assisted C–H bond functionalization has been intensely investigated in the past decades. It is also important to note that the cleavage of the inert C–H bond (110 kcal mol^{−1}) requires harsh conditions. Moreover, the protocol suffers limited substrate scope as well as functional group tolerance. Therefore, C–H bond activation has not yet found widespread importance in organic synthesis. Site-selective C–H activation catalyzed by transition metals is a challenging task in organic chemistry.² Selectivity in C–H functionalization is addressed through the use of a suitable directing group on a substrate where coordination of the metal on a specific site of the substrate controls the outcome of the reaction. However, the use of a directing group strategy suffers from the installation and removal of the directing group, which is an additional synthetic step and can be avoided. Therefore, the utilization of the intrinsic directing group is highly anticipated in C–H activation reactions.

Due to the limitations of the direct C–H functionalization where controlling site selectivity is a major concern for an organic chemist due to the presence of multiple C–H bonds having similar bond dissociation energy and reactivity, we have proposed a substrate controlled strategy where the directing group is a part of the substrate. The site selectivity can be easily controlled due to the coordination ability of the directing group

present in the substrate, which therefore improves the reaction's outcome.

Generally, the synthesis of organic compounds with multi-functional groups is one of the essential thrust areas in the field of synthetic organic chemistry due to their importance in serving as building blocks for the construction of various useful molecules.³ Nitrogen-containing heterocyclic motifs are prominent in many biologically active compounds, pharmaceuticals and materials. 1,2,3,4-Tetrahydroquinolines are important scaffolds due to their excellent pharmacological properties; for example, several tetrahydroquinolines possess potent antimetastatic antitumor effects through inhibition of tubulin polymerization at the colchicine site.⁴ Therefore, several research groups⁵ have shown interest in functionalizing the tetrahydroquinoline scaffold to identify bioactive compounds with

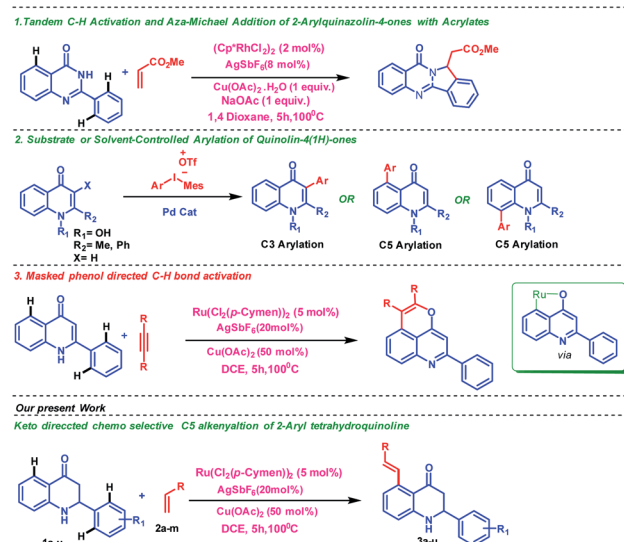


Fig. 1 Comparison between previous reports and our work.

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improved biological activity and interesting material-related properties. Few reports are available in the literature where ketone is utilized as the directing group⁶ despite the presence of a strong coordinating center. Peng group reported tandem C–H activation and aza-Michael addition of 2-arylquinazolin-4-ones with acrylates⁷ while Kumar and coworkers have described Pd-catalyzed regioselective arylation of quinolin-4(1*H*)-ones using diaryliodonium salts as aryl source⁸ (Fig. 1). Bhisma *et al.* showed ketone directed C–H/O–H annulation of 2-arylquinoline with alkynes⁹ where 2-arylquinolinone acts as a masked phenolic (tautomerization) substrate as directing group as shown in Fig. 1. In continuation of our research work¹⁰ in the field of C–H activation, herein, we disclose an interesting keto group directed chemoselective and non-annullable C–H functionalization of 2-aryl tetrahydroquinoline with alkenes. We have successfully achieved a high degree of chemoselectivity where a weak keto group act as an intrinsic directing group than the potent secondary amine thereby providing a good selectivity and reactivity over a variety of substrates with excellent yields (Fig. 1).

To execute our idea, we have chosen 2-phenyl tetrahydroquinoline¹³ **1a** as a model substrate to carry out the C–H activation reaction under various reaction conditions (Table 1 see in ESI†). The 2-phenyl tetrahydroquinoline (**1a**, 0.2 mmol) and methyl acrylate (**2a**, 0.4 mmol) were subjected in the presence of [Ru(*p*-cymene)Cl₂]₂ (5 mol%) as a catalyst, AgSbF₆ as an activator and Cu(OAc)₂ as an oxidant in 1,4-dioxane as solvent which interestingly provided the (*E*)-methyl 3-(4-oxo-2-phenyl-1,2,3,4-tetrahydroquinolin-5-yl)acrylate (**3a**) with 54% yield (entry 1, Table 1 see in ESI†). The product **3a** was confirmed from ¹H NMR, ¹³C NMR spectroscopy and ESI-MS. On the contrary, when the reaction performed in the same reaction condition, except Cu(OAc)₂·H₂O as an oxidant, the desired product **3a** was observed in low yield (entry 2, Table 1 see in ESI†). To increase the yield of the desired product **3a**, we change the solvent system.

In the presence of dichloroethane as a solvent and the same reaction condition, surprisingly, the desired product **3a** was observed in 94% yield. The reaction was performed in different solvent systems/additives/oxidants to attain the optimal reaction condition. However, these reactions condition failed to deliver the desired product **3a** in better yield compared to the previous experiment (entry 1, Tables 4–13 see in ESI†). Based on these studies, we conclude that the optimal reaction condition for the C–H activation reaction of 2-aryl tetrahydroquinoline involves **1a** (1 equiv.), **2a** (2 equiv.), Ru cat. (5 mol%), AgSbF₆ (20 mol%), and Cu(OAc)₂ (50 mol%) in DCE solvent at 100 °C for 5 h.

With this optimal reaction condition in our hand, we started to explore the substrate scope of different alkene for the C–H activation of 2-phenyl tetrahydroquinoline **1a**. The reaction performed well in various alkyl acrylates such as ethyl (**2b**), butyl (**2c**) tertiary butyl (**2d**), benzyl (**2f**) and phenyl acrylate (**2g**) which deliver the alkene coupled 2-phenyl tetrahydroquinoline products (**3b–d**, **f**, **g**) in excellent yields (84–93%). Structure **3b** was further confirmed through single-crystal X-ray analysis,¹² as shown in Fig. 2. Also, we employed branched acrylates like 2-

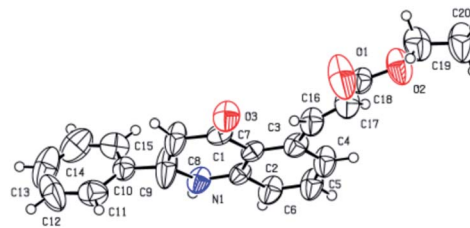
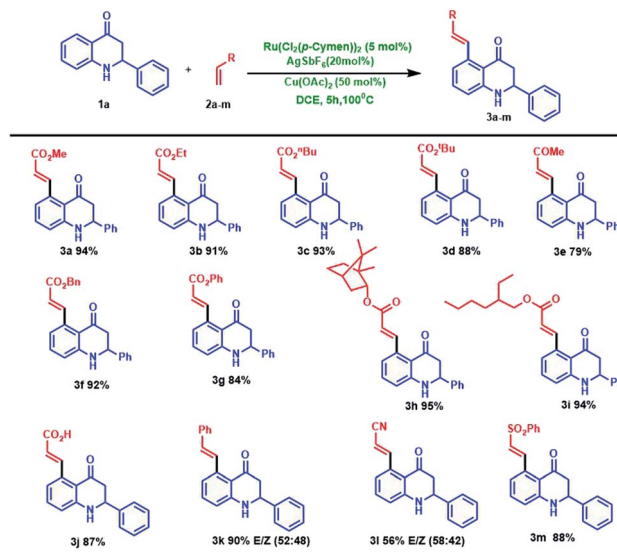


Fig. 2 ORTEP diagram of compound **3b**.¹²

ethyl hexyl (**2h**), norbornyl acrylate (**2i**) for the reaction, which underwent smoothly and leads to C5-coupled products (**3h** and **3i**) in excellent yields (95% and 94% respectively). Additionally, this coupling reaction turned out to be a versatile reaction since employing the reaction of **1a** with methyl vinyl ketone (**2e**) and phenyl vinyl sulfone (**2m**), the selective C5-olefinated products were formed (**3e** and **3m**) in good yields. It is noteworthy that on the treatment of 2-phenyl tetrahydroquinoline **1a** with acrylic acid **2j** under the standard condition, the acrylic acid coupled product (**3j**) was formed in excellent yield (87%). We have also carried out the reaction of styrene (**2k**) with acrylonitrile (**2l**), and we observed that the anticipated products **3k** and **3l** were formed in good yields (90% and 56% with *E/Z* isomer: 52 : 48 and 58 : 42 respectively) (Scheme 1).

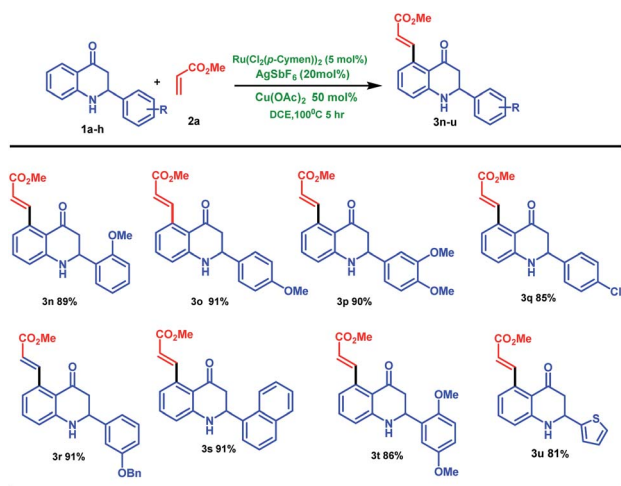
After screening various alkenes, we turned our attention towards the substrate scope of 2-aryl tetrahydroquinoline derivatives (**1b–h**) containing different substitution on the aryl group.

Notably, the highly selective C5-olefinated products (**3n–u**) were formed in excellent yields (85–91%, Scheme 2). We used 2-thiophene substituted tetrahydroquinoline **1i** with methyl acrylate **2a** in the presence of the same reaction condition; the

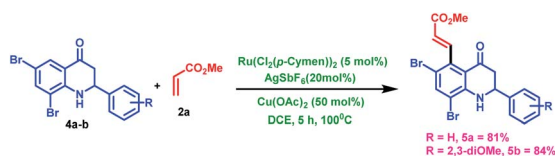


Scheme 1 Screening of various alkenes with 2 phenyl tetrahydroquinoline.^{a, b} Reaction conditions: **1a** (0.2 mmol), **2a–m** (0.4 mmol), [(Ru(*p*-cymene)Cl₂)₂] (5 mol%), Cu(OAc)₂ (50 mol%), AgSbF₆ (20 mol%), DCE solvent at 100 °C, 5 h. ^bIsolated yields.





Scheme 2 Substrate scope of azaflavone derivatives with methyl acrylate.^{a,b} Reaction conditions: **1b-h** (0.2 mmol), **2a** (0.4 mmol), $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ (5 mol%), $\text{Cu}(\text{OAc})_2$ (50 mol%), AgSbF_6 (20 mol%), DCE solvent at 100 °C, 5 h. ^bIsolated yields.



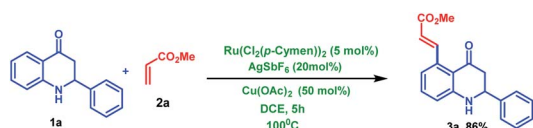
Scheme 3 Substrate scope of C6, C8 dibromo substituted azaflavone with alkene.

desired coupled product **3u** was formed in 81% yield as shown in Scheme 2.

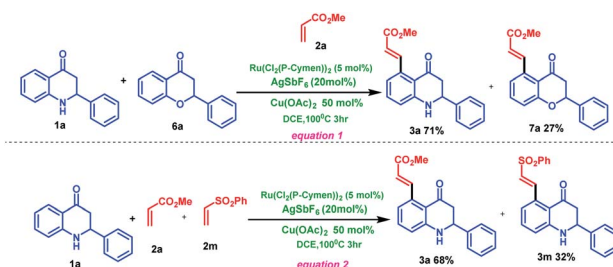
Subsequently, we explored the scope of C6, C8-bromo substituted 2-aryl tetrahydroquinoline (**4a-b**) with methyl acrylate (**2a**) in the presence of optimal reaction condition. In this case, highly selective C5-alkenylated products **5a** and **5b** were obtained selectively in high yields, as shown in Scheme 3. These bromo products (**5a** and **5b**) will be beneficial for further coupling reactions.

It is noteworthy that the reaction was scalable in a standard laboratory set-up, as shown in Scheme 4. The reaction was performed at a one-gram scale at the standard reaction conditions, and the desired product was obtained in 86% yield.

Mechanistic studies toward ruthenium-catalyzed C-H activation of 2-phenyl tetrahydroquinoline **1a** have been performed (Scheme 5). An intermolecular competition experiment between 2-phenyl tetrahydroquinoline (**1a**) and chromanone (**6a**) with methyl acrylate **2a** under standard condition lead to



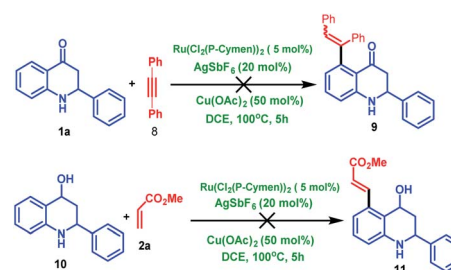
Scheme 4 Gram scale synthesis.



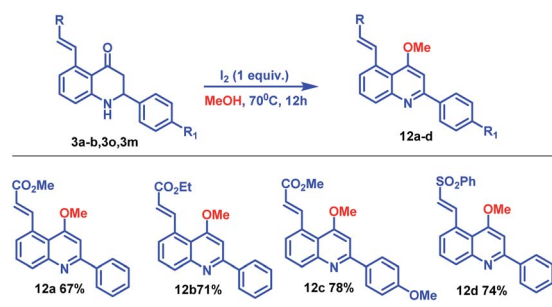
Scheme 5 Competitive reactions.

chromanone coupled product **7a** with 27% yield and tetrahydroquinoline coupled product **3a** with 71% (Scheme 5, eqn (1)). This study cleverly reveals that 2-phenyl tetrahydroquinoline **1a** is more reactive than 2-phenyl chromanone **6a** under standard reaction conditions. On the other hand, intermolecular competitive experiments between different alkenes such as methyl acrylate **2a** and phenyl vinyl sulfone **2m** with 2-phenyl tetrahydroquinoline **1a** were carried out under the standard reaction condition (Scheme 5, eqn (2)). The result indicated that the methyl acrylate coupled product **3a** is obtained in more yield (68%) compared to the phenyl vinyl sulfone coupled product **3m** (32%).

To expand the scope of the reaction further, 2-aryl tetrahydroquinoline was treated **1a** with diphenyl acetylene **8**, which fails to produce C5-coupled product **9**. To identify the carbonyl group's importance, we have carried out a control experiment where we utilized the corresponding alcohol substrate (**10**) under the same reaction condition, which failed to produce the desired C5-coupled product **11**. This observation indicates that

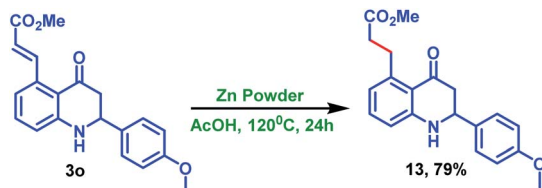


Scheme 6 Control experiment for directing group and alkyne.



Scheme 7 Synthesis of alkyl (*E*)-3-(4-methoxy-2-phenylquinolin-5-yl) acrylate.





Scheme 8 Selective alkene reduction of C5-coupled 2-phenyl tetrahydroquinoline **3o**.

the carbonyl group is very crucial for the C–H activation reaction (Scheme 6).

To probe the synthetic applicability of this newly synthesized C5-coupled 2-aryl tetrahydroquinoline moiety, we performed chemical transformation of C5-coupled azaflavanone (**3**) as shown in Scheme 7.¹⁴ Accordingly, on the treatment of azaflavanone (**3a**, **3b**, **3o**, and **3m**) with iodine (1 equiv.) in the presence of methanol solvent, desired substituted quinoline derivatives (**12a–d**) were obtained in excellent yields (Scheme 7). These quinoline derivatives have great significance in organic synthesis and materials chemistry.

Furthermore, the treatment of **3o** with zinc powder in acetic acid condition successfully afforded the alkene reduced product **13** in a chemoselective manner without reducing the carbonyl moiety, as shown in Scheme 8.

A plausible catalytic cycle for the C–H activation reaction of 2-aryl tetrahydroquinoline is shown in Scheme 9. Active ruthenium complex was generated using $\{\text{Ru}(p\text{-cymene})\text{Cl}_2\}_2$, silver hexafluoroantimonate, and $\text{Cu}(\text{OAc})_2$.^{10a,b,11} After the formation of active ruthenium complex, it coordinates at the C5-position of 2-aryl tetrahydroquinoline **1a** by the elimination of acetic acid. The formation of ruthenacycle **B** occurs through the chelation of Ru with the oxygen atom of the keto group. The migratory insertion of methyl acrylate **2a** into ruthenacycle **B**

leads to the intermediate **C**. Finally, desired C5-alkenylated product **3a** is generated by β -hydride elimination (reductive elimination) from the intermediate **C** and reoxidation by $\text{Cu}(\text{OAc})_2$ regenerate the catalytically active cationic species as shown in Scheme 9.

Conclusion

To conclude, we successfully developed a simple and efficient protocol for the site-selective C5-alkenylation of 2-aryl tetrahydroquinoline derivatives with a wide variety of alkenes *via* C–H bond activation for the first time. A diverse library of C5-alkenylated 2-aryl tetrahydroquinoline derivatives was synthesized using simple reaction conditions in excellent yields. This new protocol provides a facile route for the synthesis of C5-alkenylated 2-aryl tetrahydroquinolines and also serves as a useful tool for further functional group transformations. It is clear from the experimental results that the keto group is acting as a directing group instead of an amine group present in the substrate. Since the azaflavanone are well known for their biological activities, we believe that the newly prepared C5-alkenylated 2-aryl tetrahydroquinolines also have similar biological activities, which will be very interesting to study.

Conflicts of interest

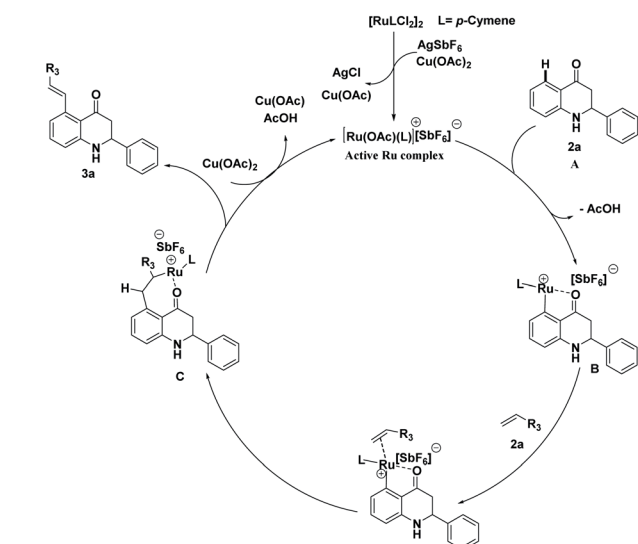
There are no conflicts to declare.

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References

- Selected review; (a) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front.*, 2017, **4**, 1435; (b) D. L. Davies, S. A. Macgregor and C. L. McMullin, *Chem. Rev.*, 2017, **117**, 8649; (c) N. K. Mishra, S. Sharma, J. Park, S. Han and I. S. Kim, *ACS Catal.*, 2017, **7**, 2821; (d) F. Roudesly, J. Oble and G. Poli, *J. Mol. Catal. A: Chem.*, 2017, **426**, 275; (e) Y. Yang, J. Lan and J. You, *Chem. Rev.*, 2017, **117**, 8787; (f) X. S. Xue, P. Zhou, B. Ji and J. P. Cheng, *Chem. Rev.*, 2017, **117**, 8622; (g) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333; (h) S. Agasti, B. Mondal, T. K. Achar, S. K. Sinha, A. S. Suseelan, K. J. Szabo, F. Schoenebeck and D. Maiti, *ACS Catal.*, 2019, **9**, 9606; (i) A. Deb, S. Bag, R. Kancherla and D. Maiti, *J. Am. Chem. Soc.*, 2014, **136**, 13602.
- Selected review; (a) P. Arockiam, C. Bruneau and P. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (b) T. Iwai and M. Sawamura, *ACS Catal.*, 2015, **5**(9), 5031; (c) T. Gensch, M. N. Hopkinson, F. Glorius and W. Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (d) F. Kakiuchi, Y. Tanaka, T. Sato, N. Chatani and S. Murai, *Chem. Lett.*, 1995, 679; (e) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org.*



Scheme 9 Proposed catalytic cycle for the C5-alkenylation of 2-aryl tetrahydroquinoline.



- Chem. Front.*, 2014, **1**, 843; (f) T. W. Lyons and M. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (g) G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450; (h) S. Bag and D. Maiti, *Synthesis*, 2016, **48**, 804–815.
- 3 (a) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447; (b) M. Bakthadoss, J. Srinivasan and R. Selvakumar, *Synthesis*, 2012, **44**, 755; (c) B. H. Rotstein, S. Zaretsky, V. Rai and A. K. Yudin, *Chem. Rev.*, 2014, **114**, 8323; (d) D. Basavaiah, S. Pandiaraju, M. Bakthadoss and K. Muthukumar, *Tetrahedron: Asymmetry*, 1996, **7**, 997; (e) M. Bakthadoss, G. Sivakumar and D. S. Sharada, *Synthesis*, 2013, 237–245; (f) M. Bakthadoss, N. Sivakumar and A. Devaraj, *Tetrahedron Lett.*, 2015, **56**, 4980; (g) A. P. Marcos, P. Clarissa, N. Dayse, M. Buriol and P. MachadoKatritzky, *Chem. Rev.*, 2009, **109**, 4140; (h) M. Bakthadoss and A. Devaraj, *Tetrahedron Lett.*, 2015, **56**, 3954; (i) M. Bakthadoss, D. Kannan and R. Selvakumar, *Chem. Commun.*, 2013, **49**, 10947; (j) P. Wu, A. K. Feldman, A. K. Nugent, *et al.*, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 3928; (k) D. Basavaiah, M. Bakthadoss and G. Jayapal Reddy, *Synth. Commun.*, 2002, **32**, 689; (l) M. Bakthadoss, N. Sivakumar and A. Devaraj, *Synthesis*, 2011, **4**, 0611; (m) H. H. Li, C. Liu, Y. Zhang, Y. Sun, B. Wang and W. Liu, *Org. Lett.*, 2015, **17**, 932; (n) B. M. Trost and J. S. Tracy, *Org. Lett.*, 2017, **19**, 2630; (o) M. Bakthadoss, D. Kannan, N. Sivakumar, P. Malathi and V. Manikandan, *Org. Biomol. Chem.*, 2015, **13**, 5597; (p) M. Bakthadoss and R. Selvakumar, *J. Org. Chem.*, 2016, **81**, 3391.
- 4 (a) A. G. Cole, A. Metzger, M. R. Brescia, L. Y. Qin, K. C. Appell, C. T. Brain, A. Hallett, P. Ganju, A. A. Denholm, J. R. Wareing, *et al.*, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 119; (b) D. S. Su, J. J. Lim, E. Tinney, B. L. Wan, M. B. Young, K. D. Anderson, D. Rudd, V. Munshi, C. Bahnck, P. J. Felock, *et al.*, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5119.
- 5 (a) B. Nammalwar and R. A. Bunce, *Molecules*, 2014, **19**, 204; (b) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031; (c) V. Sridharan, P. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157; (d) M. Muthukrishnan, V. Sridharan and J. C. Menéndez, *Chem. Rev.*, 2019, **119**(8), 5057.
- 6 (a) P. Kishor and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144; (b) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kurama and A. K. Sahoo, *Chem. Commun.*, 2013, **49**, 5225; (c) S. Pradhan, M. Mishra, P. B. De, S. Banerjee and T. Punniyamurthy, *Org. Lett.*, 2020, **22**, 1720; (d) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764.
- 7 X. Jiang, Q. Yang, J. Yuan, Z. Deng, X. Mao, Y. Peng and C. Yu, *Tetrahedron*, 2016, **72**, 1238.
- 8 M. K. Mehra, S. Sharma, K. Rangan and D. Kumar, *Eur. J. Org. Chem.*, 2020, **16**, 2409.
- 9 A. Banerjee, S. K. Santra, P. R. Mohanta and B. K. Patel, *Org. Lett.*, 2015, **17**, 5678.
- 10 (a) M. Bakthadoss, P. V. Kumar and T. S. Reddy, *Eur. J. Org. Chem.*, 2017, 4439; (b) M. Bakthadoss and P. V. Kumar, *Adv. Synth. Catal.*, 2018, **360**, 2650; (c) M. Bakthadoss, P. V. Kumar, R. Kumar and V. Agarwal, *Org. Biomol. Chem.*, 2019, **17**, 4465; (d) M. Bakthadoss, P. V. Kumar, R. Kumar and M. surendar, *New J. Chem.*, 2019, **43**, 14190; (e) A. Murugan, V. N. Babu, A. Polu, N. Sabarinathan, M. Bakthadoss and D. S. Sharada, *J. Org. Chem.*, 2019, **84**, 7796; (f) S. Arepally, V. N. Babu, M. Bakthadoss and D. S. Sharada, *Org. Lett.*, 2017, **19**, 5014.
- 11 (a) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams and C. G. Frost, *ACS Catal.*, 2016, **6**, 5520; (b) R. Das and M. Kapur, *Chem.–Eur. J.*, 2016, **22**, 16986; (c) Q. Z. Zheng, Y. F. Liang, C. Qina and N. Jiao, *Chem. Commun.*, 2013, **49**, 5654; (d) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (e) K. Graczyk, W. Ma and L. Ackermann, *Org. Lett.*, 2012, **16**, 4110; (f) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 2030; (g) M. Selvaraju, Y. L. Wang and C. M. Sun, *Org. Chem. Front.*, 2017, **4**, 1358.
- 12 The structure of the compound **3b** was evidenced by single-crystal XRD analysis. CCDC 2005037 contains the supplementary crystallographic data for this paper.
- 13 S. Chandrasekhar, K. Vijeender and Ch. Sridhar, *Tetrahedron Lett.*, 2007, **48**, 4935.
- 14 M. J. Mphahlele, F. K. Mogamisi, M. Tsanwani, S. M. Hlatshwayoa and R. M. Mampab, *J. Chem. Res.*, 1999, 706.

