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Multicomponent remote C(sp^2)–H bond addition by Ru catalysis: An efficient access to the alkylarylation of 2*H*-imidazoles

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ABSTRACT

Sequential C–H bond addition with two different coupling partners is a powerful method for the rapid and modular construction of complex molecules based on simple starting materials. Herein, an efficient ruthenium-catalysed multicomponent long-range C–H functionalization of 2*H*-imidazoles was developed. This protocol showed good substrate suitability and yielded alkyl arylation products with potential biological activity.

As a multipurpose synthetic method with high atom economy, C–H functionalization of the ubiquitous C–H bond enables various functional couplings catalyzed by transition metals, leading to its wide application in synthetic chemistry [1–5]. Considering the limitation of two-component C–H functionalization, an effective combination with a multicomponent strategy would be highly desirable. Multicomponent reactions (MCRs) provide convenient and comprehensive synthetic routes by assembling various heterocyclic scaffolds from simple starting materials, although they are trapped in the precise regulation of the reaction sequence [6–10].

The most recent primary approach to the modular construction of molecular complexity is the sequential addition of multiple components that forms potential stereo centers and performs various chemical combinations. This efficient transformation occurs in two ways: formation of a new coupling partner from two different coupling partners, followed by C–H functionalization (Scheme 1a, path a) [11–15]. The other way is to extend the reaction by introducing a second different coupling partner after activation of the C–H bond and addition to the first coupling partner (path b) [16–22].

In addition, the 2*H*-imidazole moiety embedded in drugs and active molecules is an important intermediate in synthesis [23–29]. Our group pioneered the use of 2*H*-imidazole as a lead group for performing various annulations in the field of C–H activation [30–32]. In view of this, the elaboration of a modular design approach to increase the complexity of 2*H*-imidazole derivatives is of great research value. Inspired by the above research progress, we have disclosed the Ru-catalyzed multicomponent addition reaction of 2*H*-imidazoles with bromodifluoroacetates *via* an olefin as a bridge with a long C(sp^2)-H bond (Scheme 1b), which provides an efficient approach for the alkyl arylation of *2H*-imidazoles with good substrate compatibility and tolerance to functional groups.

At the beginning of our studies, we investigated the coupling reaction of 2*H*-imidazoles **1a**, 4-methoxystyrene **2a** and bromodifluoroacetates **3a** (Table 1). First, we investigated the ligands required for the reaction, and only in phosphine ligand systems containing strong electron-withdrawing groups could traces of coupling products **4** (entries 1–5) be detected. Considering the importance of ligands for metal catalysts, we prepared a series of ruthenium catalysts with different anionic ligands based on literature reports to screen the reaction conditions (entries 6–8) [33,34], and $Ru(OAc)_2$(*p*-cymene) showed the optimal catalytic activity. Subsequent tests with different alkaline additives showed that potassium carbonate was best suited for this reaction (entries 9–13). Further heating was beneficial for the progress of the reaction, yielding **4aa** and **4aa'** in an overall yield of 76% (entry 14). Increasing the amount of catalyst led to a slight improvement in reaction efficiency (entry 15). In addition, ether solvent and toluene did not show any better effect compared to DCE (entries 16–18). Control experiments showed that ruthenium catalysts

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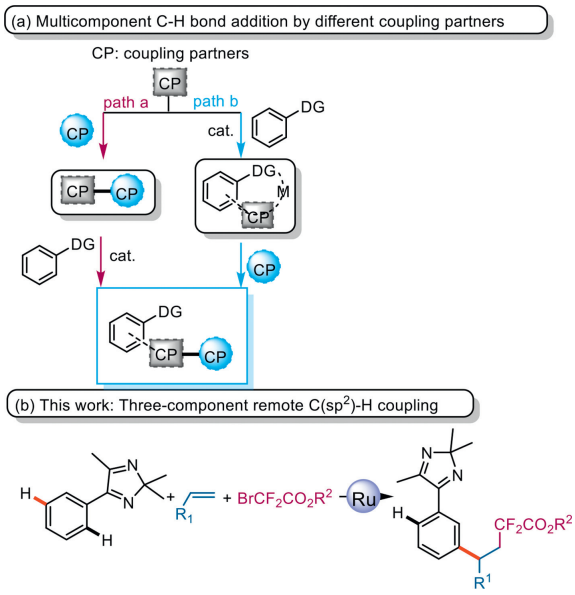
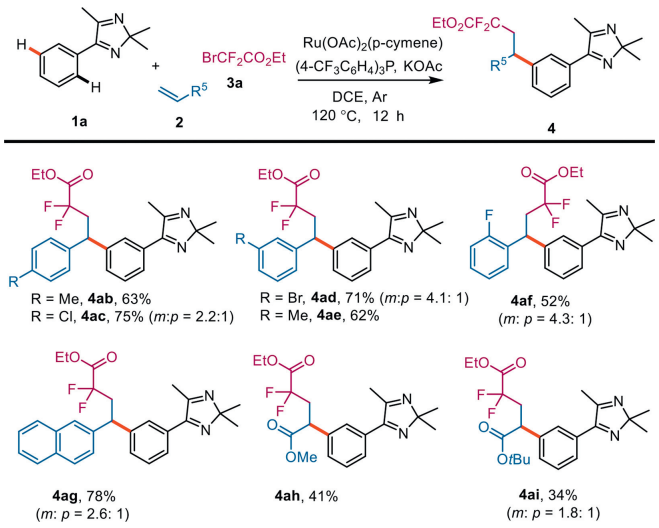


Scheme 1. Multicomponent sequential C–H addition with two different coupling partners in C–H functionalization.



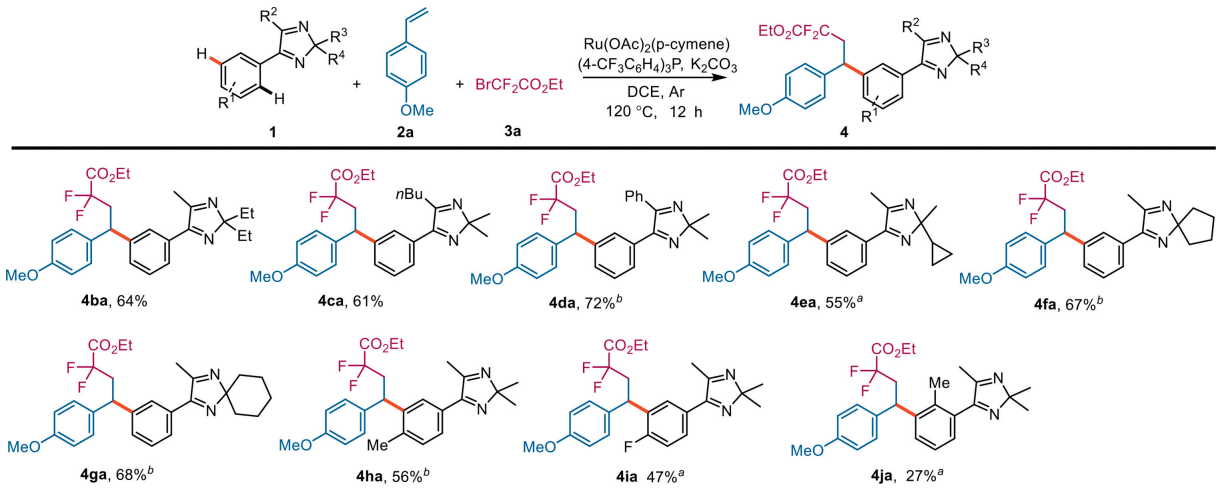
Scheme 3. Substrate scope of olefins **2**. [a] Unless otherwise stated, reaction conditions are as follows: **1a** (0.1 mmol), **2** (0.3 mmol), **3a** (0.3 mmol), [$Ru(OAc)_2$(*p*-cymene)] (5 mol%), P(4-$CF_3C_6H_5)_3$ (0.2 equiv.), KOAc (0.5 equiv.), 120 °C, DCE (1 mL), Ar, 16 h, isolated total yield. Major isomer is shown.

and phosphine ligands were essential for the reaction (entries 19 and 20).

Under the best conditions, we investigated the possibilities of 2*H*-imidazoles for their suitability as three-component coupling products **4** (Scheme 2). The introduction of ethyl, butyl and phenyl substituents had no significant effect on the reaction efficiency and afforded **4ba-4da** in 61%–72% yields. In addition, the cycloalkanes also participated in the reaction and afforded the compounds **4ea-4ga** in 55%–68% yields. The incorporation of electron donating or withdrawing groups in the *para* position of the aromatic ring enabled the conversion of the substrates **1h-1i** into the corresponding products **4ha-4ia** in 47%–56% yields. Unfortunately, the introduction of substituents in the *ortho* position of the aromatic ring led to a significant decrease in reaction efficiency, resulting in the product **4ja** in only 27% yield.

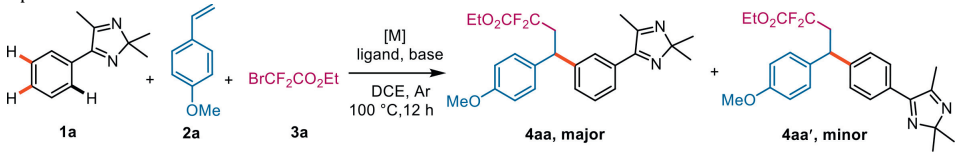
We then turned our attention to the substrate region of the olefins (Scheme 3). By introducing substituents in the *para* or *meta* positions of the aromatic styrene rings, the corresponding compounds **4ab-4ae** can be obtained in good yield. However, the reaction activity of styrene containing fluorine in the *ortho* position was lower, so that the product **4af** was obtained in only 52% yield due to steric hindrance. The positional selectivity of products **4ab** and **4ae** was consistent, as both afforded the single *meta* products, while substrates **2c**, **2d**, and **2f** with electron-withdrawing groups afforded the regional isomers **4ac'**, **4ad'**, and **4af'**, which may be attributed to the influence of electronic effects. The 2-naphthalene-ethylene **2g** was suitable for this transformation and formed the corresponding compounds **4ag** in 78% yield. Taking into account the influence of electronic effects, methyl acrylate **2h** and *tert*–butyl acrylate **2i** showed lower activity in the reaction.

The next step was to test the applicability of the reaction to brominated difluoroalkanes (Scheme 4). Various bromodifluoroacetamides were suitable for this system. Cyclopropyl- and butyl–substituted difluoroacetamides could be readily used for



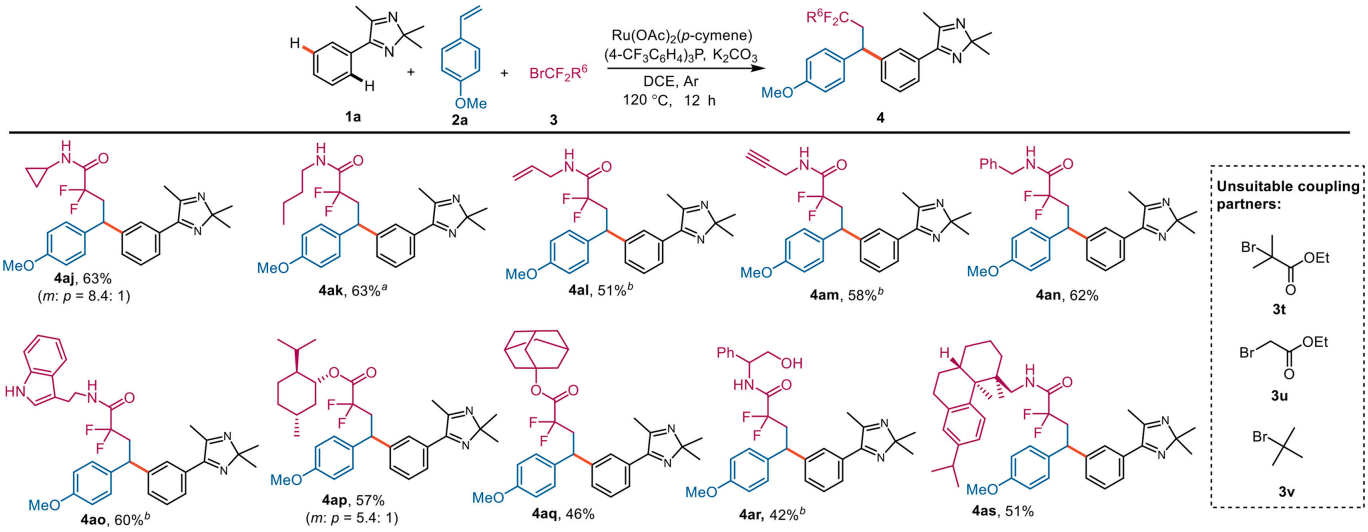
Scheme 2. Substrate scope of 2*H*-imidazoles **1**. Unless otherwise stated, reaction conditions are as follows: Condition A: **1** (0.1 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), [$Ru(OAc)_2$(*p*-cymene)] (5 mol%), P(4-$CF_3C_6H_5)_3$ (0.2 equiv.), K_2CO_3 (2.0 equiv.), 120 °C, DCE (1 mL), Ar, 12 h, isolated total yield. Major isomer is shown. [a] [$Ru(OAc)_2$(*p*-cymene)] (10 mol%). [b] Condition B: **1** (0.1 mmol), **2a** (0.4 mmol), **3a** (0.6 mmol), [$Ru(OAc)_2$(*p*-cymene)] (5 mol%), P(4-$CF_3C_6H_5)_3$ (0.2 equiv.), KOAc (2.0 equiv.), 120 °C, DCE (1 mL), Ar, 18 h, isolated total yield.

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	Ligand	Base	*m*:*p* [b]	Total yields (%)[c]
1	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	K_2CO_3	–	–
2	$[RuCl_2(p\text{-cymene})]_2$	$P(4\text{-}MeC_6H_4)_3$	K_2CO_3	–	–
3	$[RuCl_2(p\text{-cymene})]_2$	$P(4\text{-}FC_6H_4)_3$	K_2CO_3	–	–
4	$[RuCl_2(p\text{-cymene})]_2$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	–	<5%
5	$[RuCl_2(p\text{-cymene})]_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	K_2CO_3	–	trace
6	$[Ru(MesCO_2)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	24
7	$[Ru(AdCO_2)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	11
8	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	58
9	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	Na_2CO_3	10.5: 1	23
10	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	NaOAc	10.5: 1	32
11	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	KOAc	10.5: 1	54
12	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_3PO_4	10.5: 1	26
13	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	KF	–	–
14[d]	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	76
15[d,e]	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	80
16[f]	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	10.5: 1	38
17[g]	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	–	trace
18[h]	$[Ru(OAc)_2(p\text{-cymene})]$	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	–	trace
19[d]	–	$P(4\text{-}CF_3C_6H_4)_3$	K_2CO_3	–	–
20[d]	$[Ru(OAc)_2(p\text{-cymene})]$	–	K_2CO_3	–	–

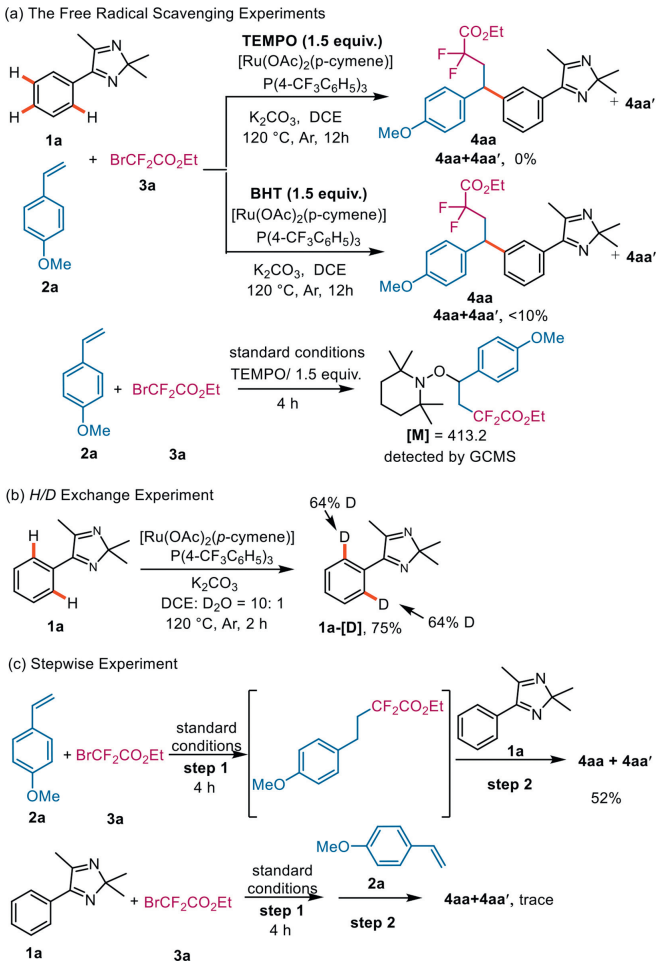
[a] Unless otherwise stated, reaction conditions are as follows: **1a** (0.1 mmol), **2a** (3.0 equiv.), **3a** (3.0 equiv.), catalyst (5 mol%), ligand (0.2 equiv.), base (2.0 equiv.), DCE (1.0 mL), under Ar, 100 °C, 12 h. MTBE = *tert*–butyl methyl ether, DCE = 1,2-dichloroethane.
[b] Detected by ^1H NMR.
[c] Isolated total yields.
[d] 120 °C.
[e] $[Ru(OAc)_2(p\text{-cymene})]$ (10 mol%).
[f] MTBE (1.0 mL).
[g] Dioxane (1.0 mL).
[h] Toluene (1.0 mL).



Scheme 4. Substrate scope of brominated difluoroalkanes **3**. Unless otherwise stated, reaction conditions are as follows: Condition A: **1a** (0.1 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), $[Ru(OAc)_2(p\text{-cymene})]$ (5 mol%), $P(4\text{-}CF_3C_6H_5)_3$ (0.2 equiv.), K_2CO_3 (2.0 equiv.), 120 °C, DCE (1 mL), Ar, 12 h, isolated total yield. Major isomer is shown. [a] $[Ru(OAc)_2(p\text{-cymene})]$ (10 mol%). [b] Condition B: **1** (0.1 mmol), **2a** (0.4 mmol), **3a** (0.6 mmol), $[Ru(OAc)_2(p\text{-cymene})]$ (5 mol%), $P(4\text{-}CF_3C_6H_5)_3$ (0.2 equiv.), KOAc (2.0 equiv.), 120 °C, DCE (1 mL), Ar, 18 h, isolated total yield.

this transformation and gave the compounds **4aj-4ak** in 63% yield. The alkenyl and alkynyl substrates **3l-3m**, which were suitable for further functionalization, were also successfully converted and afforded the corresponding compounds in 51%–58% yields. The benzyl- and tryptamine-substituted coupling partners showed good reactivity and afforded the products **4an** and **4ao** in 60%–62% yields. Inspired by the broad compatibility of the functional groups, the late functionalization of natural products was tested and the complex difluorinated products **4ap-4as** were obtained in 42%–57% yield.

To investigate the reaction mechanism, the radical scavenging experiments were performed with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) (Scheme 5a), which suppressed this catalytic system. Meanwhile,



Scheme 5. Preliminary mechanistic investigation.

without the presence of **1a**, benzyl radicals were generated by the addition of **2a** and **3a** with TEMPO. Subsequently, deuterium-labeling was performed under standard conditions in the absence of **2a** and **3a** (Scheme 5b). Here, 64% deuterium was detected at the two *ortho* positions of the 2*H*-imidazole **1a**. The stepwise experiment showed that styrene and bromodifluoroacetate reacted first in the system (Scheme 5c).

Based on previous studies on Ru metachemistry and experimental results [11–14], a possible mechanism was proposed in Scheme 6. The catalytic cycle starts with a reversible C–H cyclometalation between Ru(II) and 2*H*-imidazole **1a** to form ruthenium complex **I**. Subsequently, benzyl radicals **2a'** are formed by addition of **2a** and **3a** *via* a SET process. The newly formed radical **2a'** completes the C_{Ar}–H bond addition at the *para* or *meta* position to the C–Ru bond and yields intermediates **II** or **II'**, followed by rearomatization to ruthenacycles **III** or **III'**. Finally, the expected three-component coupling products **4aa** and **4aa'** are released by demetallation. At the same time, the active ruthenium(II) is regenerated.

In summary, we have successfully developed a Ru-catalyzed three-component remote C–H functionalization of 2*H*-imidazoles, which provides new ideas for the modular construction of complex 2*H*-imidazole scaffolds. Using radical scavenging experiments, we have shown that the reaction is based on a radical mechanism, and a possible mechanism is presented.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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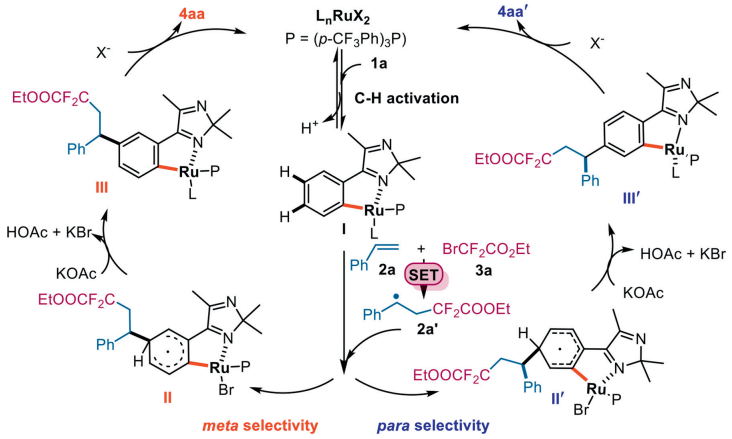
References

[1] J. Wencel-Delord, F. Glorius, Nat. Chem. 5 (2013) 369–375.
[2] T. Cernak, K.D. Dykstra, S. Tyagarajan, et al., Chem. Soc. Rev. 45 (2016) 546–576.
[3] C. Sambiagio, D. Schönbauer, R. Blieck, et al., Chem. Soc. Rev. 47 (2018) 6603–6743.
[4] P. Gandeepan, T. Müller, D. Zell, et al., Chem. Rev. 119 (2019) 2192–2452.
[5] X.L. Han, P.P. Lin, Q. Li, Chin. Chem. Lett. 30 (2019) 1495–1502.
[6] H.P. Wan, L. Gan, Y. Liu, Org. Biomol. Chem. 15 (2017) 9031–9043.
[7] J.S. Zhang, L. Liu, T. Chen, et al., Chem. Asian J. 13 (2018) 227–229.
[8] T. Shilpa, R. Dhanya, S. Saranya, et al., ChemistrySelect 5 (2020) 898–915.
[9] G.S. Susan Treesa, M. Neetha, S. Saranya, et al., ChemistrySelect 5 (2020) 7400–7416.
[10] D.S. Brandes, J.A. Ellman, Chem. Soc. Rev. 51 (2022) 6738–6756.
[11] X.G. Wang, Y. Li, H.C. Liu, et al., J. Am. Chem. Soc. 141 (2019) 13914–13922.
[12] W.Y. Shi, Y.N. Ding, C. Liu, et al., Chem. Commun. 56 (2020) 12729–12732.
[13] Y.Y. Luan, X.Y. Gou, W.Y. Shi, et al., Org. Lett. 24 (2022) 1136–1140.
[14] H.C. Liu, X.P. Gong, Y.Z. Wang, et al., Org. Lett. 24 (2022) 3043–3047.
[15] J. Wu, W. Wei, J. Pöhlmann, et al., Angew. Chem. Int. Ed. 62 (2023) 202219319.
[16] J.A. Boerth, S. Maity, S.K. Williams, et al., Nat. Catal. 1 (2018) 673–679.
[17] T. Pinkert, T. Wegner, S. Mondal, et al., Angew. Chem. Int. Ed. 58 (2019) 15041–15045.
[18] S. Maity, T.J. Potter, J.A. Ellman, Nat. Catal. 2 (2019) 756–762.



Scheme 6. Possible reaction mechanism.

[19] A.G. Herraiz, N. Cramer, ACS Catal. 11 (2021) 11938–11944.
[20] R. Mi, X. Zhang, J. Wang, et al., ACS Catal. 11 (2021) 6692–6697.
[21] T. Pinkert, M. Das, M.L. Schrader, et al., J. Am. Chem. Soc. 143 (2021) 7648–7654.
[22] S. Dongbang, J.A. Ellman, Angew. Chem. Int. Ed. 60 (2021) 2135–2139.
[23] A. Mumtaz, A. Saeed, N. Fatima, et al., Bangladesh J. Pharmacol. 11 (2016) 756–764.
[24] I. Ali, M.N. Lonea, H.Y. Aboul-Enein, Med. Chem. Commun. 8 (2017) 1742–1773.
[25] N. Shalmali, M.R. Ali, S. Bawa, Mini-Rev. Med. Chem. 1 (2018) 142–163.
[26] N. Rani, P. Kumar, R. Singh, et al., Curr Top. Med. Chem. 11 (2020) 1130–1155.
[27] E.L. Gerasimova, E.R. Gazizullina, M.V. Borisova, et al., Molecules 26 (2021) 6534–6552.
[28] F. Hu, L. Zhang, K.S. Nandakumar, et al., Curr Top. Med. Chem. 21 (2021) 2514–2528.
[29] S. Rulhaniaa, S. Kumar, B. Nehraa, et al., J. Mol. Struct. 1232 (2021) 129982.
[30] X.L. Wu, L. Dong, Org. Lett. 20 (2018) 6990–6993.
[31] Y. Luo, H. Liu, J. Zhang, et al., Org. Lett. 22 (2020) 7604–7608.
[32] Y. Luo, H.Y. Zhou, Y.C. Gang, et al., Org. Lett. 24 (2022) 6940–6944.
[33] L. Ackermann, R. Vicente, H.K. Potukuchi, et al., Org. Lett. 12 (2010) 5032–5035.
[34] J. Zhang, R. Shrestha, J.F. Hartwig, et al., Nat. Chem. 8 (2016) 1144–1151.