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Transition Metal-Free Approach for the Late-Stage Benzylic C(sp³)–H Etherifications and Esterifications

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Herein, we report a transition metal-free approach for the regioselective functionalisation of benzylic C(sp³)-H bonds using alcohols and carboxylic acids as the nucleophiles. This approach provides a straightforward route for the synthesis of various benzylic ethers and esters to provide a wide generality of this system. Expediently, twelve pharmaceutically relevant compounds have been synthesized using this strategy.

Late-stage functionalization (LSF) of natural products and drug molecules provides an efficient and straightforward route to access valuable molecules.[1] With the state-of-art toolbox such as photoredox catalysis and electrocatalysis, specific C–H bonds have been addressed regioselectively for the formation of C–O, C–N, C–F, and C–C bonds with high atom-economy, thus, speeding up the process of drug discovery.[2] It has been reported that the benzylic C–H bonds commonly exist in bioactive compounds and about 25% of the top-selling pharmaceuticals contain this structural motif.[3] Moreover, the recent booming of LSF reactions at benzylic C–H bonds has been also reflected in the rapid development of drug discovery.[4] The low bond strength of the benzylic C–H bonds instigates towards gaining high site selectivity in complex molecules and that should bring enhanced metabolism and pharmacokinetic properties in the existing drug molecules.[5]

Indeed, with these efforts, direct halogenations,[6] oxidations,[7] and hydroxylations[8] have been developed with remarkable success. Additionally, the recent surge in challenging late-stage etherifications via the functionalization of C–H bonds and using alcohols as the coupling partner is highly noteworthy.[9] For example, Yoon *et al.* have developed an excellent benzylic C(sp³)–H etherification via Ir-based photoredox catalysis combined with stoichiometric copper oxidant.[9a] Most recently, Stahl *et al.* discovered the copper–catalyzed benzylic C(sp³)–H coupling with alcohols to form a wide range of benzylic ethers including complex pharmacophores and drug molecules.[9b]

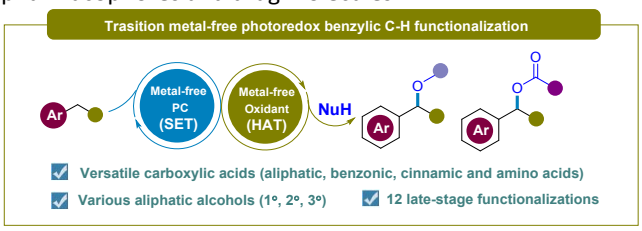

Figure 1. Transition metal-free LSF of benzylic C-H bonds.

Parallel to the etherification, the importance of carboxylic acid in drug design is fully proven by the fact that more than 450 drugs are carboxylic acid-containing molecules.[10] However, the presence of carboxylic acids in drugs or leads could bring some undesired consequences.[11] Thus the modifications of carboxylic acids, such as esterification, provide an alternative to mitigate those effects. The cross-coupling reactions to afford benzylic esters were also reported *via* palladium catalysis and iron catalysis.[12] However, benzylic substrates always served as solvents which generated a huge amount of waste. Most recently, photoredox-catalyzed benzylic esterification was also reported using (diacetoxyiodo)benzene as oxidant and the source of acetoxy group. However, it has limited substrate scope and only acetoxy group can be installed.[13] It is clear that most of the reported late-stage benzylic C–H bond functionalization reactions always required transition metal-based catalysts. In this respect, transition metal-free systems are quite rare for the LSF of benzylic C–H bonds.[9c-9g] Prompted by our continuous interests in transition metal–free photoredox catalysis,[14] herein, we report a transition metal-free approach for the regioselective functionalization of benzylic C(sp³)–H bonds using alcohols and carboxylic acids as the nucleophiles. This approach provides a straightforward route for the synthesis of various benzylic ethers, and esters (**Figure 1**). In the beginning, we proceeded with a systematic optimization of the etherification reaction using 4-ethyl anisole (**1a**) as the source of the benzylic C–H bond and methanol (**A**) as the coupling partner to obtain 1-methoxy-4-(1-methoxyethyl)benzene (**1c**) as the final product (**Table S1**). To our delight, an optimized

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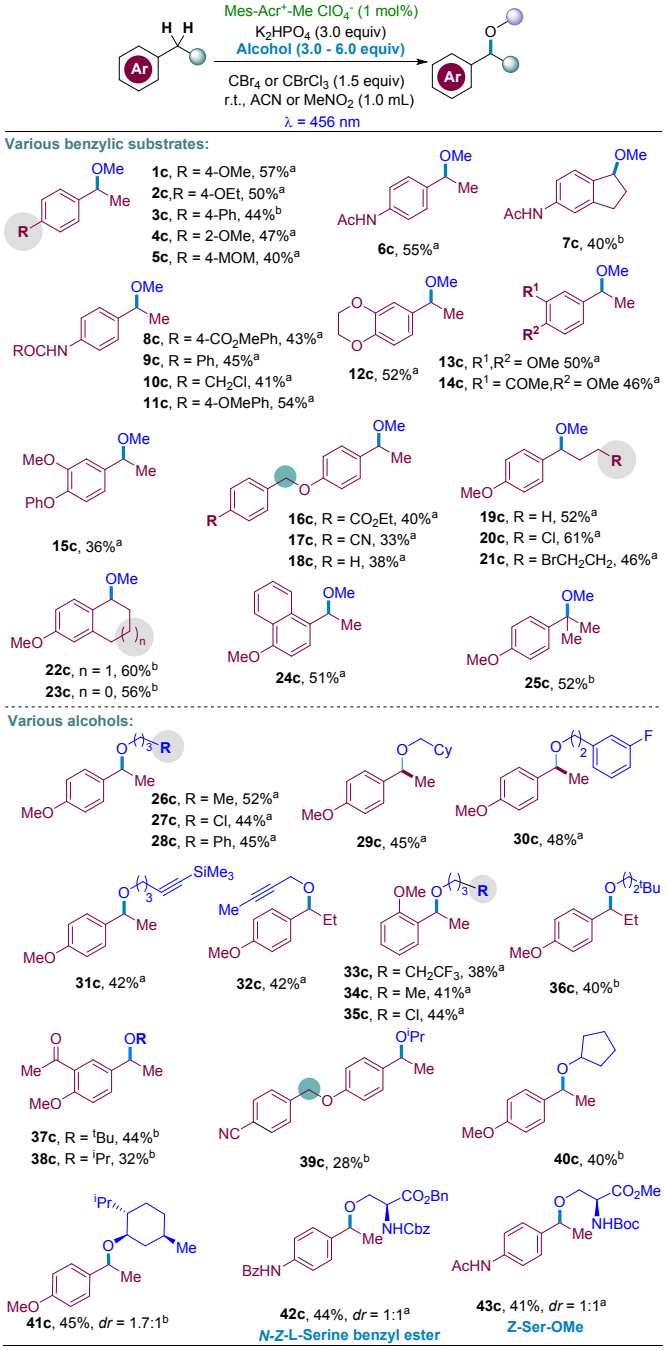
reaction condition was achieved when 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$-Me ClO_4^-) as the photocatalyst (**PC**), carbon tetrabromide and K_2HPO_4 as the oxidant and base respectively were used. The yield of the etherification reaction was relatively limited, which was supposed to be due to the competitive overoxidation to the benzylic ketones or aldehydes.[15] However, this effect of overoxidation was diminished in the case of esterification reactions due to the higher oxidation potential of the corresponding benzyl ester, providing better yield. (For detailed screening; see **SI**).

Having established a standard set of reaction conditions, the substrate scope was extended to various benzylic substrates to determine the generality (**Scheme 1**). To our delight, a plethora of ethyl benzenes bearing electron-donating groups at *para*- or *ortho*- positions, including the methoxy (**1c**, **4c**, **13c, 14c**), ethoxy (**2c**), phenyl (**3c**), amide (**6c**–**11c**), phenoxyl (**15c**), benzyloxy (**16c, 17c, 18c**), groups, were well tolerated in this reaction with methanol as a nucleophile. Afterward, other benzylic substrates, such as *n*-propylbenzene (**19c**), 3-phenylpropyl chloride (**20c**), indane (**7c**, **23c**), and 1,2,3,4-tetrahydronaphthalene (**22c**) containing electron-donating groups were all transformed into the desired methoxylated products. Moreover, the tertiary benzylic C–H bond (**25c**) also underwent the methoxylation reaction when nitromethane was used as the solvent, and $CBrCl_3$ was used as an oxidant. Next to the examination of benzylic sites, different alcohols were investigated.

Various alcohols were readily tolerated under standard conditions as can be seen from **Scheme 1**. Firstly, diverse primary alcohols such as *n*-butanol (**26c**), 3-chloro-1-propanol (**27c**), and others (**28c**–**35c**), were examined under standard conditions. Afterward, secondary and tertiary alcohols including isopropanol and *tert*-butanol (**37c**–**40c**) were also applied to obtain the corresponding benzylic ethers in moderate yields using nitromethane as the solvent, and $CBrCl_3$ as the oxidant. (–)-Menthol (**41c**), functioning as a fortifier for peppermint flavors in pharmaceuticals and foods, was also compatible with these modified conditions. More importantly, serine derivatives also underwent the etherification reaction to afford functionalized amino acids (**42c**, **43c**). Even though yields were relatively limited because of the overoxidation of products, this protocol still provided a concise and straightforward way to access precious benzylic ethers via transition metal-free photocatalysis.

After the investigations of different alcohols as nucleophiles, we aimed to use carboxylic acids as the nucleophiles. The initial investigation between 4-ethyl anisole (**1a**) and benzoic acid (**44b**) afforded only 25% of the desired product, probably due to the extrusion of CO_2 after the oxidation of benzoate anion by the excited state of the photocatalyst.[16] However, the yield increased up to 70% when 4-ethyl anisole was added after all the other reagents had stirred for half an hour under the irradiation of visible-light (**Scheme 2**). We assumed that prior stirring of benzoic acids without the benzylic substrate facilitated the formation of the benzoate anion, which circumvented the formation of by-products. With optimized reaction conditions in hand, we applied diverse benzoic acids bearing electron-withdrawing and donating groups (**44c**–**51c**) as nucleophiles under this reaction condition. Yields of the desired benzylic esters (**46c**–**49c**) went up to 95% in the presence of strong electron-withdrawing groups. Moreover, the current protocol was further applied to cinnamic acids (**55c**) and benzoic acids (**56c**) to obtain the desired benzylic esters. It was also compatible with aliphatic carboxylic acids (**53c**), however, a significantly slower reaction rate (48 h) was observed. With further optimization of solvents, the reaction was speeded up and higher yields were obtained within 24 h even using

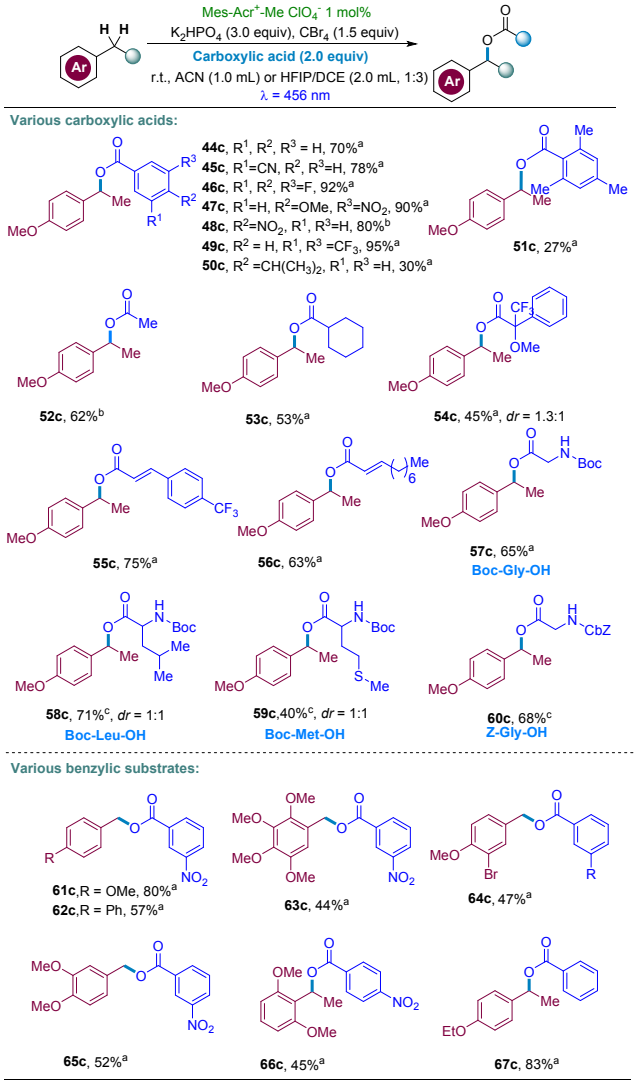


Scheme 1. Substrate scope of benzylic etherification. a) benzylic substrate (0.2 mmol), catalyst (0.002 mmol), K_2HPO_4 (0.6 mmol), CBr_4 (0.3 mmol), alcohol (0.6–1.2 mmol), acetonitrile (1.0 mL), Kessil Lamp (λ = 456 nm), 2.5–6 h; b) Variation: $CBrCl_3$ (0.3 mmol), nitromethane (1.0 mL), alcohol (1.2 mmol)

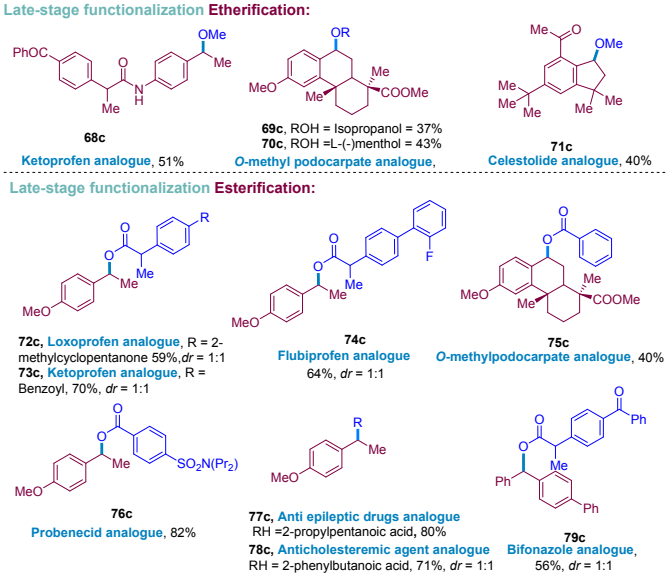
challenging acetic acid as a nucleophile (**52c**). Further to extend

the scope of this reaction, amino acids were applied under this reaction condition. To our delight, our initial attempt with Boc-Gly-OH resulted in a good yield of the corresponding amino acid-based ester (**57c**). Inspired by this, our substrate scope was extended towards Boc-Leu-OH and 71% of the desired amino acid ester (**58c**) was obtained. Delightfully, other two amino acids such as Boc-Met-OH and Z-Gly-OH (**59** and **60c**), also successfully provided desired products under similar reaction conditions. It was clear that this catalytic strategy had a strong tolerance for diverse carboxylic acids including benzoic acids, cinnamic acids, aliphatic carboxylic acids, and amino acids. Expediently, the primary benzylic positions which were more susceptible towards oxidation reactions, were also suitable to undergo the esterification to form the desired benzylic esters with good to excellent yields (**61c**–**67c**) albeit a longer reaction time was required.

The presence of benzylic C-H bonds in numerous drug molecules or building blocks, inspired us to further explore our catalytic strategy for the LSF of natural products and drug molecules (**Scheme 3**). Ketoprofen, a well-known nonsteroidal anti-inflammatory drug (NSAID), was diversified via etherification (**68c**) and esterification (**73c**, **79c**). Even though the diastereoselectivity of **68c** is excellent, the specific configuration of the diastereoisomer is under analysis. *O*-methylpodocarpate, a potential anti-influenza agent, was also selectively functionalized at its benzylic site, thereby, various *O*-methylpodocarpate derivatives were constructed by using diverse alcohols (**69c, 70c**) and benzoic acid (**75c**) as the corresponding nucleophiles. The specific configuration of *O*-methylpodocarpate derivatives were determined according to the literature report.[9a] Additionally, celestolide was also taken into consideration for the etherification reactions by using methanol as the coupling partner. Based on the strong compatibility with various carboxylic acids, we aimed to diversify existing drug molecules and bioactive compounds with our approaches. Loxoprofen, flurbiprofen, probenecid acids, and 2-phenylbutyric acid (**72c**, **74c, 76c, 78c**) also underwent esterification reactions to form valuable benzylic esters. Overall, twenty-four drugs and bioactive compounds were functionalized efficiently. In addition, a cost comparative study between our protocol and other state-of-the-art LSF processes has been evaluated, indicating that our protocol has the lowest raw material costs and energy costs per gm of product produced (see **Figure S24** for details).



Scheme 2. Substrate scope of benzylic esterification. a) benzylic substrate (0.2 mmol), catalyst (1.0 mol%), K_2HPO_4 (0.6 mmol), CBr_4 (0.3 mmol), carboxylic acid (0.4 mmol), acetonitrile (1.0–2.0 mL), Kessil Lamp (λ = 456 nm), 5.5 h - 43 h; b) Variation: Solvent (DCE (1.5 mL) and HFIP (0.5 mL)). c) Variation: blue LED

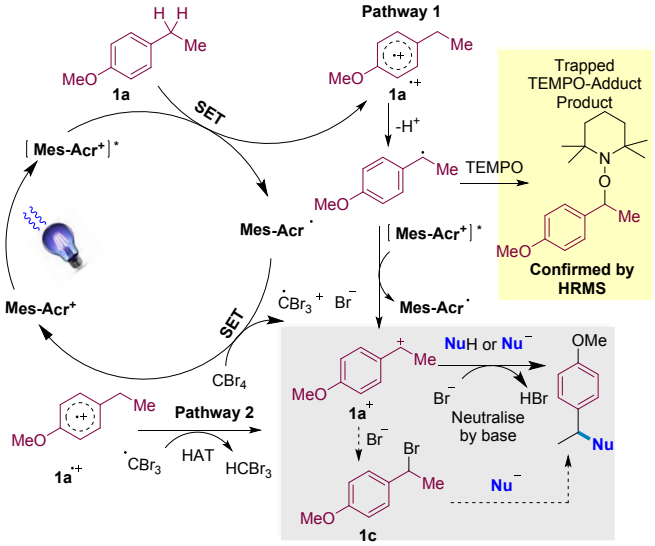


Scheme 3. Late-stage functionalization

To shed light on the reaction mechanism, control experiments were carried out to prove the necessity of each of the reagents. Furthermore, dramatically declining yields in the presence of 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and butylated hydroxytoluene (BHT) indicated the involvement of a radical process. Moreover, the kinetic isotope effect was studied which strongly suggested that the cleavage of the C–H bond (KIE) was not the rate-determining step. (**Figure S7**). From the etherification with different alcohols, it could be also concluded that alcohols of increased steric bulkiness reacted more slowly (**Figure S8**). Further to obtain a clear insight into this reaction, Gibbs's free energy calculations on reactants, products, and intermediates were achieved. The energies of the intermediates for etherification and esterification were calculated separately, and the results exhibited a detailed mechanistic pathway (**Figure S10**). The formation of radical cation (**1a**$^{\bullet+}$) from the reactant **1a** by the oxidant CBr_4 the required energy which was easily obtainable under the irradiation of visible light in the presence of

acridinium salt. **Figure S10** illustrated the plausible mechanism of the reactions and the mapped energies of all the intermediates. Moreover, Stern-volmer fluorescence quenching experiment shows **1a** is the only reagent in the reaction mixture that can quench the excited catalyst supports our proposed reaction mechanism. (**Figure S10, Figure S11**)

Figure 2. Proposed mechanism



The mechanism has been proposed in **Figure 2**. At first, 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$-Me ClO_4^-) was irradiated under the visible light to generate the excited state of the photocatalyst (*Mes-Acr$^+$). The strongly positive excited state reduction potential of the catalyst ($E_{1/2}$ (cat*/cat$^\bullet$)= +2.06 V vs SCE)[17] led to the oxidation of **1a** ($E_{1/2}$ = +1.52 V)[40] through SET process to form the radical cation of **1a** which could further reacted with the base to form the radical of **1a**, confirmed by trapping the radical via the formation of TEMPO adduct. Afterward, CBr_4 ($E_{1/2}$ = -0.30 V vs. SCE)[18] underwent SET process to afford the tribromomethyl radical ($^\bullet CBr_3$),[19] meanwhile, the Mes-Acr• ($E_{1/2}$ (cat$^\bullet$/cat)= -0.57 V vs SCE) returned to the original state. There are two possible pathways to generate the carbocation. Firstly, the radical cation of **1a** could further be oxidized the excited state of the photocatalyst to afford the carbocation (**1a**$^+$) (**Pathway 1**). The other pathway was conjectured that the $^\bullet CBr_3$ continued as a HAT reagent, abstracted a hydrogen atom from **1a**$^{\bullet+}$ to generate the corresponding carbocation (**1a**$^+$)[4a,15] which further reacted with nucleophiles to build up the desired products (**Pathway 2**). It is also possible to undergo the addition reactions to form benzyl bromide which was confirmed by the detection of a trace amount in the NMR spectrum and HR-MS spectrum.

In summary, we have developed a robust, cost and energy-efficient strategy to introduce diverse nucleophiles including various alcohols and carboxylic acids *via* the functionalization of benzylic C–H bonds of simple aromatic building blocks as well as complex drug molecules and natural products. Moreover, this transition metal-free protocol exhibited mild reaction conditions, unparalleled site selectivity, broad compatibility, and wide late-stage modifications of benzylic C–H bonds which should find a potential alternative in drug discovery. Furthermore, in combination with experiments and DFT calculations, the key intermediates in this reaction have been proved. Further pharmacology studies of those valuable drug derivatives are currently under investigation.

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REFERENCES

1. (a) B. Hong, T. Luo and X. Lei, *ACS Cent. Sci.* 2020, **6**, 622–635. (b) L. Guillemard, N. Kaplaneris, L. Ackermann and M. Johansson, J. *Nat. Rev. Chem.* 2021, 1-24.
2. R. Cannalire, S. Pelliccia, L. Sancineto, E. Novellino, G. C. Tron and M. Giustiniano, *Chem. Soc. Rev.* 2021, **50**, 766–897.
3. N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.* 2010, **87**, 1348–1349.
4. (a) G. Pandey, R. Laha and D. Singh, *J. Org. Chem.* 2016, **81**, 7161–7171. (b) Z. W. Hou, D. J. Liu, P. Xiong, X. L. Lai, J. Song and H. C. Xu, *Angew. Chem. Int. Ed.* 2021, **133**, 2979–2983.
5. T. N. Thompson, *Med. Res. Rev.* 2021, **21**, 412–449.
6. J. B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc*. 2013, **135**, 17494–17500.
7. W. Schilling, D. Riemer, Y. Zhang, N. Hatami and S. Das, *ACS Catal.* 2018, **8**, 5425–5430.
8. A. H. Abazid, N. Clamor and B. J. Nachtsheim, *ACS Catal.* 2020, **10**, 8042–8048.
9. (a) B. J. Lee, K. S. DeGlopper and T. P. Yoon, *Angew. Chem., Int. Ed.* 2020, **59**, 197–202. (b) H. Hu, S. J. Chen, M. Mandal, S. M. Pratik, J. A. Buss, S. W. Krska, C. J. Cramer and S. S. Stahl, *Nat. Catal.* 2020, **3**, 358–367. (c) Q. Y. Meng, L. Lezius and A. Studer, *Nat. Commun.* 2021, **12**, 1–8. (d) W. Xu, W. Wang, T. Liu, J. Xie and C. Zhu, *Nat. Commun.* 2019, **10**, 1–8. (e) S. P. Pitre, C. D. McTiernan, H. Ismaili, J. C. Scaiano, *J. Am. Chem. Soc.* 2013, **135**, 13286. (f) T. M. Nguyen, D. A. Nicewicz, *J. Am. Chem. Soc.* 2013, **135**, 9588. (g) M. Riener, D. A. Nicewicz, *Chem. Sci.* 2013, **4**, 2625.
10. A. S. Kalgutkar, J. S. Daniels, RSC Drug Discovery series; Smith, D. A., Ed.; Royal Society of Chemistry: Cambridge, 2010, 99–167.
11. P. Lassalas, B. Gay, C. Lasfargeas, M. J. James, V. Tran, K. G. Vijayendran, K. R. Brunden, M. C. Kozlowski, C. J. Thomas and C. J. Ballatore, *Med. Chem.* 2016, **59**, 3183–3203.
12. H. Liu, G. Shi, S. Pan, Y. Jiang, and Y. Zhang, *Org. Lett.* 2013, **15**, 4098–4101.
13. B. Maeda, Y. Sakakibara, K. Murakami and K. Itami, *Org. Lett.* 2021, **23**, 5113–5117.
14. (a) W. Schilling, Y. Zhang, P. K. Sahoo, S. K. Sarkar, S. Gandhi, H. W. Roesky and S. Das, *Green Chem.* 2021, **23**, 379–387. (b) Y. Zhang, W. Schilling and S. Das, *ChemSusChem* 2019, **12**, 2898–2910. (c) Y. Zhang, D. Riemer, W. Schilling, J. Kollmann and S. Das, *ACS Catal.* 2018, **8**, 6659–6664. (d) Y. Zhang, W. Schilling, D. Riemer, S. Das, *Nat. Protoc.* 2020, **15**, 822-839. (e) D. Riemer, W. Schilling, A. Goetz, Y. Zhang, S. Gehrke, I. Tkach, O. Hollóczki and S. Das, *ACS Catal.* 2018, **8**, 11679–11687.
15. J. W.Tucker, J. M. Narayanam, P. S. Shah and C. R. Stephenson, *Chem. Commun.* 2011, **47**, 5040–5042.
16. H. Cao, H. Jiang, H. Feng, J. M. C. Kwan, X. Liu and J. Wu, *J. Am. Chem. Soc*. 2018, **140**, 16360–16367.
17. G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature* 2016, **539**, 268–271
18. K. Fukui, K. Morokuma, H. Kato and T. Yonezawa, *Bull. Chem. Soc. Jpn* 1963, **36**, 217–222.
19. C. Dai, J. M. Narayanam, C. R. Stephenson, *Nat. Chem.,* 2011, **3**, 140–145.