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TsOH-catalyzed dehydroxylative cross-coupling of alcohols with phenols: rapid access to propofol derivatives†

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Modification of the parent structure of molecules often alters their physicochemical properties and biological activities. Herein, a practical, efficient, and highly regioselective C–H alkylation of phenols with alcohols *via* dehydroxylative cross-coupling was developed to produce *para*-alkylated phenols with excellent regioselectivities and yields, using which propofol derivatives were rapidly synthesized. This process is performed under mild and simple conditions and is well-compatible with a variety of alcohols (secondary and tertiary benzylic alcohols as well as allyl alcohols) as alkylated agents. In addition, high aryl ether derivatives were also obtained using this catalytic system.

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Phenols and their derivatives are vital compounds that not only serve as intermediates in organic synthesis but also act as core scaffolds in numerous natural products, pharmaceuticals, agrochemicals, and dyes.¹ For instance, propofol is a typical example of phenols serving as an intravenous anesthetic, which is widely applied in anesthesia induction, anesthesia maintenance, ICU patient sedation, and epidural anesthesia.² Propofol shows the advantages of rapid onset, high plasma clearance, rapid reduction of blood concentration and suitability for continuous infusion; however, the injection pain limits its clinical application. Modification of the parent structure of drugs often alters their physicochemical properties and biological activities. Therefore, structural modification of phenols and their derivatives for the rapid construction of complicated molecules could provide wide applications in organic synthesis, pharmaceutical chemistry, as well as new drug development.

Dehydrative coupling of phenols and their derivatives is of great importance in the synthesis of organic molecules.³ Obviously, Friedel–Crafts alkylation of phenols and their derivatives is the most studied and classical procedure.⁴ In this case, alkyl halides were typically employed as electrophiles, which is in contrast with the principles of “green chemistry” (producing large amounts of waste and salt contaminants and requiring harsh reaction conditions). In addition, the formation of *ortho*-, *para*-, and poly-alkylated products hinders its application. Therefore, the development of a straightforward method for the selective alkylation of phenols and their derivatives that is

highly efficient, economical, and environmentally friendly is highly desirable.

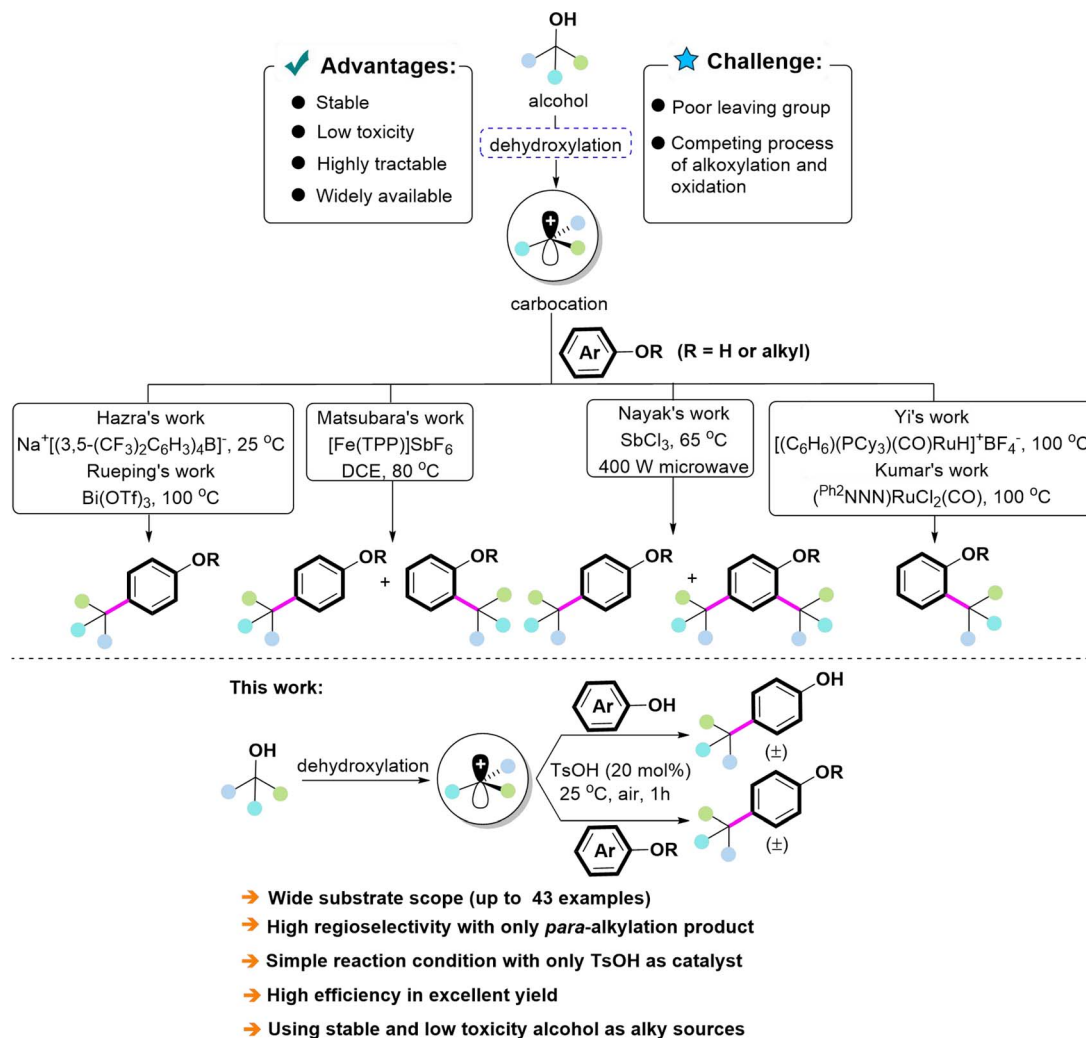
Carbon-based *pro*-electrophiles have been employed as alkylated sources due to the drawbacks of alkyl halides.⁵ In this content, alcohols, which are characterized by stability, wide availability, high tractability, and low toxicity, have been identified as excellent electrophile partners in coupling reactions.⁶ In this process, water is the only byproduct of the dehydration of alcohol, which is consistent with the requirements of green chemistry. A variety of catalytic systems for the activation of alcohols have been established for the alkylation of phenols and their derivatives.⁷ For instance, differential catalytic systems including SbCl₃-microwave,⁸ Fe(TPP)SbF₆,⁹ Bi(OTf)₃,¹⁰ (Ph₂NNN)RuCl₂(CO),¹¹ [(C₆H₆)(PCy₃)(CO)RuH]⁺BF₄[−],¹² and Na⁺[(3,5-(CF₃)₂C₆H₃)₄B][−]¹³ have been developed for this purpose. Despite these advancements, the following challenges remain: (1) the hydroxyl group is a poor leaving group, which makes the activation of alcohols difficult. (2) The competing process of alkoxylation and oxidation hinders the application of alcohols in catalytic C–H coupling reactions. Therefore, the development of a concise and efficient catalytic system for the selective alkylation of phenols and aryl ethers using alcohols as the alkylated sources is still in demand.

With our research interest in alkylation, we developed alkylation reactions with carboxylic acid, alkynes, or ketones as alkylated sources and Cp*Ir complexes as catalysts.¹⁴ In continuation of our work on alkylation, we hereby disclose a TsOH-catalyzed dehydroxylative cross-coupling of alcohols with phenols by which only *para*-alkylated products were afforded in excellent yields (Scheme 1). This process performs under mild and simple conditions, and is well compatible with a variety of alcohols (secondary and tertiary benzylic alcohols, allyl alcohols) as alkylated agents. In addition, high-value aryl

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Scheme 1 Dehydroxylative cross-coupling of alcohols with phenols/aryl ethers.

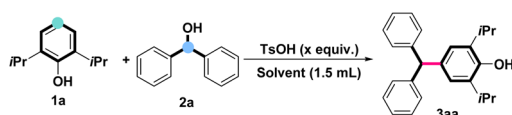
ether derivatives were also achieved *via* this catalytic system (Scheme 1).

In pursuit of the optimal conditions for the dehydroxylative cross-coupling of alcohols with phenols, we started our research by using propofol (**1a**) and diphenylmethanol (**2a**) as a model reaction (Table 1). It is known that Lewis acid could activate the dehydroxylation of alcohols to generate carbon cation intermediates (See the ESI, Scheme S1†). According to our previous work,¹⁴ TsOH was chosen as the catalyst to realize the dehydroxylative cross-coupling of alcohols with phenols and their derivatives. Unsurprisingly, the alkylated product (**3aa**) of propofol was generated in the mixture solvent (*p*-xylene/H₂O = 1 : 4) in 34% yield at 80 °C after 12 h (Table 1, entry 1). Screening of other solvents, such as 1,4-dioxane, TFEA, DMF, MeCN, *p*-xylene, and H₂O (Table 1, entries 2–8), evidenced that TFEA was the optimal media to afford the corresponding product **3aa** in 98% yield (Table 1, entry 3). Treatment of **1a** and **2a** using differential loadings of TsOH delivered similar yields of the desired product (Table 1, entries 9–12). The control experiment indicated the TsOH was essential for this transformation (Table

1, entry 13). Further loading of alcohol screening revealed that **1a** could be fully converted into the desired alkylated product **3aa** even if 1.0 equivalent of **2a** was employed (Table 1, entry 18). It is interesting to note that high yields of **3aa** could also be achieved by lowering the reaction temperature or shortening the reaction time (Table 1, entries 19–25).

With the optimal conditions in hand, we investigated the alcohol scope in conjunction with propofol (Scheme 2). As shown in Scheme 2, a wide range of substituted secondary diaryl alcohols, including electron-donating groups of methyl and methoxy, proved to be suitable as alkylated sources, delivering the desired products (**3ab–3ae**) in excellent yields. Notably, larger steric hindrance of 1-naphthyl alcohol could also undergo this dehydroxylative cross-coupling to afford product **3af** in 82% yield. Interestingly, using 9*H*-fluoren-9-ols as alkylated sources could also provide the corresponding products **3ag** and **3ah** in yields of 60% and 95%, respectively. However, no desirable alkylated products but 1,1-diarylethenes were formed in moderate to good yields (**3ai** and **3aj**) when diaryl tertiary alcohols (**2i**, **2j**) were loaded as alkylated sources under standard



Table 1 Optimization of the conditions^a

Entry	TsOH (equiv.)	2a (equiv.)	Solvent	Reaction time	Yield of 3aa ^b (%)
1 ^c	1.0	2.0	<i>p</i> -Xylene/H ₂ O	12 h	34
2	1.0	2.0	1,4-Dioxane	12 h	92
3	1.0	2.0	TFEA	12 h	98
4	1.0	2.0	DMF	12 h	n.r
5	1.0	2.0	MeCN	12 h	92
6 ^c	1.0	2.0	TFEA/H ₂ O	12 h	68
7	1.0	2.0	<i>p</i> -Xylene	12 h	96
8	1.0	2.0	H ₂ O	12 h	22
9	0.8	2.0	TFEA	12 h	97
10	0.6	2.0	TFEA	12 h	97
11	0.4	2.0	TFEA	12 h	98
12	0.2	2.0	TFEA	12 h	98
13	—	2.0	TFEA	12 h	n.r.
14	0.2	1.8	TFEA	12 h	96
15	0.2	1.6	TFEA	12 h	99
16	0.2	1.4	TFEA	12 h	98
17	0.2	1.2	TFEA	12 h	97
18	0.2	1.0	TFEA	12 h	98
19 ^d	0.2	1.0	TFEA	12 h	98
20 ^e	0.2	1.0	TFEA	12 h	97
21 ^f	0.2	1.0	TFEA	12 h	99
22 ^d	0.2	1.0	TFEA	10 min	90
23 ^d	0.2	1.0	TFEA	20 min	92
24 ^d	0.2	1.0	TFEA	30 min	95
25 ^d	0.2	1.0	TFEA	1 h	99

^a Reaction condition: **1a** (0.5 mmol), and solvent (1.5 mL) under air condition at 80 °C for 12 h. ^b Yield was determined by NMR with dimethyl terephthalate as internal standard. ^c The ratio of the mixed solvent was 1 : 4 (v/v). ^d 25 °C. ^e 40 °C. ^f 60 °C.

conditions. Importantly, alkylated agents of 1-arylethanol were also surveyed. Regardless of the positions and substituents of the alcohols, a wide range of 1-arylethanol was compatible with this catalytic system, affording the corresponding products **3ak–3as** in excellent yields. Similarly, other substrates of 1-phenyl alkyl alcohols were also amenable to the catalytic system, furnishing **3at–3aw** in 83–87% yields. Again, substrates of enol and alkynyl alcohol were compatible with the standard conditions to give the desirable products **3ax** and **3ay** in excellent yields.

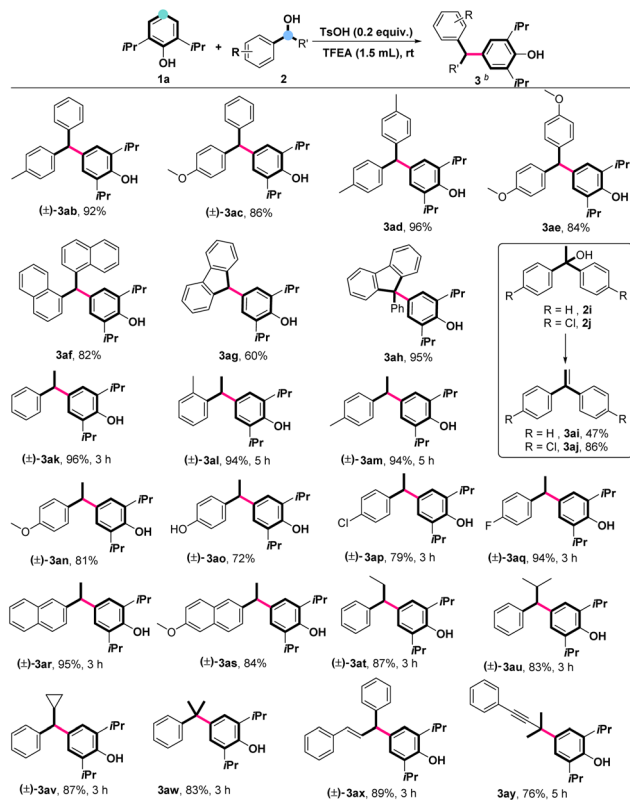
The promising results showcased above motivated us to further explore the dehydroxylative cross-coupling of diphenylmethanol (**2a**) with general phenols. As indicated in Scheme 3, a range of substituted phenols, including *o*-methyl (**2b**, **2g**), *o*-ethyl (**2c**, **2h**), *o*-isopropyl (**2d**), *o*-tertiary (**2e**) substituted phenols, were subjected under aforementioned optimal conditions to deliver desired products (**3ba–3ea**, **3ga** and **3ha**) in excellent yields. Apparently, the sensitive functional group of allyls on phenol has no influence on the yield of the products, affording **3fa** and **3ia** in 73% and 89%, respectively. Moreover, a substrate with a larger hindrance of 2,6-di-*tert*-butylphenol could also be compatible with this system to afford

the desired product **3ja** in excellent yield, indicating good substrate versatility.

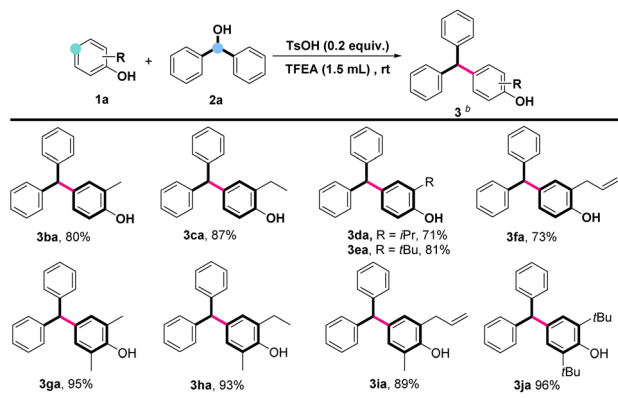
The substrate scope of this established methodology was also investigated with various aryl ethers. As shown in Scheme 4, a variety of substituted anisoles were alkylated with diphenylmethanol (**2a**) under standard conditions to produce the corresponding products (**5aa–5ac**, **5ae–5ah**) in excellent yields. Allyl phenyl ether (**4d**), which contains an unsaturated double bond, was employed under standard conditions and delivered **5d** in 85% yield. Additionally, alkylation of benzo-tetrahydrofuran could also take place to give product **5ai** in 60% yield. Interestingly, using thioether as a substrate exhibited similar excellent results to furnish product **5aj** in 90% yield. In addition, Electron-rich arylamine of *N,N*-dimethylaniline was also compatible with this catalytic system, giving the desired product in moderate yield (**5bk**).

To demonstrate the synthetic utility of this dehydroxylative cross-coupling protocol, the gram-scale experiment was performed (Scheme 5). The model reaction of propofol (**1a**) and diphenylmethanol (**2a**) could be conducted on a 10.0 mmol scale, giving 3.27 grams of **3aa** in the yield of 95%, showing promising prospects in industrial production.





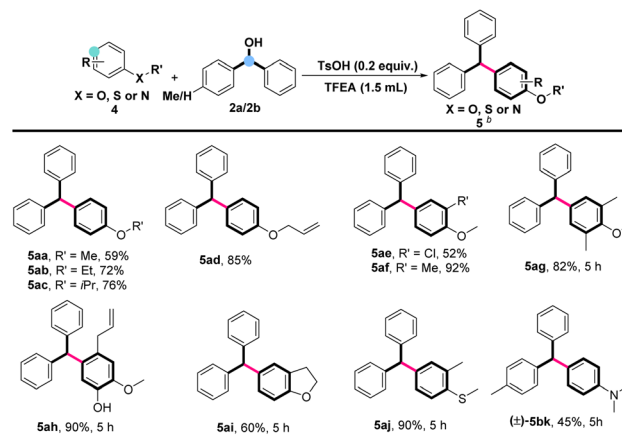
Scheme 2 Dehydroxylative coupling of aryl alcohols with propofol. ^a Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), TsOH (0.2 equiv.), and TFEA (1.5 mL) for 1 hour at room temperature. ^b Isolated yield.



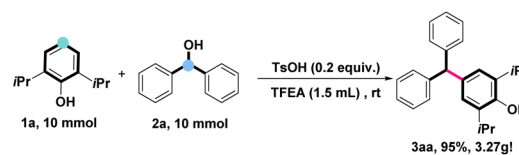
Scheme 3 Dehydroxylative cross-coupling of phenols with diphenyl methanol. ^a Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), TsOH (0.2 equiv.), and TFEA (1.5 mL) for 1 hour at room temperature. ^b Isolated yield.

Conclusions

In conclusion, a practical and efficient dehydroxylative cross-coupling of alcohols with phenols and their derivatives was developed to produce *para*-alkylated phenols/aryl ethers in excellent regioselectivities and yields and propofol derivatives could be rapidly accessed. This process was performed under mild and with only TsOH as a catalyst, is well compatible with



Scheme 4 Dehydroxylative cross-coupling of aryl ethers with diphenyl methanol. ^a Reaction conditions: **2a** (0.5 mmol), **4** (0.5 mmol), TsOH (0.2 equiv.), and TFEA (1.5 mL) for 1 hour at room temperature. ^b Isolated yield.



Scheme 5 Gram-scale experiment.

a variety of alcohols (secondary and tertiary benzylic alcohols, allyl alcohols) as alkylated agents. In addition, high-value aryl ether derivatives were also furnished using this catalytic system. Studies on the physicochemical properties and biological activities of propofol derivatives are in progress and will be reported soon.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Yuqiu Liang, and Chengxiu Liu: investigation, data curation, validation, visualization, manuscript, and supplementary information writing and editing. Youchun Li and Lu Ouyang: conceptualization, funding acquisition, project administration, resources, supervision, visualization, revising the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) K. A. Scott, P. B. Cox and J. T. Njardarson, Phenols in Pharmaceuticals: Analysis of a Recurring Motif, *J. Med. Chem.*, 2022, **65**, 7044–7072; (b) W. Zhao, B. Wang, Y. Liu, L. Fu, L. Sheng, H. Zhao, Y. Lu and D. Zhang, Design, synthesis, and biological evaluation of novel 4Hchromen-4-one derivatives as antituberculosis agents against multidrug-resistant tuberculosis, *Eur. J. Med. Chem.*, 2020, **189**, 112075; (c) E. E. A. Osman, N. S. Hanafy, R. F. George and S. M. El-Moghazy, Design and synthesis of some barbituric and 1,3-dimethylbarbituric acid derivatives: A non-classical scaffold for potential PARP1 inhibitors, *Bioorg. Chem.*, 2020, **104**, 104198.
- S. H. Lee, S. E. Lee, S. Chung, H. J. Lee and S. Jeong, Impact of time interval between remifentanyl and propofol on propofol injection pain, *J. Clin. Anesth.*, 2016, **34**, 510–515.
- (a) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, Transition-Metal-Catalyzed C-H Alkylation Using Alkenes, *Chem. Rev.*, 2017, **117**, 9333–9403; (b) Z.-Y. Tian, Y. Ma and C.-P. Zhang, Alkylation Reactions with Alkylsulfonium Salts, *Synthesis*, 2022, **54**, 1478–1502; (c) S. B. Ankade, A. B. Shabade, V. Soni and B. Punji, Unactivated Alkyl Halides in Transition-Metal-Catalyzed C-H Bond Alkylation, *ACS Catal.*, 2021, **11**, 3268–3292.
- (a) C. Friedel and J. M. Crafts, A new general synthetic method of producing hydrocarbons, *J. Chem. Soc.*, 1877, **32**, 725–791; (b) R. M. Roberts and A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry. A Discovery*, Marcel Dekker, New York, 1984; (c) M. Rueping and B. J. Nachtsheim, A Review of New Developments in the Friedel-Crafts Alkylation-From green chemistry to asymmetric catalysis, *Beilstein J. Org. Chem.*, 2010, **6**, 6.
- (a) X.-H. Chen, T. Lhazom and H.-L. Cui, NH₄OAc/DMSO-Promoted Benzoylation of Pyrrolo[2,1-a]isoquinolines, *J. Org. Chem.*, 2023, **88**, 13598–13609; (b) R.-J. Tang, T. Milcent and B. Crousse, Bisulfate Salt-Catalyzed Friedel-Crafts Benzoylation of Arenes with Benzylic Alcohols, *J. Org. Chem.*, 2018, **83**, 14001–14009; (c) R. Liu, Y. Wei and M. Shi, Rhodium(III)-Catalyzed C-H Benzoylation of Indole's C3 Position with Aza-o-Quinone Methides, *Adv. Synth. Catal.*, 2020, **362**, 3649–3654; (d) X. Li, Y. Mao, P. Fan and C. Wang, Nickel/Photo-Cocatalyzed Acyl C-H Benzoylation of Aldehydes with Benzyl Chlorides, *Eur. J. Org. Chem.*, 2022, **2022**, e202200214; (e) G. Schäfer and J. W. Bode, Friedel-Crafts benzoylation of activated and deactivated arenes, *Angew. Chem., Int. Ed.*, 2011, **50**, 10913–10916; (f) K. J. Schwarz, C. Yang, J. W. Fyfe and T. N. Snaddon, Enantioselective α -Benzoylation of Acyclic Esters Using π -Extended Electrophiles, *Angew. Chem., Int. Ed.*, 2018, **57**, 12102–12105.
- (a) M. Dryzhakov, E. Richmond and J. Moran, Recent Advances in Direct Catalytic Dehydrative Substitution of Alcohols, *Synthesis*, 2016, **48**, 935–959; (b) P. H. Huy, Lewis Base Catalysis Promoted Nucleophilic Substitutions-Recent Advances and Future Directions, *Eur. J. Org. Chem.*, 2020, **2020**, 10–27; (c) S. Estopiná-Durán and J. E. Taylor, Brønsted Acid-Catalysed Dehydrative Substitution Reactions of Alcohols, *Chem. Eur. J.*, 2021, **27**, 106–120; (d) H. Li, A. Riisager, S. Saravanamurugan, A. Pandey, R. S. Sangwan, S. Yang and R. Luque, Carbon-Increasing Catalytic Strategies for Upgrading Biomass into Energy-Intensive Fuels and Chemicals, *ACS Catal.*, 2018, **8**, 148; (e) J. Huang, J. Chen, Z. Huang, T. Liu, Y. Ding, H. Li and C. He, Solventless autothermic production of energy-intensive furanic biofuels expedited by photothermal effect, *Fuel*, 2024, **359**, 130458; (f) H. Li, S. Saravanamurugan, S. Yang and A. Riisager, Catalytic Alkylation of 2-Methylfuran with Formalin Using Supported Acidic Ionic Liquids, *ACS Sustainable Chem. Eng.*, 2015, **3**, 3274.
- (a) M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima and K. Ishii, Secondary Benzoylation Using Benzyl Alcohols Catalyzed by Lanthanoid, Scandium, and Hafnium Triflate, *J. Org. Chem.*, 2003, **68**, 9340–9347; (b) K. Mertins, I. Lovel, J. Kischel, A. Zapf and M. Beller, Gold-Catalyzed Benzoylation of Arenes and Heteroarenes, *Adv. Synth. Catal.*, 2006, **348**, 691–695; (c) J. Liu, E. Muth, U. Florke, G. Henkel, K. Merz, J. Sauvageau, E. Schwake and G. Dyker, Alkylation of Arenes with Benzylic and Propargylic Alcohols-Classical versus Fancy Catalysts, *Adv. Synth. Catal.*, 2006, **348**, 456–462; (d) S.-S. Meng, X. Tang, X. Luo, R. Wu, J.-L. Zhao and A. S. C. Chan, Borane Catalyzed Chemoselectivity-Controllable N-alkylation and ortho C-alkylation of Unprotected Arylamines Using Benzylic Alcohols, *ACS Catal.*, 2019, **9**, 8397–8403; (e) S. Estopiná-Durán, E. B. Mclean, L. J. Donnelly, B. M. Hockin and J. E. Taylor, Arylboronic Acid Catalyzed C-Alkylation and Allylation Reactions Using Benzylic Alcohols, *Org. Lett.*, 2020, **22**, 7547–7551.
- P. Shukla, M. K. Choudhary and S. K. Nayak, Microwave-Accelerated Alkylation of Arenes/Heteroarenes with Benzylic Alcohols Using Antimony(III) Chloride as Catalyst: Synthesis of O-Heterocycles, *Synlett*, 2011, **11**, 1585–1591.
- S. Teranishi, T. Kurahashi and S. Matsubara, Cationic Iron(III) Porphyrin Catalyzed Dehydrative Friedel-Crafts Reaction of Alcohols with Arenes Dehydrative Friedel-Crafts Reaction, *Synlett*, 2013, **24**, 2148–2152.
- M. Rueping, B. J. Nachtsheim and W. Ieawsuwan, An Effective Bismuth-Catalyzed Benzoylation of Arenes and Heteroarenes, *Adv. Synth. Catal.*, 2006, **348**, 1033–1037.
- K. Das, E. Yasmin and A. Kumar, Pincer-Ruthenium Catalyzed Oxygen Mediated Dehydrative Etherification of Alcohols and Ortho-Alkylation of Phenols, *Adv. Synth. Catal.*, 2022, **364**, 3895–3909.
- N. Yadav, J. Khan, A. Tyagi, S. Singh and C. K. Hazra, Rapid Access to Arylated and Allylated Cyclopropanes via Brønsted Acid-Catalyzed Dehydrative Coupling of Cyclopropylcarbinols, *J. Org. Chem.*, 2022, **87**, 6886–6901.
- D.-H. Lee, K.-H. Kwon and C.-S. Yi, Dehydrative C-H Alkylation and Alkenylation of Phenols with Alcohols:



Expedient Synthesis for Substituted Phenols and Benzofurans, *J. Am. Chem. Soc.*, 2012, **134**, 7325–7328.

- 14 (a) L. Ouyang, R. Miao, Z. Yang and R. Luo, Iridium-catalyzed Reductive Amination of Carboxylic Acids, *J. Catal.*, 2023, **418**, 283–289; (b) L. Ouyang, Y. Liang, S. Wang, R. Miao, J. Liao, Z. Yang and R. Luo, Iridium-Catalyzed Reductive

Hydroamination of Terminal Alkynes in Water, *J. Catal.*, 2023, **427**, 115096; (c) L. Ouyang, Y. Liang, S. Wang, J. Liao and R. Luo, Access of arylmethanes *via* iridium-catalyzed deoxygenative cross-coupling of aryl ketones with anilines/phenols, *J. Catal.*, 2024, **433**, 115492.

