


 Cite this: *New J. Chem.*, 2024, 48, 4224

 Received 4th December 2023,
 Accepted 12th February 2024

DOI: 10.1039/d3nj05580a

rsc.li/njc

A catalytic, regioselective Friedel–Crafts alkylation of beta-naphthol with allylic alcohols has been developed. This procedure allows for selective α -alkylation of β -naphthol with a *p*-toluenesulfonic acid catalyst. This transformation demonstrated functionalized naphthol synthesis under mild reaction conditions with high product yields – 20 examples with up to 96% yields. The synthetic utility further proved the versatility of the allyl naphthol products.

Beta-naphthol and its derivatives are important structural motifs found in a diverse range of functional compounds. They have shown broad applications and attracted significant attention in recent years.^{1–10} For example, beta-naphthol (Fig. 1, **A**) has been used as a urinary biomarker, indicating airborne exposure to polyaromatic hydrocarbons such as naphthalene.¹ 6-Bromonaphthalen-2-ol (Fig. 1, **B**) and (*S*)-naproxen (Fig. 1, **C**) serve as molecular recognition tools through phosphorescence and as pharmaceutical agents, respectively.^{2,3} Larger naphthol derivatives, such as beta-naphthol-based polymers (Fig. 1, **D**), are used for biofuel production.⁴ In addition, 1,1'-bi-2-naphthol (BINOL) derivatives (Fig. 1, **E**) have been used as chiral ligands and catalysts for various catalytic and enantioselective transformations.^{5–9,11} Moreover, a liposomal-encapsulated DVM1 is developed as a cancer cell imaging agent (Fig. 1, **F**).¹²

With its wide applications, beta-naphthol has been functionalized *via* different transformations: alkylation,^{13–22} cyclization,^{16,23–29} and arylation.^{30–35} In particular, C–H functionalization of arenols *via* Friedel–Crafts (FC) alkylation reaction constructs a new C–C bond. FC alkylation of beta-naphthol tolerates various functional groups such as enone,^{36,37} imine,³⁸ and alcohol.^{39–41} This reaction has been comprehensively studied with primary and secondary alcohols

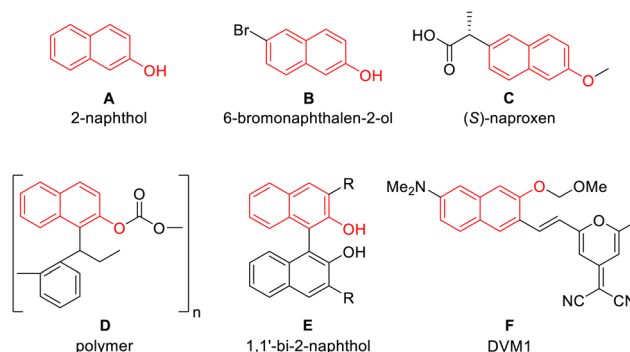
Catalytic, regioselective Friedel–Crafts alkylation of beta-naphthol†

 Jeffrey Ash,^a Emarose Ahmed,^a Ngantu Le,^a Hai Huang^{id}^b and Jun Yong Kang^{id}^{*a}

(Scheme 1). For example, the Nakata group reported a dehydrative FC alkylation of beta-naphthol with benzylic alcohols using a SnBr₄ catalyst. (Scheme 1a).^{39,40} Yang and co-workers released a similar transformation using a phosphomolybdic acid catalyst (Scheme 1b).⁴¹ In addition, Yaragorla and co-workers disclosed microwave-assisted benzylation of naphthol with primary and secondary alcohols (Scheme 1c).⁴² Furthermore, Muzart and Rodriguez reported nucleophilic substitution reactions of allylic and benzylic alcohols.^{43,44} This method, however, is limited to arenes and heteroarenes.

FC alkylation of β -naphthol with allylic alcohol substrates, however, is underdeveloped owing to their instability and regioselectivity issues.^{45–48} In addition to the challenging regioselectivity control, the poor leaving group ability of the hydroxyl group induces further challenges.^{39,40} Another challenge is the competition between the desired activation of allylic alcohol electrophile and the undesired deactivation of naphthol nucleophile by acid catalysts. Recognizing the scarcity of FC alkylation reaction of beta-naphthols using allylic alcohols and the need to understand better their regioselectivity, an efficient FC alkylation of beta-naphthol with allylic alcohols is highly desirable.

Although allylic alcohol substrates have demonstrated metal-catalyzed alkylation with indole derivatives, FC alkylation between naphthols and allylic alcohols is underdeveloped.^{45,47–49} If allylic


 Fig. 1 1. Representative β -naphthol applications.

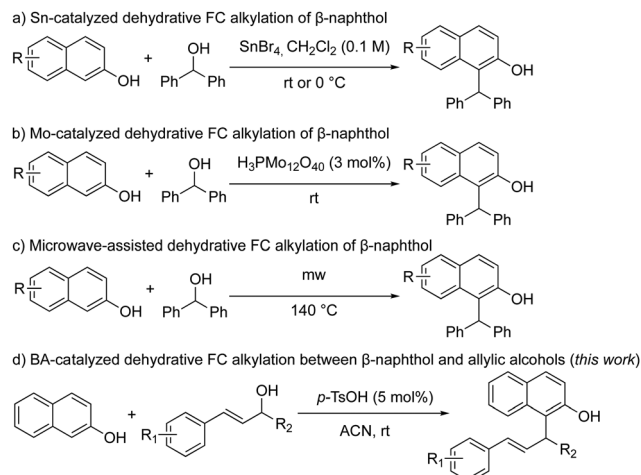
^a Department of Chemistry and Biochemistry, University of Nevada Las Vegas, 4505 S. Maryland Parkway, Las Vegas, Nevada, 89154-4003, USA. E-mail: junyong.kang@unlv.edu

^b Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, School of Petrochemical Engineering, Changzhou University, Changzhou, 213164, P. R. China

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3nj05580a>



Communication

Scheme 1 Methods of dehydrative FC alkylation of β -naphthol.

alcohols can participate in FC alkylation of beta-naphthol, it will generate new structural scaffolds beneficial for exploring significant naphthol derivatives (Fig. 1). Importantly, this FC alkylation can serve as a metal-free alternative to the Tsuji–Trost allylation reaction of arenols.^{50–55} To the best of our knowledge, FC allylation of beta-naphthol with allylic alcohol remains elusive. Considering these synthetic shortcomings, we were interested in developing a facile, efficient FC alkylation of β -naphthol with allylic alcohols using an inexpensive, commercially available Brønsted acid catalyst (Scheme 1d). Hence, we hypothesized that FC alkylation of beta-naphthol with allylic alcohol could be achieved by identifying an appropriate Brønsted acid catalyst to form versatile naphthol scaffolds.

To test our hypothesis, beta-naphthol **1a** and (*E*)-4-phenylbut-3-en-2-ol **2a** were used as the model substrates (Table 1). First, readily available Brønsted acids were screened (Table 1, entries 1–4). Acetic acid ($pK_a = 4.76$), trifluoroacetic acid ($pK_a = 0.23$), and 4-nitrobenzoic acid ($pK_a = 3.41$) were unsuitable catalysts for this FC reaction (Table 1, entries 1, 2, and 4). However, when a stronger Brønsted acid such as *p*-TsOH ($pK_a = -2.8$) was used, the desired product **3a** was obtained in 84% yield in DCM (Table 1, entry 3). The regiochemistry of the reaction could be rationalized by the sterically less hindered carbocation, to which beta-naphthol selectively attacks the carbocation to afford the product **3a**. This outcome is consistent with the precedent-related transformation.^{53,56} Solvent effects were evaluated to optimize the reaction conditions further. When the reaction was run in acetonitrile, the yield was increased to 91% (Table 1, entry 5). A nonpolar solvent such as toluene was also suitable, but a lower yield (58%) was obtained (Table 1, entry 6). Solvents containing an oxygen heteroatom, such as tetrahydrofuran, ether, and ethanol, did not furnish the target product (Table 1, entries 7–9). This is presumably due to competition between the solvent protonation and the allylic alcohol protonation. Lastly, a control experiment was conducted without a catalyst, and it generated no target products, revealing the catalyst requirement for this transformation (Table 1, entry 10).

With the optimized reaction conditions established, the scope of the allylic alcohol was tested to study the electronic

Table 1 Optimization of reaction condition^a

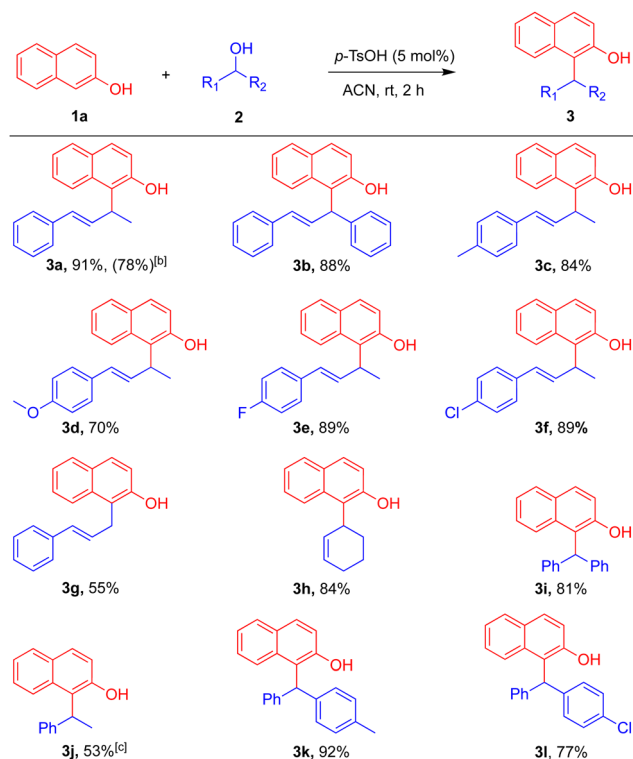
Entry	Catalyst	Solvent	Yield (%)
1	C1	DCM	—
2	C2	DCM	—
3	C3	DCM	84
4	C4	DCM	—
5	C3	ACN	91
6	C3	Toluene	58
7	C3	THF	—
8	C3	Ether	—
9	C3	Ethanol	—
10	No catalyst	ACN	—

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol) in solvent (1.0 mL) at room temperature for 2 h. Isolated yield.

and steric effects on the reaction (Scheme 2). Switching the methyl group of the allylic alcohol with a phenyl group **2b** also generated the product **3b** with an 88% yield. Allylic alcohols **2c** and **2d** containing electron-donating groups (4-Me and 4-MeO) provided the target products **3c** and **3d** in 84% and 70% yields, respectively. Halogenated allylic alcohols **2e** and **2f** were well tolerated to furnish the desired products **3e** and **3f** in 89% yields. Next, a primary allylic alcohol **2g** was tested, and the corresponding product **3g** was obtained in a moderate yield (55%), presumably due to the decreased stability of the primary carbocation intermediate. Cyclic allylic alcohol **2h** was also well tolerated to afford the desired product **3h** in 84% yield. However, a heteroarene allylic alcohol (furan allylic alcohol) was an unsuccessful substrate. Then, the reaction was tested with diaryl alcohol to see whether a complementary benzylation could be achieved. Diphenyl methanol **2i** successfully underwent FC arylation to provide the product **3i** with an 81% yield. Aryl-, alkyl-substituted secondary alcohol **2j**, however, did not form the target product under the standard conditions. Nevertheless, when the reaction was heated at reflux for 12 hours, the desired product **3j** was generated with a 53% yield. Compared to the diphenyl carbocation intermediate, this less stable carbocation intermediate may account for the low yield (Scheme 2, **3i** vs. **3j**). Other diaryl methanols with different electronics, **1k** and **1l** (4-Me and 4-Cl), also afforded the corresponding products **3k** and **3l** in 92% and 77% yields, respectively. Finally, to demonstrate the scalability of this reaction and its applicability in pharmaceutical processes, a scale-up experiment (3.0 mmol) with **1a** was carried out to provide the target product **3a** with a 78% yield.

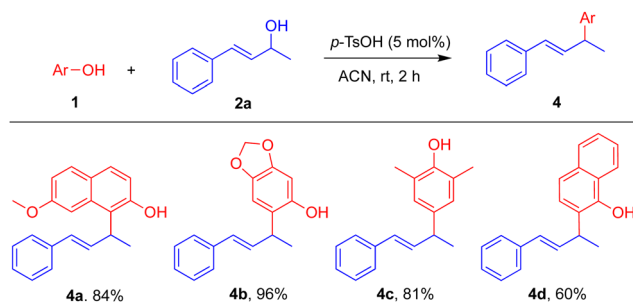
Next, the scope of arenol was evaluated (Scheme 3). A naphthol with an electron donating group (7-MeO) **1b** was tested, and it provided the desired product **4a** with 84% yield. A π -electron-rich arenol such as sesamol **1c** also generated the target product **4b** in 96% yield. To alter the regioselectivity from



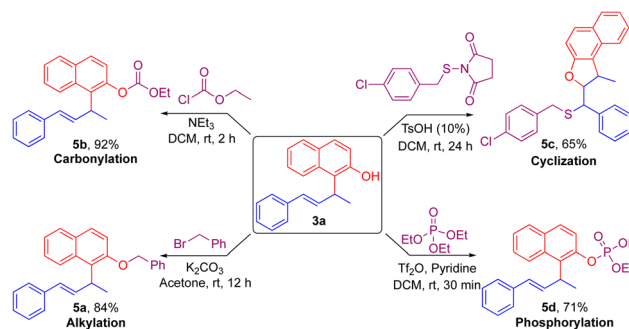


ortho to *para*, 2,6-dimethyl phenol **1d**, an *ortho*-blocked arenol, was subjected to the reaction conditions. This reaction afforded the corresponding *para*-substituted product **4c** in 81% yield. In addition, alpha-naphthol **1e** was evaluated as the nucleophile, and it furnished the corresponding product **4d** in 60% yield. These results demonstrate that an array of arenols, including alpha-naphthol, is suitable for this FC alkylation reaction with allylic alcohols. Importantly, this procedure solely controls the regioselectivity.

Having a wide range of substrate scope demonstrated, the synthetic utility of **3a** was explored (Scheme 4). Using Williamson ether conditions, alcohol alkylation of **3a** provided benzyl naphthyl ether product **5a** (84% yield), which can serve as a



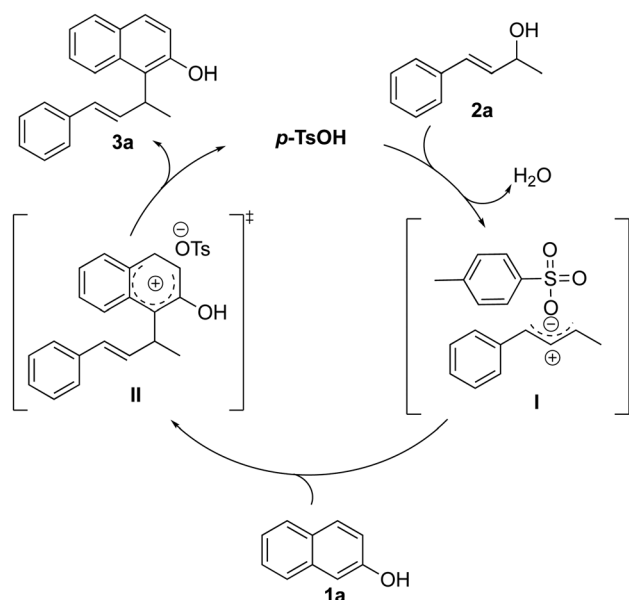
Scheme 3 Substrate scope of arenol nucleophile^a. ^a Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), *p*-TsOH (0.01 mmol) in ACN (1.0 mL) at room temperature for 2 h. Isolated yield.



Scheme 4 Synthetic utility of beta-naphthol **3a**.

thermal paper sensitizer.⁵⁷ Next, **3a** was treated with an acid chloride to furnish aryl carbonate product **5b**, which has been used for the carboxylesterase studies.⁵⁸ In addition, when *n*-thiosuccinimide was used as an electrophilic sulfur species, **3a** was transformed into benzohydrofuran **5c** which is known for cytoprotective agents.⁵⁹ Furthermore, phosphorylation of **3a** was demonstrated with a phosphoryl pyridinium intermediate to form **5d** in 71% yield.⁶⁰ This naphthyl phosphate increases both hydrophobicity and acidity for prodrug application.⁶¹ Based on these results, the hydroxyl and olefin groups on the allylic naphthol products can effectively serve as synthetic handles for further significant functionalization.

On the basis of the substrate scope study and literature,^{62,63} a plausible mechanism is proposed (Scheme 5). First, the hydroxyl group of the allylic alcohol **2a** is protonated by the *p*-TsOH catalyst and then is eliminated to form a secondary allylic carbocation intermediate **I**. Next, the intermediate **I** undergoes FC alkylation reaction with beta-naphthol **1a** at the α -position to form the Wheland complex **II**.^{64,65} Finally, the carbocation intermediate **II** is deprotonated to yield the target product **3a** and the *p*-TsOH catalyst is regenerated.



Scheme 5 Plausible mechanism.



We have developed a catalytic, regioselective, and atom-economic Friedel–Crafts alkylation reaction of beta-naphthol using allylic alcohols. This reaction provides both allylation and benzylation products from beta-naphthols employing *p*-TsOH as an inexpensive and readily available catalyst. The reaction demonstrates a wide range of substrate scope, including alpha-naphthol. In addition, the synthetic utility of the allylic naphthol product proves to be valuable transformations, including cyclization to synthesize a highly functionalized benzohydrofuran. Finally, this transformation can serve as a general method for regioselective FC alkylation of various arenols under mild, metal-free conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by University of Nevada Las Vegas.

Notes and references

- M. Yang, M. Koga, T. Katoh and T. Kawamoto, *Arch. Environ. Contam. Toxicol.*, 1999, **36**, 99–108.
- Y.-Q. Zhai, S.-Z. Zhang, J.-W. Xie and C.-S. Liu, *Anal. Chim. Acta*, 2003, **494**, 71–80.
- Y. A. Ammar, M. A. Salem, E. A. Fayed, M. H. Helal, M. S. A. El-Gaby and H. K. Thabet, *Synth. Commun.*, 2017, **47**, 1341–1367.
- M. R. Nimlos, A. N. Wilson, C. Mukarakate and M. J. Price, *US Pat.*, 10364322, 2018.
- Q. Ma, X. Zhang, L. Ji and S. Liao, *Polym. Chem.*, 2019, **10**, 6662–6668.
- M. Terada, *Chem. Commun.*, 2008, 4097–4112, DOI: [10.1039/B807577H](https://doi.org/10.1039/B807577H).
- M. Rueping, U. Uria, M.-Y. Lin and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732–3735.
- Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng and L.-Z. Gong, *Org. Lett.*, 2009, **11**, 4620–4623.
- S. E. Denmark and D. J. P. Kornfilt, *J. Org. Chem.*, 2017, **82**, 3192–3222.
- M. Montesinos-Magraner, C. Vila, G. Blay and J. R. Pedro, *Synthesis*, 2016, 2151–2164.
- J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857–898.
- Y. Jung, B. W. Kim, J. Jung, B. M. Kim and D. Kim, *Bull. Korean Chem. Soc.*, 2021, **42**, 115–118.
- S. Wu, J. Dong, D. Zhou, W. Wang, L. Liu and Y. Zhou, *J. Org. Chem.*, 2020, **85**, 14307–14314.
- M. Zhu, D.-C. Wang, M.-S. Xie, G.-R. Qu and H.-M. Guo, *Chem. – Eur. J.*, 2018, **24**, 15512–15516.
- U. Kaya, P. Chauhan, S. Mahajan, K. Deckers, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2017, **56**, 15358–15362.
- J. An, L. Lombardi, S. Grilli and M. Bandini, *Org. Lett.*, 2018, **20**, 7380–7383.
- M. Jin, W. Ren, D.-W. Qian and S.-D. Yang, *Org. Lett.*, 2018, **20**, 7015–7019.
- B. G. Das, S. Shah, A. Das and V. K. Singh, *Org. Lett.*, 2021, **23**, 6262–6266.
- S.-B. Tang, H.-F. Tu, X. Zhang and S.-L. You, *Org. Lett.*, 2019, **21**, 6130–6134.
- Z. Fu, J. Zhu, S. Guo and A. Lin, *Chem. Commun.*, 2021, **57**, 1262–1265.
- D.-C. Wang, P.-P. Cheng, T.-T. Yang, P.-P. Wu, G.-R. Qu and H.-M. Guo, *Org. Lett.*, 2021, **23**, 7865–7872.
- L. Ding, W.-T. Wu, L. Zhang and S.-L. You, *Org. Lett.*, 2020, **22**, 5861–5865.
- D. Wang and X. Tong, *Org. Lett.*, 2017, **19**, 6392–6395.
- G.-T. Li, Q. Gu and S.-L. You, *Chem. Sci.*, 2015, **6**, 4273–4278.
- Z. Li, J. Peng, C. He, J. Xu and H. Ren, *Org. Lett.*, 2020, **22**, 5768–5772.
- L. Liu, X. Ji, J. Dong, Y. Zhou and S.-F. Yin, *Org. Lett.*, 2016, **18**, 3138–3141.
- T. Kaicharla, A. Jacob, R. G. Gonnade and A. T. Biju, *Chem. Commun.*, 2017, **53**, 8219–8222.
- A. Jacob, T. Roy, T. Kaicharla and A. T. Biju, *J. Org. Chem.*, 2017, **82**, 11269–11274.
- Y. Zhang, S. Li, Y. Zhu, X. Yang, H. Zhou and Y. Li, *J. Org. Chem.*, 2020, **85**, 6261–6270.
- Z. He, A. P. Pulis and D. J. Procter, *Angew. Chem., Int. Ed.*, 2019, **58**, 7813–7817.
- L.-W. Qi, S. Li, S.-H. Xiang, J. Wang and B. Tan, *Nat. Catal.*, 2019, **2**, 314–323.
- G. Coombs, M. H. Sak and S. J. Miller, *Angew. Chem., Int. Ed.*, 2020, **59**, 2875–2880.
- M. Moliterno, R. Cari, A. Puglisi, A. Antenucci, C. Sperandio, E. Moretti, A. Di Sabato, R. Salvio and M. Bella, *Angew. Chem., Int. Ed.*, 2016, **55**, 6525–6529.
- S. Narute, R. Parnes, F. D. Toste and D. Pappo, *J. Am. Chem. Soc.*, 2016, **138**, 16553–16560.
- J.-M. Tian, A.-F. Wang, J.-S. Yang, X.-J. Zhao, Y.-Q. Tu, S.-Y. Zhang and Z.-M. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 11023–11027.
- E. Paradisi, P. Righi, A. Mazzanti, S. Ranieri and G. Bencivenni, *Chem. Commun.*, 2012, **48**, 11178–11180.
- Y.-L. Zhao, Q.-X. Lou, L.-S. Wang, W.-H. Hu and J.-L. Zhao, *Angew. Chem., Int. Ed.*, 2017, **56**, 338–342.
- C.-Y. Li, M. Xiang, J. Zhang, W.-S. Li, Y. Zou, F. Tian and L.-X. Wang, *Org. Biomol. Chem.*, 2021, **19**, 7690–7694.
- N. Suzuki and K. Nakata, *Eur. J. Org. Chem.*, 2017, 7075–7086.
- N. Suzuki, S. Tsuchihashi and K. Nakata, *Tetrahedron Lett.*, 2016, **57**, 1456–1459.
- G.-P. Yang, D. Dilixiati, T. Yang, D. Liu, B. Yu and C.-W. Hu, *Appl. Organomet. Chem.*, 2018, **32**, e4450.
- R. Dada, G. Singh, A. Pareek, S. Kausar and S. Yaragorla, *Tetrahedron Lett.*, 2016, **57**, 3739–3742.
- J. Le Bras and J. Muzart, *Tetrahedron*, 2007, **63**, 7942–7948.
- R. Sanz, A. Martínez, D. Miguel, J. M. Álvarez-Gutiérrez and F. Rodríguez, *Adv. Synth. Catal.*, 2006, **348**, 1841–1845.
- S. Pradhan, M. Mishra, P. B. De, S. Banerjee and T. Punniyamurthy, *Org. Lett.*, 2020, **22**, 1720–1725.
- M. Barbero, S. Cadamuro and S. Dughera, *Synthesis*, 2006, 3443–3452.



- 47 C. Pan, G. Huang, Y. Shan, Y. Li and J.-T. Yu, *Org. Biomol. Chem.*, 2020, **18**, 3038–3042.
- 48 Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga and M. Kanai, *Angew. Chem., Int. Ed.*, 2015, **54**, 9944–9947.
- 49 Y.-L. Liu, L. Liu, Y.-L. Wang, Y.-C. Han, D. Wang and Y.-J. Chen, *Green Chem.*, 2008, **10**, 635–640.
- 50 H. Ohmiya, Y. Makida, D. Li, M. Tanabe and M. Sawamura, *J. Am. Chem. Soc.*, 2010, **132**, 879–889.
- 51 Y. Zhang, S.-C. Yin and J.-M. Lu, *Tetrahedron*, 2015, **71**, 544–549.
- 52 H. Tsukamoto, M. Sato and Y. Kondo, *Chem. Commun.*, 2004, 1200–1201.
- 53 K.-Q. Wu, H. Li, A. Zhou, W.-R. Yang and Q. Yin, *J. Org. Chem.*, 2023, **88**, 2599–2604.
- 54 A. Cullen, A. J. Muller and D. B. G. Williams, *RSC Adv.*, 2017, **7**, 42168–42171.
- 55 W. Rao and P. W. H. Chan, *Org. Biomol. Chem.*, 2008, **6**, 2426–2433.
- 56 G. Wang, L. Gao, H. Chen, X. Liu, J. Cao, S. Chen, X. Cheng and S. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 1694–1699.
- 57 T. Kikuchi, S. Gontani, K. Miyanaga, T. Kurata, Y. Akatani and S. Matsumoto, *Acta Cryst. E*, 2019, **75**, 242–245.
- 58 T. L. Huang, A. Székács, T. Uematsu, E. Kuwano, A. Parkinson and B. D. Hammock, *Pharm. Res.*, 1993, **10**, 639–648.
- 59 M. R. Hellberg, A. Namil and J. C. Nixon, WO9932474, 1999.
- 60 H. Huang, J. Ash and J. Y. Kang, *Org. Lett.*, 2018, **20**, 4938–4941.
- 61 B. J. Foust, M. M. Poe, N. A. Lentini, C.-H. C. Hsiao, A. J. Wiemer and D. F. Wiemer, *ACS Med. Chem. Lett.*, 2017, **8**, 914–918.
- 62 S. Estopiñá-Durán and J. E. Taylor, *Chem. Eur. J.*, 2021, **27**, 106–120.
- 63 S. Yamabe and S. Yamazaki, *J. Phys. Org. Chem.*, 2009, **22**, 1094–1103.
- 64 G. W. Wheland, *J. Am. Chem. Soc.*, 1942, **64**, 900–908.
- 65 G. A. Olah, *Acc. Chem. Res.*, 1971, **4**, 240–248.

