Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Org. Biomol. Chem.*, 2024, **22**, 80

Received 31st October 2023,
Accepted 22nd November 2023

DOI: 10.1039/d3ob01784b

rsc.li/obc

Sterically demanding Csp^2(*ortho*-substitution)–Csp^3(tertiary) bond formation *via* carboxylate-directed Mizoroki-Heck reaction under extra-ligand-free conditions†

Wei Zeng,‡[a,b] Ai-Wen Chen,‡[a,b] Ming-Jie Yan[a,b] and Jie Wang *[a,b,c]

Construction of the sterically demanding Csp^2(*o*S)–Csp^3(T) bond was achieved by carrying out the Pd-catalyzed carboxylate-directed Mizoroki-Heck reaction under extra-ligand-free aqueous conditions. The cooperative role of the presence of water with the absence of phosphine ligand was proposed to accelerate the migratory insertion process considerably, delivering a broad substrate scope.

Due to the importance of sp^3 carbon atoms[1] in accessing a diversified chemical space for drug discovery, there has been much recent interest in developing new methods to construct Csp^2–Csp^3 bonds.[2] There are extra challenges when targeting the sterically demanding Csp^2(*o*S)–Csp^3(T) bonds characterized by an *ortho*-substituted sp^2 carbon attached to a tertiary sp^3 carbon center, which are often found in complex natural products. Over the past decade, although a plethora of interesting new approaches have emerged allowing for versatile access to tertiary Csp^2–Csp^3 bonds intermolecularly, only a few of them could tolerate *ortho*-substitution on the sp^2 coupling partner, including the Friedel–Crafts reaction,[3] directed Mizoroki-Heck reaction[4] and C–H functionalization,[5] redox-relay Heck reaction,[6] and the widely studied cross-coupling reactions.[7] Of these approaches, the directing group strategy is particularly highly reliable and shows adequate regio- and stereo-chemical control.[8] For example, the amine-directed intermolecular Mizoroki-Heck reaction developed by Hallberg was used to construct a Csp^2(*o*S)–Csp^3(T) bond efficiently in a highly regio- and *enantio*-selective manner (Fig. 1A).[4] Aniline derivatives and aryl iodide are effective directing groups in ruthenium-catalyzed and electrochemically catalyzed C–H alkylation reactions, securing a versatile construction of Csp^2(*o*S)–Csp^3(T) bonds.[5] In this context, we are interested in constructing Csp^2(*o*S)–Csp^3(T) bonds using the directivity of carboxylic acid, particularly due to the ubiquitous nature, good stability, and remarkable transformational versatility of this functional group in organic synthesis. Although the directivity of free carboxylic acid was previously well documented in palladium-catalyzed C–H functionalizations,[9] it has hardly been used at all in Mizoroki-Heck reactions.[10] While this strategy

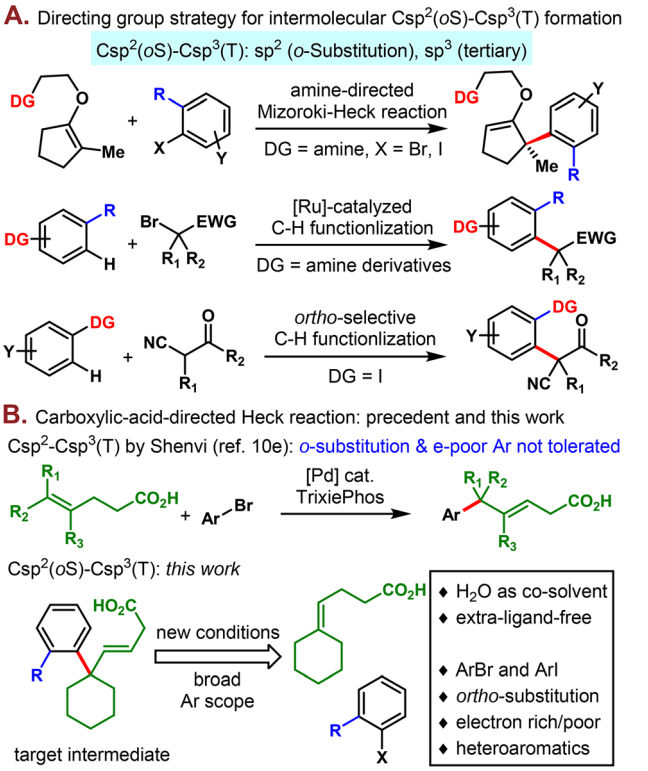


Fig. 1 (A) Directing group strategy for intermolecular Csp^2(*o*S)–Csp^3(T) bond formation. (B) Construction of the Csp^2–Csp^3 bond *via* the directivity of carboxylic acid: precedent and this work.

[a]*School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing 210023, China. E-mail: jiewang@simm.ac.cn*
[b]*State Key Laboratory of Chemical Biology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*
[c]*University of Chinese Academy of Sciences, Beijing 100049, China*

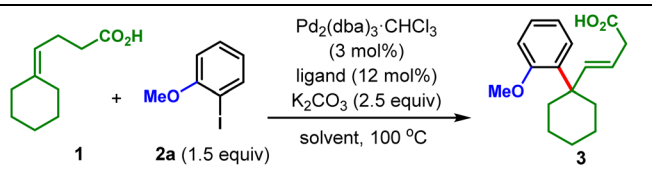
†Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ob01784b

‡These authors contributed equally to this work.

has been studied by White,[10a] Zhao[10b] and Chou[10c] for Csp^2–Csp^2 bond formation, the method reported by Shenvi and co-workers is, to the best of our knowledge, the only example for constructing a Csp^2–Csp^3(T) bond with a sterically hindered quaternary carbon center (Fig. 1B).[10d–e] However, *ortho*-substituted and electron deficient aryl bromides were reported to be incompatible as commented in their article and supporting information. Here, in this work, we present the development of a new extra-ligand-free aqueous condition allowing access to the extremely challenging Csp^2(*o*S)–Csp^3(T) bonds. Aryl bromides or iodides of different electronic characteristics and other substitution patterns were well tolerated.

Our reaction conditions were optimized with γ,δ-unsaturated carboxylic acid **1** and aryl halide **2** as model substrates (Table 1). Initially, the conditions reported by Shenvi and coworkers were attempted with 2-bromoanisole as the aryl coupling partner. However, the desired product **3** was not detected even in the slightest amount (entry 1).[10e] To our delight, by simply changing 2-bromoanisole to 2-iodoanisole (**2a**), **1** was delivered in 30% yield under the otherwise same conditions (entry 2). Ligand screening revealed that inclusion of PPh_3 and DavePhos increased the yields slightly (entry 3) while P(*o*-Tol)$_3$ and JohnPhos provided product in less than 10% yield (entry 4). Bidentate phosphine ligands were also tested and proved to be ineffective for this chemistry (see ESI† for details). Interestingly, we found that the reaction also proceeded to some extent in the absence of phosphine ligand, with a low yield of 15% obtained (entry 5). Under these extra-ligand-free conditions, other single solvents such as DMA, 1,4-dioxane, and DMSO all performed poorly (entry 6). Gratifyingly, a thorough solvent screen led us to discover H_2O to be a crucial co-solvent for increasing the reaction yield significantly (entries 7–9), and the optimal DMF/H_2O ratio was identified to be 5 : 1, providing **3** in 60% yield (entry 9). The H_2O promotion phenomenon was also observed to be general, for several other solvents tested (entries 10–12 *vs.* entry 6). DMSO/H_2O gave the same yield as did DMF/H_2O (entry 12 *vs.* entry 9) and showed comparable efficiencies for other substrates except for strongly electron-deficient ones (see ESI† for a detailed list of substrates tested). Under the newly developed conditions, addition of phosphine ligands exhibited a deleterious effect on the reaction yields (entries 13 and 14). Finally, changing the temperature (entry 15), palladium source (entry 16) and base (entry 16) all delivered inferior results.

Table 1 Optimization of reaction conditions[a]



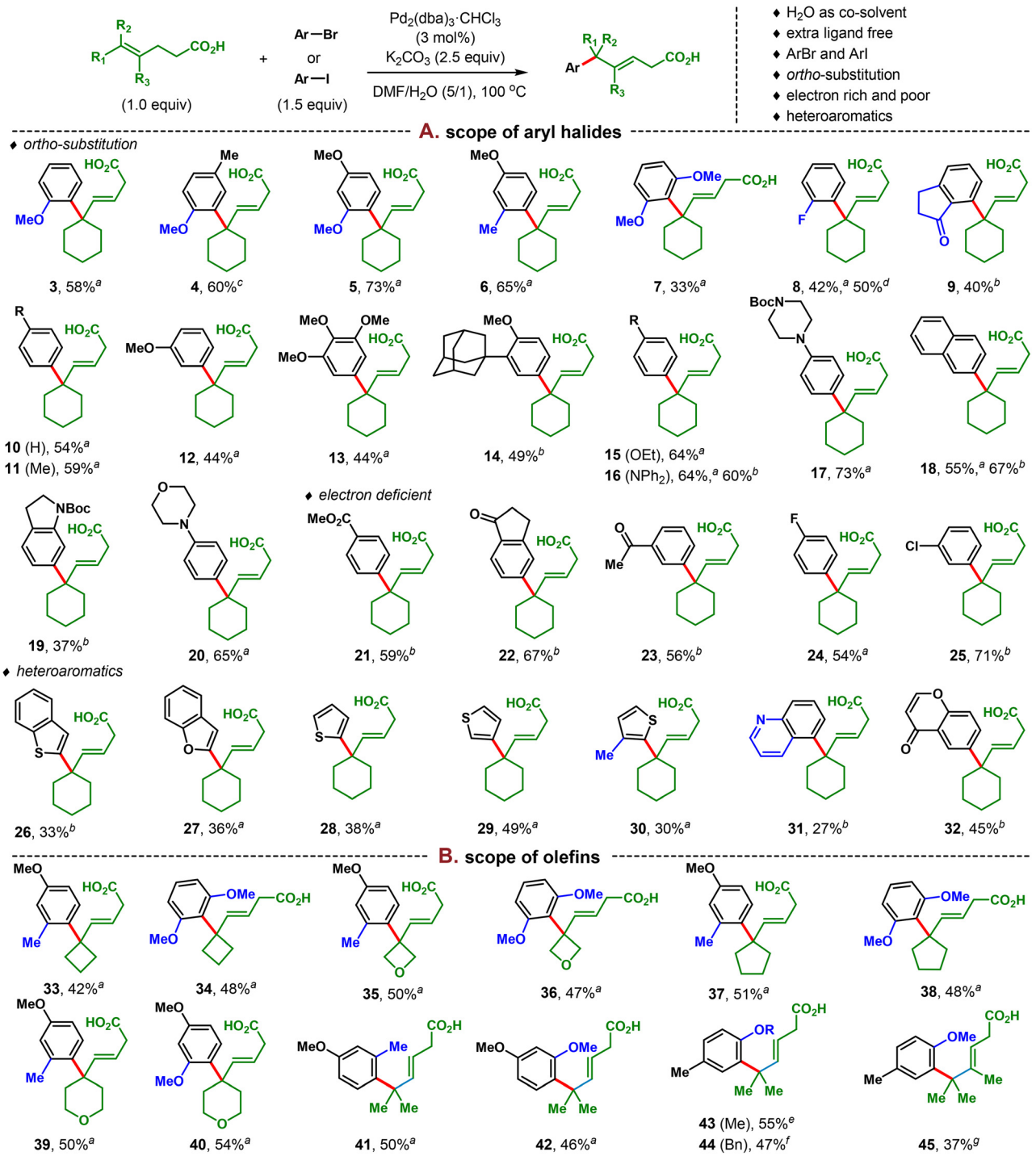
1 2a (1.5 equiv) 3

Entry	Ligand	Solvent	Yield[b]
1[c]	TrixiePhos	DMF	0%
2	TrixiePhos	DMF	30%
3	PPh_3/DavePhos	DMF	39%/33%
4	P(*o*-Tol)$_3$, JohnPhos	DMF	<10%
5	—	DMF	15%
6	—	DMA, 1,4-dioxane, DMSO	<5%
7[d]	—	DMF/H_2O (1/1)	44%
8[e]	—	DMF/H_2O (2/1)	52%
9	—	**DMF/H_2O (5/1)**	**60% (58%)**[f]
10	—	DMA/H_2O (5/1)	32%
11	—	1,4-dioxane/H_2O (5/1)	30%
12	—	DMSO/H_2O (5/1)	60%
13	TrixiePhos	DMF/H_2O (5/1)	36%
14	PPh3/DavePhos	DMF/H_2O (5/1)	39%/39%
15[g]	—	DMF/H_2O (5/1)	47–51%
16[h]	—	DMF/H_2O (5/1)	12–45%
17[i]	—	DMF/H_2O (5/1)	15–45%

[a] Reaction conditions: **1** (0.1 mmol), **2a** (1.5 equiv.), $Pd_2(dba)_3$·$CHCl_3$ (3 mol%), ligand (12 mol%) if used, and K_2CO_3 (2.5 equiv.) were dissolved in solvent (0.6 mL) and heated to 100 °C under an Ar atmosphere. [b] Yield determined from a crude ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] 2-Bromoanisole was used instead of **2a**. [d] DMF (0.3 mL) and H_2O (0.3 mL). [e] DMF (0.4 mL) and H_2O (0.2 mL). [f] Isolated yield. [g] Reaction temperature was 90 or 110 °C. [h] $Pd(OAC)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, or $Pd(PPh_3)_4$ was used instead of $Pd_2(dba)_3$·$CHCl_3$. [i] $NaHCO_3$, Na_2CO_3, Cs_2CO_3, *t*BuONa, or Et_3N was used instead of K_2CO_3. See ESI† for more details.

With the optimized conditions in hand, we set out to investigate the substrate scope. It turned out that the new conditions developed above were generally effective across a range of substrates (>40 examples) as shown in Scheme 1. The aryl coupling partner scope was first investigated (Scheme 1A). Various *ortho*-substituents ranging from electron-rich to electron-poor ones including MeO (**3**, **4**, **5**, **7**), Me (**6**), F (**8**), and carbonyl (**9**) were well tolerated. Even a highly hindered bis-*ortho*-substituted substrate provided product in 33% yield (**7**). Commercial aryl halides with other substitution patterns and different electronic characteristics were then evaluated. While a similar efficiency was observed for electron-rich and electron-neutral arenes (**11**–**20**) as was observed for the Shenvi conditions, a significant improvement in yields for electron-poor ones was obtained.[10e] For example, aryl bromides with strongly electron-withdrawing groups in the *para* position were previously reported to be unreactive, while that in the *meta* position was delivered in low yield. In contrast, under our conditions, these substrates all provided products in moderate to good yields (**21**–**23**). Moderately electron-deficient F- and Cl-substituted arenes also worked well, providing **24** and **25** in 54% and 71% yields, respectively. Various heteroaromatic substrates were also tested and showed improved efficiency. In this regard, electron-rich heterocycles such as benzothiophene (**26**), benzofuran (**27**), and either 2- or 3-thiophene with or without *ortho*-substitution (**28**–**30**) all gave moderate yields. Electron-poor ones such as quinoline (**31**) and chromone (**32**) also proved to be viable substrates under our conditions.

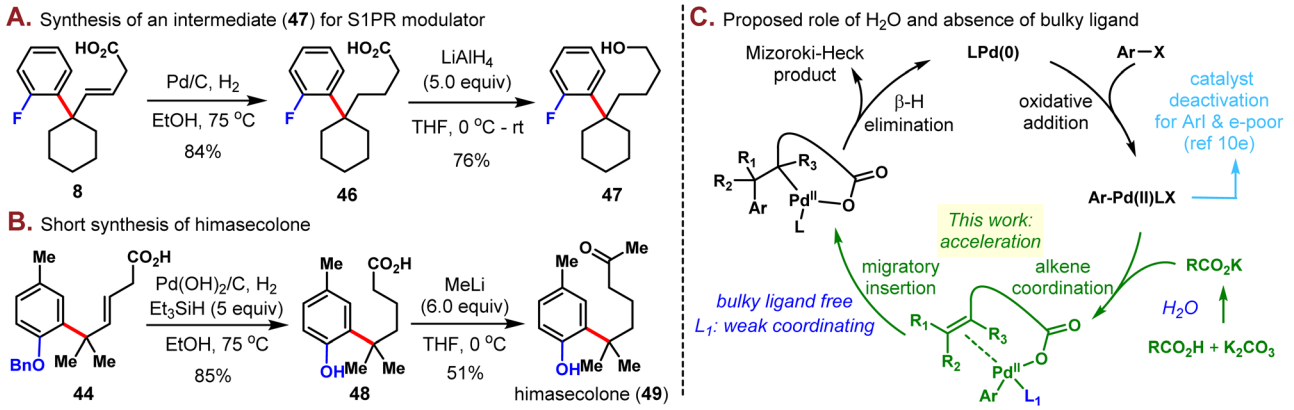
Next, several other γ,δ-unsaturated carboxylic acids were evaluated with *o*-OMe- or bis-*o*-OMe-substituted aryl coupling partners as shown in Scheme 1B. Yields of 37–55% were obtained consistently for all the 4–6-membered cyclic, heterocyclic, and noncyclic substrates (**33**–**45**). The *ortho*-benzyl ether protecting group was also tolerated, providing slightly lower yield than provided by the *ortho*-OMe counterpart (47% *vs.* 55% for **44** and **43**). With a more hindered tetrasubstituted



Scheme 1 Reaction conditions: olefin (0.1 mmol, 1.0 equiv.), aryl halide (1.5 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mol%), and K_2CO_3 (2.5 equiv.) were dissolved in DMF/H_2O (5/1, 0.6 mL) and stirred at 100 °C under an argon atmosphere for 5–12 hours. Yield referred to isolated yield unless otherwise noted. [a] ArI was used. [b] ArBr was used. [c] DMF/H_2O (5/1, 1.2 mL) was used. [d] Olefin (0.5 mmol), ArI (1.5 equiv.), DMF/H_2O (5/1, 6.0 mL). [e] 1.0 mmol scale. [f] ArI (1.0 mmol), olefin (1.5 equiv.). [g] ArI (3.0 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol%).

olefin (**45**), a useful yield of 37% was also obtained after slight modification to the original conditions including use of 10 mol% catalyst.

The successful implementation of this newly developed condition also relied largely on the judicious choice of aryl bromide or iodide precursors. Empirically, aryl iodides outperformed the corresponding aryl bromides for electron-rich and neutral substrates (**1**, **5**, **6**, **12**, **13**, **15**, **17**, **20**, and **30**), while aryl bromides worked better for electron-deficient ones (**8**, **23**, **25**). The generally moderate yields obtained throughout the investi-



Scheme 2 (A) Synthesis of drug intermediate **47** and (B) natural product himasecolone (**49**). (C) Proposed role of H_2O and absence of bulky ligand.

gation of substrate scope mainly stemmed from byproduct where the double bond migrated to be conjugated with the carboxylic acid through chain walking (typically 1/5–1/10 with regards to the shown products) and, in some cases, incomplete conversions.

While reactions with most of the substrates shown in Scheme 1 were performed on a 0.1 mmol scale, scale-up proved uneventful and was exemplified by substrates **8** and **44** on 0.5 and 1.0 mmol scales, respectively. They were then easily converted to known respective intermediates and natural products containing Csp^2(oS)–Csp^3(T) bonds, further demonstrating the utility of this new method (Schemes 2A and B). To this end, compound **47**, a synthetic intermediate for S1P receptor modulator,[11] was straightforwardly accessed from **8** in two steps and 64% overall yield by successive reduction of the alkene and carboxylic acid functional group. As another example, the sesquiterpenoid natural product himasecolone (**49**)[12] was synthesized simply from **44** by carrying out a one-step Bn deprotection/alkene hydrogenation followed by transforming the carboxylic acid group to methyl ketone in 43% overall yield. In both cases, the strategic construction of the synthetically challenging Csp^2(*o*S)–Csp^3(T) moiety in an early stage provided extreme immediacy and simplicity for subsequent functional group manipulations.

Based on previous reports of palladium-catalysed Mizoroki-Heck reactions in aqueous media,[13] we arrived at an understanding of the mechanistic advantages of the current conditions (Scheme 2C). Oxidative addition and migratory insertion have often been regarded as rate-determining steps in Heck reactions.[14] In the carboxylate-directed Heck reaction, we assumed the ArPd(II) carboxylate formation, coordination to alkene, and subsequent migratory insertion to be a relatively slow process, but one accelerated under our H_2O-containing and ligand-free conditions.[15] The H_2O co-solvent not only increased the solubility of the inorganic base K_2CO_3 and the effective concentration of palladium carboxylate,[16] but also promoted the migratory insertion to follow cationic mechanism by displacing the poisonous iodide or bromide anion from the coordination shell of palladium, the effect of which could be more pronounced under extra-ligand-free conditions.[17] On the other hand, the omission of a bulky phosphine ligand also contributed significantly to this process by allowing for a free coordination site on the palladium center, reducing the steric congestion and thus increasing the rate of migratory insertion.[18] While the sluggish migratory insertion step was accelerated substantially, the reaction showed better tolerance for the rate of oxidative addition, that is to say, a wide range of both aryl bromides and iodides with varied electronic characteristics could be used. In the case of electron-deficient substrates (**9**, **21–23**, **31–32**), our aqueous conditions free of phosphine ligand might have led to slower oxidative addition of aryl bromides,[19] which probably better matched the accelerated downstream migratory insertion step and prevented the Ar-Pd(II) accumulation and deactivation process proposed by Shenvi and coworkers.[10e]

Conclusions

In summary, the construction of sterically demanding Csp^2(*o*S)–Csp^3(T) bonds (>20 examples) was achieved by carrying out palladium-catalyzed carboxylate-directed Mizoroki-Heck reactions. The extra-ligand-free aqueous conditions were suitable for aryl halides with various substitution patterns and electronic characteristics, and the utility of this method was further demonstrated through a few-step synthesis of the Csp^2(*o*S)–Csp^3(T)-bond-containing S1PR modulator and sesquiterpenoid natural product himasecolone. Mechanistically, we proposed that the high substrate scope arose from the rapid migratory insertion, which was significantly accelerated by the use of H_2O as co-solvent and the absence of phosphine ligand acting cooperatively.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support for this work was provided by the National Natural Science Foundation of China (Grant No. 22101290), Chinese Academy of Sciences and Shanghai Institute of Materia Medica. We thank Professor Hui-Xiong Dai for helpful discussions.

References

1 (*a*) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (*b*) W. P. Walters, J. Green, J. R. Weiss and M. A. Murcko, *J. Med. Chem.*, 2011, **54**, 6405–6416.

2 For selected reviews on Csp2–Csp3 cross-couplings, see: (*a*) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417–1492; (*b*) G. C. Fu, *ACS Cent. Sci.*, 2017, **3**, 692–700; (*c*) M. L. Neidig, S. H. Carpenter, D. J. Curran, J. C. DeMuth, V. E. Fleischauer, T. E. Iannuzzi, P. G. N. Neate, J. D. Sears and N. J. Wolford, *Acc. Chem. Res.*, 2018, **52**, 140–150; (*d*) R. Shi, Z. Zhang and X. Hu, *Acc. Chem. Res.*, 2019, **52**, 1471–1483; (*e*) A. Guérinot and J. Cossy, *Acc. Chem. Res.*, 2020, **53**, 1351–1363; (*f*) W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin and H. Gong, *Chem. Soc. Rev.*, 2021, **50**, 4162–4184.

3 S. Zhang, M. Vayer, F. Noël, V. D. Vuković, A. Golushko, N. Rezajooei, C. N. Rowley, D. Lebœuf and J. Moran, *Chem*, 2021, **7**, 3425–3441.

4 P. Nilsson, M. Larhed and A. Hallberg, *J. Am. Chem. Soc.*, 2003, **125**, 3430–3431.

5 (*a*) S. Bauri, S. Kumar and A. Rit, *Adv. Synth. Catal.*, 2023, **365**, 2385–2391; (*b*) Z. Deng, W. Fan, J. Liu, G. Tu, P. Huang, X. Xu, J. Tan, S. J. Ji and Y. Zhao, *Chem. – Eur. J.*, 2023, **29**, DOI: **10.1002/chem.202300905**; (*c*) X. Lv, Y. Cheng, Y. Zong, Q. Wang, G. An, J. Wang and G. Li, *ACS Catal.*, 2023, **13**, 7310–7321; (*d*) X. Zheng, P. Peng, C. Huang and Q. Lu, *CCS Chem.*, 2023, **5**, 1086–1095.

6 (*a*) T.-S. Mei, H. H. Patel and M. S. Sigman, *Nature*, 2014, **508**, 340–344; (*b*) C. C. Oliveira, A. Pfaltz and C. R. D. Correia, *Angew. Chem., Int. Ed.*, 2015, **54**, 14036–14039.

7 (*a*) A. Joshi-Pangu, C.-Y. Wang and M. R. Biscoe, *J. Am. Chem. Soc.*, 2011, **133**, 8478–8481; (*b*) X. Wang, G. Ma, Y. Peng, C. E. Pitsch, B. J. Moll, T. D. Ly, X. Wang and H. Gong, *J. Am. Chem. Soc.*, 2018, **140**, 14490–14497; (*c*) T. G. Chen, H. Zhang, P. K. Mykhailiuk, R. R. Merchant, C. A. Smith, T. Qin and P. S. Baran, *Angew. Chem., Int. Ed.*, 2019, **58**, 2454–2458; (*d*) B. Li, J.-L. Shi and Y. Xia, *Org. Lett.*, 2023, **25**, 2674–2679.

8 For selected reviews, see: (*a*) M. Oestreich, *Eur. J. Org. Chem.*, 2005, 783–792; (*b*) K. Murali, L. A. Machado, R. L. Carvalho, L. F. Pedrosa, R. Mukherjee, E. N. Da Silva Junior and D. Maiti, *Chem. – Eur. J.*, 2021, **27**, 12453–12508; (*c*) J. Das, W. Ali and D. Maiti, *Trends Chem.*, 2023, **5**, 551–560.

9 For selected reviews, see: (*a*) K. M. Engle, T. S. Mei, M. Wasa and J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (*b*) G. Shi and Y. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 1419–1442; (*c*) M. P. Drapeau and L. J. Goossen, *Chem. – Eur. J.*, 2016, **22**, 18654–18677.

10 (*a*) J. H. Delcamp, A. P. Brucks and M. C. White, *J. Am. Chem. Soc.*, 2008, **130**, 11270–11271; (*b*) S. Yang, L. Liu, Z. Zhou, Z. Huang and Y. Zhao, *Org. Lett.*, 2021, **23**, 296–299; (*c*) S. Y. Tsai, Y. W. Huang and C. M. Chou, *Adv. Synth. Catal.*, 2023, **365**, 699–703; (*d*) J. J. Roach, Y. Sasano, C. L. Schmid, S. Zaidi, V. Katritch, R. C. Stevens, L. M. Bohn and R. A. Shenvi, *ACS Cent. Sci.*, 2017, **3**, 1329–1336; (*e*) T. R. Huffman, Y. Wu, A. Emmerich and R. A. Shenvi, *Angew. Chem., Int. Ed.*, 2019, **58**, 2371–2376.

11 P. X. Nguyen, T. M. Heidelbaugh and J. R. Cappiello, (Allergan Inc.), WO 2014/093253A1, 2014.

12 (*a*) P. K. Agarwal and R. P. Rastogi, *Phytochemistry*, 1981, **20**, 1319–1321; (*b*) S. V. Trivedi and V. R. Mamdapur, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1986, **25**, 1160.

13 (*a*) L.-M. Tao, Q.-G. Li, W.-Q. Liu, Y. Zhou and J.-F. Zhou, Water-Promoted Palladium-Catalysed Heck Cross-Coupling Reactions of Aryl Halides with Alkenes in TBAB, *J. Chem. Res.*, 2011, **35**, 154–156; (*b*) F. Christoffel and T. R. Ward, Palladium-Catalyzed Heck Cross-Coupling Reactions in Water: A Comprehensive Review, *Catal. Lett.*, 2017, **148**, 489–511; (*c*) S. N. Jadhav and C. V. Rode, An efficient palladium catalyzed Mizoroki–Heck cross-coupling in water, *Green Chem.*, 2017, **19**, 5958–5970.

14 C. S. Consorti, F. R. Flores and J. Dupont, *J. Am. Chem. Soc.*, 2005, **127**, 12054–12065.

15 L. Xu, M. J. Hilton, X. Zhang, P.-O. Norrby, Y.-D. Wu, M. S. Sigman and O. Wiest, *J. Am. Chem. Soc.*, 2014, **136**, 1960–1967.

16 F. Zhao, M. Shirai and M. Arai, *J. Mol. Catal. A: Chem.*, 2000, **154**, 39–44.

17 I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066.

18 (*a*) J. H. Groen, J. G. P. Delis, P. W. N. M. van Leeuwen and K. Vrieze, *Organometallics*, 1997, **16**, 68–77; (*b*) V. H. Menezes da Silva, N. H. Morgon, C. R. D. Correia and A. A. C. Braga, *J. Organomet. Chem.*, 2019, **896**, 5–15.

19 (*a*) F. Barrios-Landeros, B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 8141–8154; (*b*) B. Noverges-Pedro, M. Medio-Simón and A. Jutand, *ChemCatChem*, 2017, **9**, 2136–2144.

