Chinese Chemical Letters 33 (2022) 2997–3002

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Copper-catalyzed diversified annulations between α-diketones and alkynyl α-diketones

Xiangwen Kong[a], Fang Yu[a], Shengtong Niu[a], Fan Gong[a], Shuang Yang[a], Jinggong Liu[c], Benlong Luo[b,*], Xinqiang Fang[a,*]

[a] State Key Laboratory of Structural Chemistry, and Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Center for Excellence in Molecular Synthesis, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, Fuzhou 350100, China
[b] Pingxiang University, Pingxiang 337055, China
[c] Orthopedics Department, Guangdong Provincial Hospital of Traditional Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou 510120, China

ARTICLE INFO

Article history:
Received 11 October 2021
Revised 21 November 2021
Accepted 23 November 2021
Available online 27 November 2021

Keywords:
Copper catalysis
α-Diketones
Diversified annulations
Substituents-controlled reactivities
Atom economy

ABSTRACT

Copper-catalyzed divergent annulations between α-diketones and alkynyl α-diketones have been achieved, delivering a series of highly functionalized and biologically important *cis*-hexahydro-2*H*-cyclopenta[*b*]furan (HCPF) and 2-hydroxydihydrofuran-3(2*H*)-one (HDFO) products with high levels of stereoselectivity under identical conditions. The protocol features the use of earth-abundant copper catalyst, mild conditions, shortening synthetic routes in constructing different molecular frameworks, and reducing the corresponding possible waste production. The substituents of the nucleophilic α-diketones play crucial roles in switching the reaction pathways.

Achieving diversified reactivity under identical reaction conditions through only slightly varying the substituents of a reactant is a charming strategy in synthetic chemistry, and accords with the criteria of green chemistry, since such a strategy significantly shortens the synthetic steps in constructing different molecular skeletons, thus reducing possible wastes and the corresponding contamination. However, such a strategy has been hard to be realized because the small change of a substituent is difficult to alter the inherent reactivity of a reaction [1–8]. Compared to the more frequently used methods of getting different products through modifying reaction conditions [9–15], the aforementioned protocol is still not common and underdeveloped.

On the other hand, *cis*-hexahydro-2*H*-cyclopenta[*b*]furan (HCPF) and 2-hydroxydihydrofuran-3(2*H*)-one (HDFO) widely occur in natural products and pharmaceutically active substances (Fig. 1) [16–22]. Specifically, spirotrichilin A shows *anti*-inflammatory activity on NO production in certain cell line [16], kuhistaferone displays moderate cytotoxicity against the human tumor cell in HCT116 [17], and gracilioether J has antileishmanial activity [18]. Moreover, GRL-0489A displays remarkable enzyme inhibitory and antiviral potency, and its antiviral activity against multidrug resistant HIV-1 variants is even higher than FDA approved inhibitors [16]; antagonists of the CC-chemokine receptor 2 (CCR2) have been vigorously pursued by many pharmaceutical companies as a target for drug discovery, because the compound could have the potential for use in the acute and chronic conditions of inflammatory and autoimmune diseases [20]. However, rapid construction of both HCPF and HDFO skeletons in an efficient and stereoselective manner is still a challenge, and most of the known reports employ a sequential construction strategy to make bicyclic HCPF structures, and one-step method to form the bicycles starting from acyclic substrates remain scarce. For example, Jamison and co-workers completed the total synthesis of (-)-terpestacin, and the four-step synthesis of HCPF derivative laid the foundation of the whole process (Scheme 1a) [23,24]. Similarly, two four-step methods were both used to make the bicyclic HCPF rings for the synthesis of GRL-0489A (Scheme 1b) [19] and CCR 2 antagonist (Scheme 1c) [20]. In all the above case, pre-existed ring structures were used to make the second ring units and multiple steps were always needed, which rendered the synthesis of HCPF skeletons less efficient and less atom-economic.

We have been interested in disclosing the unique features of α-diketone chemistry, and have found that under different conditions the same set of substrates can undergo distinct pathways to afford

* Corresponding authors.
E-mail addresses: 20010060@pxu.edu.cn (B. Luo), xqfang@fjirsm.ac.cn (X. Fang).

https://doi.org/10.1016/j.cclet.2021.11.070
1001-8417/

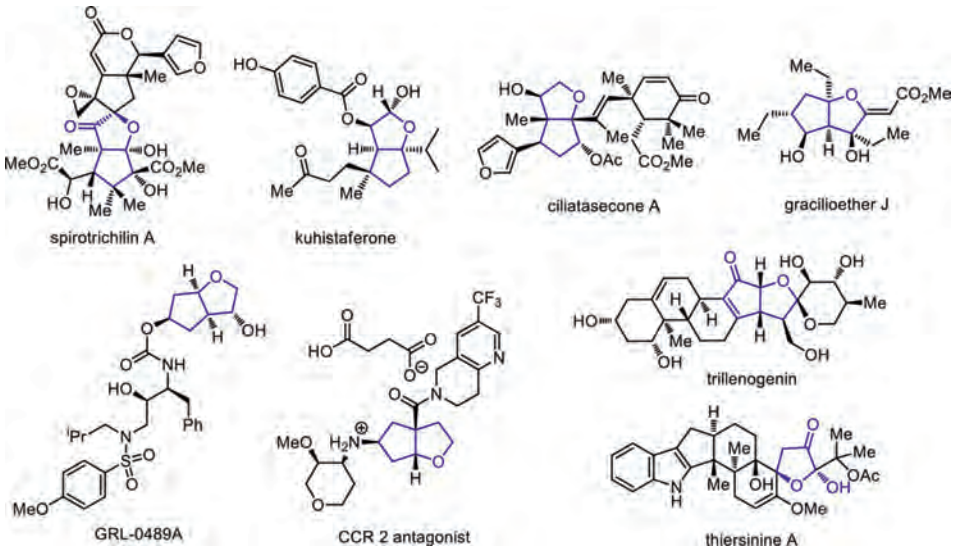
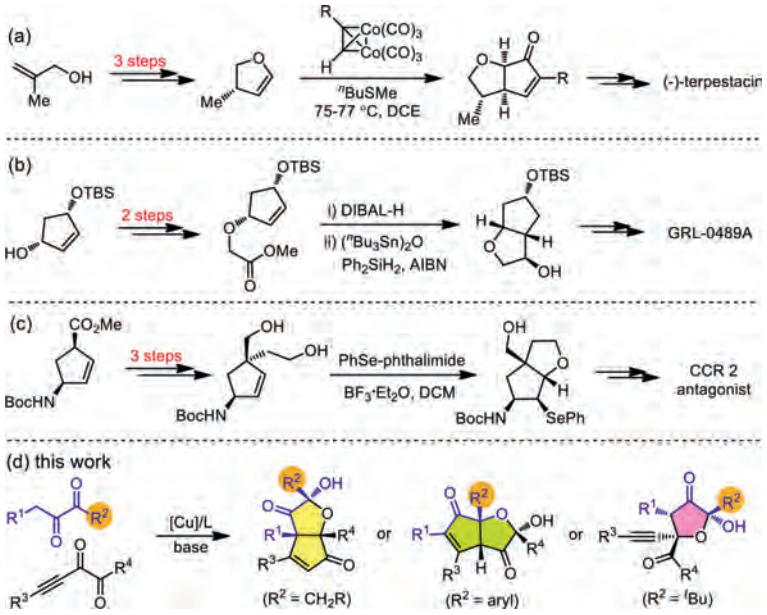


Fig. 1. Natural products and bioactive compounds containing HCPF and HDFO.

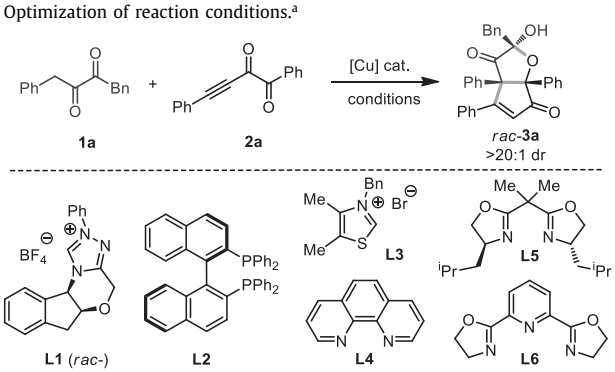


Scheme 1. Selected methods leading to HCPF compounds.

diverse products [25–27]. Here we report that under the same conditions of copper catalysis the reaction of α-diketones and alkynyl α-diketones can be switched by tuning the substituent within the nucleophilic α-diketones. Copper is earth abundant, not expensive, and less toxic. Moreover, the protocol affords a series of bicyclic products containing HCPF skeletons or HDFO units, thus providing a concise approach addressing the corresponding synthetic challenges (Scheme 1d).

As shown in Table 1, **1a** and **2a** were selected as the model substrates to test the corresponding annulation reactivity. Copper salts were employed to catalyze the process owing to the known abilities of copper in activating ynones [28–32]. Our initial test using CuCl as the catalyst, racemic *N*-heterocyclic carbene **L1** as the ligand, DABCO as the base, and CH_2Cl_2 as the solvent did not afford noticeable product (Table 1, entry 1). The solvent of MeOH was also not suitable for the reaction (Table 1, entry 2). To our delight, the use of THF and toluene was able to produce **3a** in 15% and 30% yield, respectively (Table 1, entries 3 and 4). **3a** contains a *cis*-bicyclic HCPF structure with ketone, enone, and hydroxy functionalities installed, and was obtained as the single diastereoisomer. Considering the importance of HCPF type compounds in organic synthesis and drug discovery, we continued the study to improve the yield of **3a**. Using toluene as the solvent, we surveyed a series of copper catalysts such as CuI, CuCN, and $CuBr_2$, but they could not further improve the yield of **3a** (Table 1, entries 5–7). However, $Cu(MeCN)_4BF_4$ and CuTc (copper(I) thiophene-2-carboxylate) showed better performance (Table 1, entries 8 and 9) and CuTc led to **3a** in 65% yield. Then using CuTc, a series of other bases such as Cs_2CO_3, K_2CO_3, Et_3N, DBU and $^iPr_2NEt$ were tested, but no better yield of **3a** was obtained (Table 1, entries 10–14). More different types of ligands such as bisphosphine **L2**, thiazolium **L3**, 1,10-phenanthroline **L4**, and Box-ligands **L5**-**L6** were also studied, but no higher yield was detected although most of them could deliver **3a** in certain yields (Table 1, entries 15–19). Control experiments in the absence of DABCO or CuTc could not furnish **3a** (Table 1, entries 20 and 21), indicating that both base and copper catalyst are necessary for the reaction. Only 24% yield of **3a** was gotten without ligand (Table 1, entry 22), demonstrating that ligand is able to

Table 1.
Optimization of reaction conditions.[a]



Entry	Cat.	Base	Ligand	Solvent	Yield (%)
1	CuCl	DABCO	**L1**	CH_2Cl_2	Trace
2	CuCl	DABCO	**L1**	MeOH	Trace
3	CuCl	DABCO	**L1**	THF	15
4	CuCl	DABCO	**L1**	Toluene	30
5	CuI	DABCO	**L1**	Toluene	Trace
6	CuCN	DABCO	**L1**	Toluene	19
7	$CuBr_2$	DABCO	**L1**	Toluene	33
8	$Cu(MeCN)_4BF_4$	DABCO	**L1**	Toluene	59
9 [b]	CuTc	DABCO	**L1**	Toluene	65
10	CuTc	Cs_2CO_3	**L1**	Toluene	Trace
11	CuTc	K_2CO_3	**L1**	Toluene	Trace
12	CuTc	Et_3N	**L1**	Toluene	35
13	CuTc	DBU	**L1**	Toluene	Trace
14	CuTc	$^iPr_2NEt$	**L1**	Toluene	28
15	CuTc	DABCO	**L2**	Toluene	31
16	CuTc	DABCO	**L3**	Toluene	Trace
17	CuTc	DABCO	**L4**	Toluene	34
18	CuTc	DABCO	**L5**	Toluene	23
19	CuTc	DABCO	**L6**	Toluene	21
20	CuTc	–	**L1**	Toluene	Trace
21	–	DABCO	**L1**	Toluene	Trace
22	CuTc	DABCO	–	Toluene	24
23 [c]	CuTc	DABCO	**L1**	Toluene	53

[a] Reactions conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), cat. (20 mol%), base (22 mol%), ligand (22 mol%), solvent (1 mL), 35 °C, 5 h, under argon atmosphere. The diastereomeric ratio was determined *via* ^{1}H NMR analysis of the reaction mixtures. All yields were isolated yields based on **2a**.
[b] CuTc is copper(I) thiophene-2-carboxylate.
[c] **1a** (0.2 mmol) was used.

accelerate the annulation process. Equal amount of **1a** was found to decrease the total yield of **3a** (Table 1, entry 23).

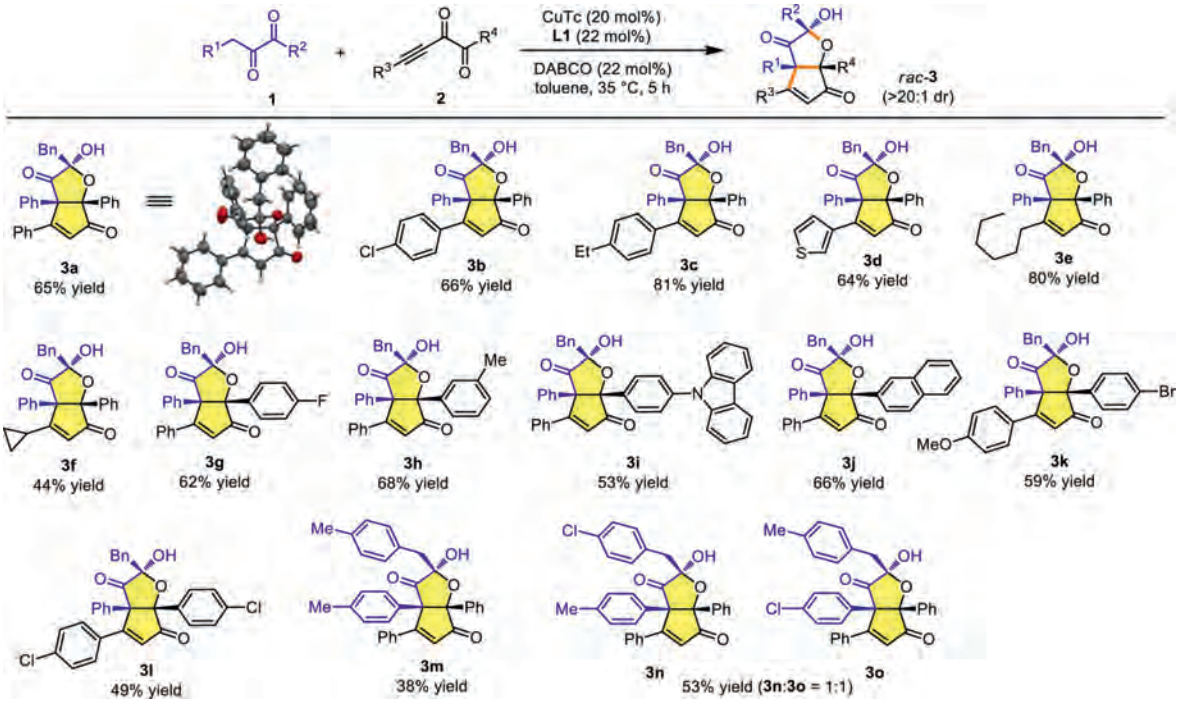
Having identified the optimal conditions, we started to examine the scope and limitation of the protocol. As shown in Scheme 2, the structure of **3a** was identified clearly using X-ray single-crystal structure analysis. The variation of R^3 group in alkynyl diketones using electron-withdrawing or donating groups did not affect the yield, leading to the formation of **3b** and **3c** in good to high yields (Scheme 2, **3b** and **3c**). Heterocyclic thienyl group showed little influence on the result (Scheme 2, **3d**), and aliphatic R^3 groups such as ^{n}hexyl and cyclopropyl proved compatible under the reaction conditions to afford **3e** and **3f** in 80% and 44% yields, respectively (Scheme 2, **3e** and **3f**). Subsequently, we studied the scope of R^4 substituent of the alkynyl diketones. We found that when R^4 were phenyl groups with electron-poor F or electron-rich Me substituents the yields were not affected, delivering **3g** and **3h** in 62% and 68% yields, respectively (Scheme 2, **3g** and **3h**). The reaction could also tolerate the phenyl ring bearing a carbazole substituent (Scheme 2, **3i**), and the use of a naphthyl group as R^4 proved suitable for the reaction (Scheme 2, **3j**). Furthermore, simultaneously varying both R^3 and R^4 groups proved possible, delivering **3k** and **3l** in moderate yields (Scheme 2, **3k** and **3l**). Changing both R^1 and R^2 also proved feasible to produce **3m**, albeit in relatively lower yield (Scheme 2, **3m**). When R^1 and R^2 groups bear different electronic properties, poor regioselectivity was observed, and both **3n** and **3o** were obtained with 1:1 ratio in 53% total yield (Scheme 2, **3n** and **3o**). When R^1 is an aliphatic group such as Me, the corresponding diketone substrate with Bn/Et substituents (**1p**) has also been tested but afforded a complicated mixture of unidentified products. To be noted is that in all cases, the products were obtained as single diastereoisomers.

Further survey of the nucleophilic diketones showed that when **1** were aryl substituted diketones, a thoroughly different reaction pathway was applied for the reaction, and relatively stable bicyclic products **4a** were isolated after the OH protection using *p*-nitrobenzoyl (PNB) group (Scheme 3, **4a**). The variation of R^1, R^2 and Ar groups all proved successful, releasing **4b, 4c** and **4d**, respectively. Both the annulation and the OH protection steps were performed in moderate yields, thus resulting the relatively low total yields. Furthermore, When ^{t}Bu-substituted diketones were studied, we found that the third mechanism predominated in the reaction, affording 2-hydroxydihydrofuran-3(2*H*)-one (HDFO) type products through a formal [3 + 2] annulation (Scheme 4, **5a**–**5d**). The reaction proved slow and certain amount of starting materials remained after 5 h. Both products **4** and **5** have three stereogenic centers and were formed with high diastereoselectivities (>20:1 dr). Moreover, **4a'** and **5b** were all confirmed *via* X-ray single-crystal structure analysis. Nucleophilic diketones with aliphatic R^1 such as Me have also been tested but showed low reactivities in forming the corresponding annulation products. Alkynyl diketones with alkyl R^3 substituent such as Me failed to deliver the corresponding products, and side reactions were detected.

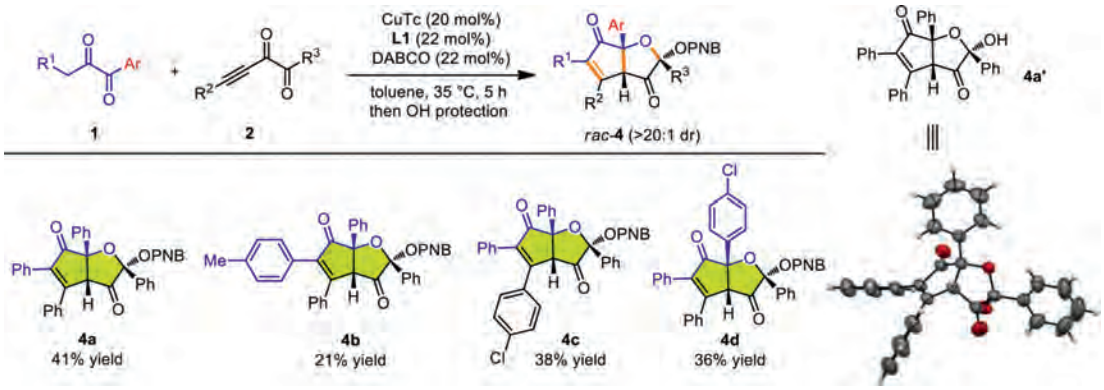
A series of further transformations using **3a** can be achieved. As shown in Scheme 5, an unexpected rearrangement occurred when **3a** was treated by PhMgBr, and after OH protection, **6a** was formed with high diastereoselectivity. In this reaction, the Grignard reagent might act as a strong base to facilitate the ring opening of **3a**, and the corresponding intermediate then undergoes a similar transformation as that occurs in the formation of **4**. The protection of **3a** afforded **6b** in 69% yield and dibromide **6c** could be produced from **6b** in good yield with the treatment of Br_2. Debromination of **6c** under transition-metal catalysis allowed access to **6d** The configuration of **6a**, **6c** and **6d** were all confirmed unambiguously *via* X-ray structure analysis.

The possible mechanisms for the diversified formation of three types of products are shown in Scheme 6. For product **3a**, the deprotonation of **1a** leads to enolate **I-1**, and after addition of **I-1** to **2a**, allenolate **I-2** is formed. A new type of enolate **I-3** is produced from the proton transfer within **I-2**, and the following aldol reaction initiates a formal [3 + 2] annulation to release **I-4**, and after protonation, **3a** is obtained (Scheme 6a). As to the formation of **4a** (Scheme 6b), after the Michael addition of enolate **II-1** to **2a, II-2** is formed, and the attack of phenyl ketone by the allenolate gives **II-3**. Then after the intramolecular annulation and protonation, **II-5** is generated. The isomerization happens for **II-5** to deliver more stable product **4a**. ^{t}Bu-substituted **1g** also produces enolate species **III-1** as the first step, but then the internal carbonyl of **2a** is attacked by **III-1**, and after a formal [3 + 2] annulation and protonation, **5a** is formed (Scheme 6c). Because the reaction cannot occur without CuTc catalyst, we postulate that copper salt is to activate the alkynyl diketones [32–34]. As to the mechanism divergence between **1a** and **1d**, after the initial Michael additions, phenyl ketone seems to be more active than benzyl ketone, thus is attacked by the allenolate intermediate.

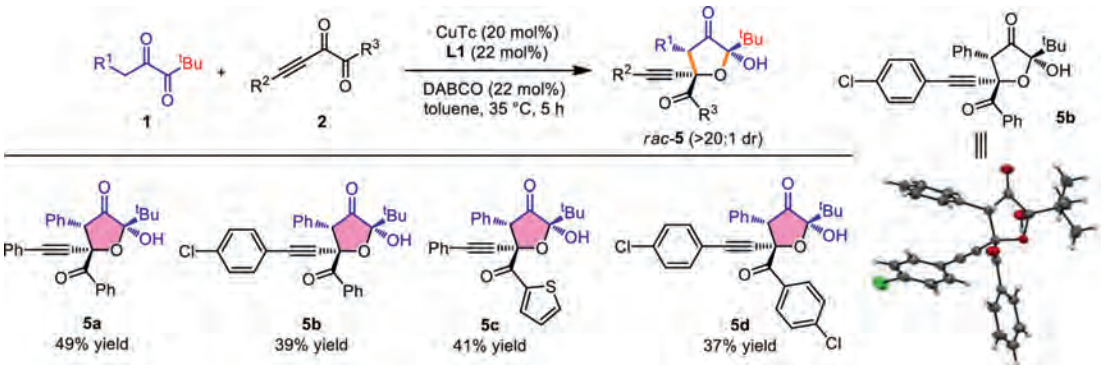
In summary, copper-catalyzed divergent annulations between α-diketones and alkynyl α-diketones have been developed, and a series of highly functionalized *cis*-hexahydro-2*H*-cyclopenta[*b*]furan (HCPF) and 2-hydroxydihydrofuran-3(2*H*)-one (HDFO) products are obtained with high levels of stereoselectivity control under mild conditions. The substituents of the



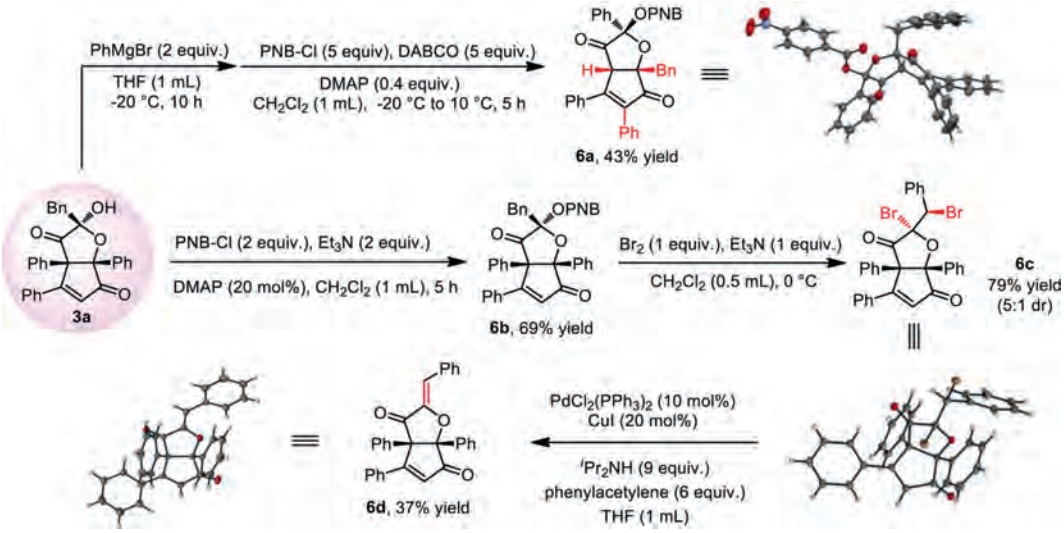
Scheme 2. Scope of functionalized HCPF **3** formation. Reactions conditions: **1** (0.3 mmol), **2** (0.2 mmol), CuTc (20 mol%), DABCO (22 mol%), **L1** (22 mol%), toluene (1 mL), 35 °C, 5 h, under argon atmosphere. The diastereomeric ratios were determined *via* ^{1}H NMR analysis of the reaction mixtures. All isolated yields were based on **2**.



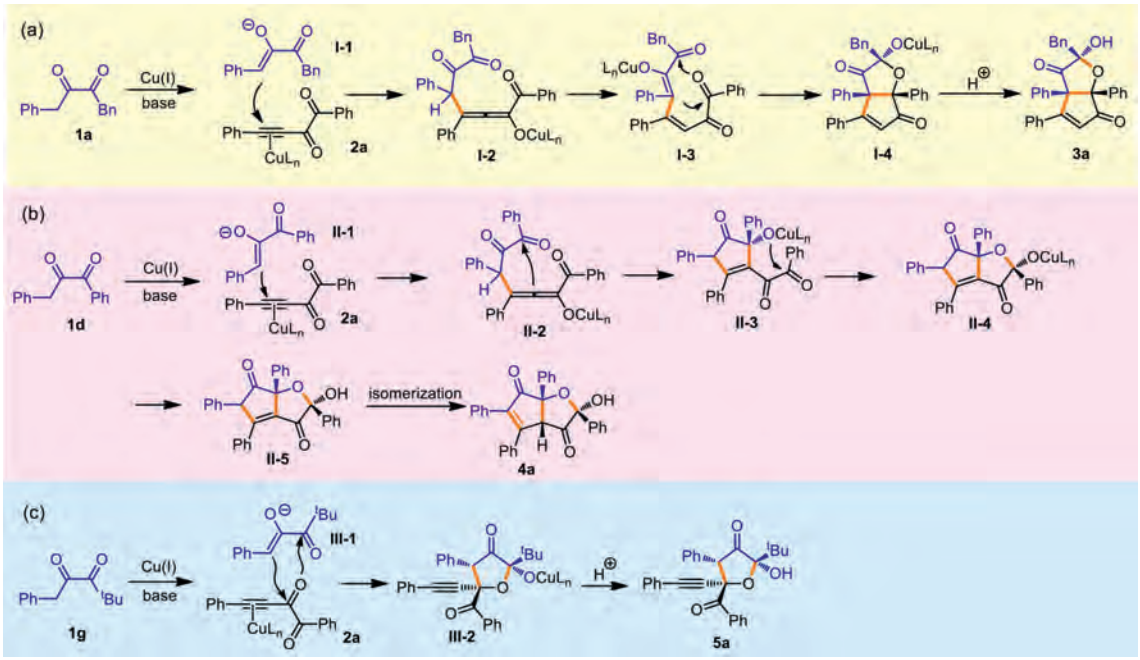
Scheme 3. Scope of functionalized HCPF **4** formation. Reactions conditions for annulations: **1** (0.3 mmol), **2** (0.2 mmol), CuTc (20 mol%), DABCO (22 mol%), **L1** (22 mol%), toluene (1 mL), 35 °C, 5 h, under argon atmosphere. Reaction conditions for OH protection and HCPF **4** formation: *p*-nitrobenzoyl chloride (PNB-Cl, 0.4 mmol), DMAP (20 mol%), DABCO (2 equiv), CH_2Cl_2 (1 mL), r.t., 5 h, under argon atmosphere. The diastereomeric ratios were determined *via* ^{1}H NMR analysis of the reaction mixtures. All yields were isolated yields based on **2**.



Scheme 4. Scope of functionalized HDFO **5** formation. Reactions conditions: **1** (0.3 mmol), **2** (0.2 mmol), CuTc (20 mol%), DABCO (22 mol%), **L1** (22 mol%), toluene (1 mL), 35 °C, 5 h, under argon atmosphere. The diastereomeric ratios were determined *via* ^{1}H NMR analysis of the reaction mixtures. All yields were isolated yields based on **2**.



Scheme 5. Synthetic applications of **3a**.



Scheme 6. Postulated mechanisms.

nucleophilic α-diketones play crucial roles in determining the reaction pathways. All three types of products were obtained in an atom-economic fashion, and the protocol greatly reduces the synthetic steps and the corresponding possible waste production. Further studies of developing an enantioselective version of this work and revealing the new chemistry of α-diketone compounds are ongoing in our group.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Nos. 22071242 and 21871260), the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB20000000), Fujian Natural Science Foundation (No. 2018J05035), and Science and Technology Research Program of the Education Department of Jiangxi Province (No. GJJ1991151).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.11.070.

References

[1] Y. Wei, M. Shi, ACS Catal. 6 (2016) 2515–2524.
[2] F.L. Hong, L.W. Ye, Acc. Chem. Res. 53 (2020) 2003–2019.
[3] C.C. Lynch, A. Sripada, C. Wolf, Chem. Soc. Rev. 49 (2020) 8543–8583.
[4] S. Kirchberg, R. Fröhlich, A. Studer, Angew. Chem. Int. Ed. 48 (2009) 4235–4238.
[5] J. Shao, X. Liu, K. Shu, et al., Org. Lett. 17 (2015) 4502–4505.
[6] J. Liu, D.K. Das, G. Zhang, et al., Org. Lett. 20 (2018) 64–67.
[7] Y. Wu, B. Tian, C. Hu, et al., Org. Biomol. Chem. 17 (2019) 5505–5508.
[8] L.J. Qi, C.Y. Shi, P.F. Chen, et al., ACS Catal. 11 (2021) 3679–3686.
[9] S. Krautwald, E.M. Carreira, J. Am. Chem. Soc. 139 (2017) 5627–5639.

[10] G. Zhan, W. Du, Y.C. Chen, Chem. Soc. Rev. 46 (2017) 1675–1692.
[11] C. Nájera, I.P. Beletskaya, M. Yus, Chem. Soc. Rev. 48 (2019) 4515–4618.
[12] I.P. Beletskaya, C. Nájera, M. Yus, Chem. Soc. Rev. 49 (2020) 7101–7166.
[13] L. Chen, K. Chen, S. Zhu, Chem 4 (2018) 1208–1262.
[14] H. Luo, T. Cao, Zhu S, Chin. J. Org. Chem. 41 (2021) 3521–3531.
[15] F. Wu, L. Chen, Y. Wang, S. Zhu, Org. Chem. Front. 6 (2019) 480–485.
[16] F.L. An, J. Luo, R.J. Li, et al., Org. Lett. 18 (2016) 1924–1927.
[17] K. Tamemoto, Y. Takaishi, K. Kawazoe, et al., J. Nat. Prod. 65 (2002) 1323–1324.
[18] C. Festa, S.D. Marino, M.V. D'Auria, et al., Tetrahedron 68 (2012) 10157–10163.
[19] A.K. Ghosh, B.D. Chapsal, G.L. Parham, et al., J. Med. Chem. 54 (2011) 5890–5901.
[20] C.A. Teleha, S. Branum, Y. Zhang, et al., Org. Process Res. Dev. 18 (2014) 1630–1640.
[21] M. Ono, Y. Yanai, T. Ikeda, M. Okawa, T. Nohara, Chem. Pharm. Bull. 51 (2003) 1328–1331.
[22] C. Li, J.B. Gloer, D.T. Wicklow, P.F. Dowd, Org. Lett. 4 (2002) 3095–3098.
[23] J. Chan, T.F. Jamison, J. Am. Chem. Soc. 125 (2003) 11514–11515.
[24] J. Chan, T.F. Jamison, J. Am. Chem. Soc. 126 (2004) 10682–10691.
[25] W. Liu, S. Niu, Z. Zhao, et al., Org. Lett. 22 (2020) 7572–7576.
[26] S. Nagaraju, S. Liu, J. Liu, et al., Org. Lett. 21 (2019) 10075–10080.
[27] X. Kong, F. Yu, Z. Chen, et al., Sci. China Chem. 64 (2021) 991–998.
[28] C. Nájera, L.K. Sydnes, M. Yus, Chem. Rev. 119 (2019) 11110–11244.
[29] S.R. Sahoo, D. Sarkar, F. Henkel, H. Reuter, J. Org. Chem. 85 (2020) 902–911.
[30] C. Li, L. Xue, J. Zhou, et al., Org. Lett. 22 (2020) 3291–3296.
[31] J. Nan, J. Zhang, Y. Hu, et al., Org. Lett. 23 (2021) 1928–1933.
[32] J. Wang, D. Ba, M. Yang, et al., J. Org. Chem. 86 (2021) 6423–6432.
[33] C. Li, L. Xue, J. Zhou, et al., Org. Lett. 22 (2020) 3291–3296.
[34] J. Nan, J. Zhang, Y. Hu, et al., Org. Lett. 23 (2021) 1928–1933.