Preprint Title	Copper-Catalyzed Domino Cyclization of Anilines and Cyclobutanone Oxime Ethers: A Scalable and Versatile Route to Spirotetrahydroquinoline Derivatives
Authors	Qingqing Jiang, Xinyi Lei, Pan Gao and Yu Yuan
Publication Date	05 März 2025
Article Type	Letter
Supporting Information File 1	supporting information.pdf; 5.8 MB
ORCID® iDs	Pan Gao - https://orcid.org/0000-0001-9305-6959

Copper-Catalyzed Domino Cyclization of Anilines and Cyclobutanone Oxime Ethers: A Scalable and Versatile Route to Spirotetrahydroquino-line Derivatives

Qingqing Jiang,[1] Xinyi Lei,[2] Pan Gao,[1]* Yu Yuan[1]*

[1]Address: School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, People's Republic of China
[2]School of Tourism and Cuisine, Yangzhou University 225002, Yangzhou, People's Republic of China

Email: gaopan@yzu.edu.cn;

Email: yyuan@yzu.edu.cn.

* Corresponding author

Abstract

In this study, we report the copper-catalyzed synthesis of tetrahydroquinoline derivatives via a domino reaction of aniline with cyclobutanone oxime. This method demonstrates a selective approach for generating bioactive tetrahydroquinoline scaffolds, which have broad applications in pharmaceutical chemistry. The reaction conditions were optimized for the effective formation of tetrahydroquinoline derivatives with varying substituents, showing high yields under mild conditions. Mechanistic studies suggest a catalytic cycle involving nucleophilic attack by the aniline on the cyclobutanone oxime, followed by cyclization to form the desired product.

Keywords

cyclobutane-fused tetrahydroquinolines, domino cyclization reaction, copper catalysis, green synthesis

Introduction

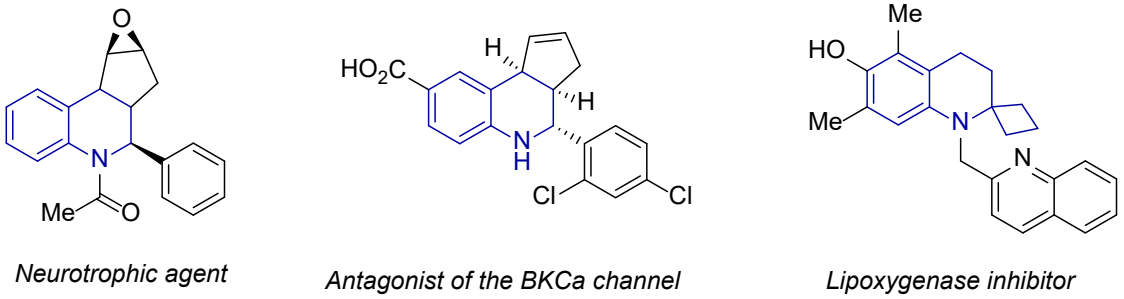
Tetrahydroquinolines (THQs) represent a privileged scaffold in medicinal chemistry, exhibiting a broad spectrum of biological activities and serving as pivotal structural elements in drug discovery.[1] Notably, tetrahydroquinoline derivatives featuring a strain-inducing ring system are prevalent in numerous bioactive molecules, including those with promising therapeutic potential for neurological disorders, oncology, and various other medical conditions (Scheme 1a).[2] Consequently, the development of efficient synthetic methodologies for constructing fused THQs is of paramount importance for advancing pharmaceutical research. Conventional synthetic strategies for THQs, which involve the formation of highly strained rings, typically employ catalytic cyclization,[3] reductive aminations,[4] and photochemical cyclization.[5] However, these approaches often necessitate multi-step syntheses of starting materials and involve intricate experimental procedures, significantly impeding their practical utility and scalability.[3-5]

Cyclobutane-fused and tetrahydroquinolines (THQs) have garnered significant attention in drug discovery due to their inherent structural rigidity and enhanced pharmacological profiles,[6] which render them highly desirable for therapeutic development. The strained cyclobutane ring, in particular, acts as a versatile and conformationally constrained building block, enabling the construction of complex molecular architectures with potent biological activities.[7] Despite their promise, the synthesis of cyclobutane-fused THQs remains a formidable challenge, primarily due to the inherent ring strain and the difficulties associated with achieving high diastereoselectivity during cyclization.[1d] Recently, Chen and co-workers developed a chiral phosphoric acid (CPA)-catalyzed multicomponent reaction of anilines, aldehydes, and azetidinones, enabling the efficient and enantioselective synthesis of tetrahydroquinoline-fused azetidines with three contiguous stereocenters in a single step.[8] Later, Tanaka, Nagashima, and their co-workers established a chemo-, regio-, and diastereoselective dearomative transformation of quinolines into tetrahydroquinoline(THQ)-based 6-6-4-membered ring systems through a combination of nucleophilic addition and borate-mediated [2+2] photocycloaddition, offering a catalyst-free approach to construct conformationally constrained

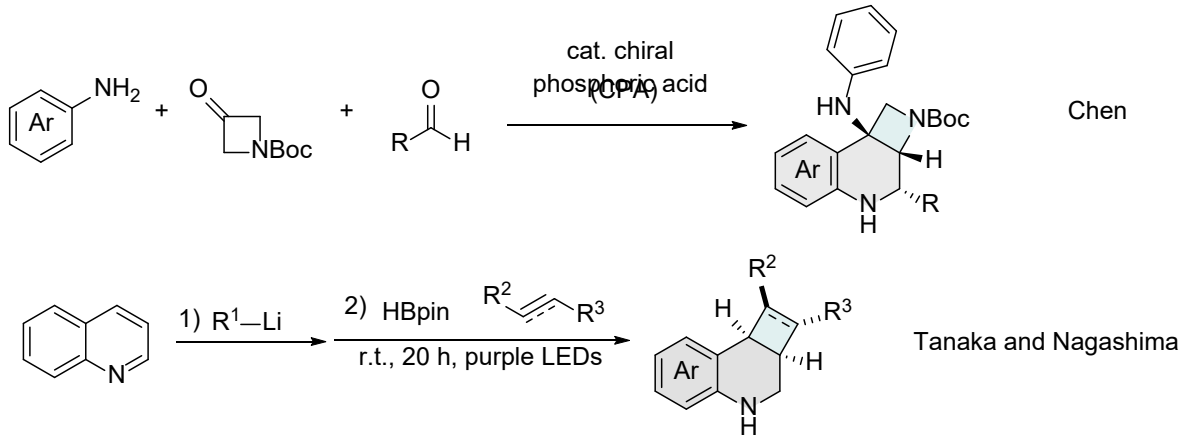
2D/3D frameworks with high functional group compatibility and stereocontrol (Scheme 1b).[9]

Given the growing significance of cyclobutane-fused tetrahydroquinolines (THQs) in biochemistry and medicinal chemistry, we have developed an efficient and convenient method for synthesizing cyclobutane-fused and conformationally constrained spirotetrahydroquinolines (STHQs) from aryl amines and cyclobutanone oxime ether using a copper-catalyzed reaction under ambient air conditions (Scheme 1c).

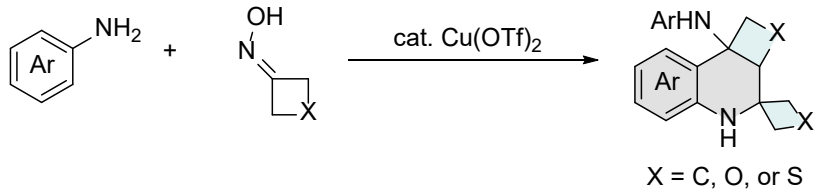
(a) Miscellaneous pharmacologically active tetrahydroquinolines(THQs) with strained ring



(b) Representative synthetic approaches to cyclobutane-fused tetrahydroquinoline (THQ) derivatives



(c) Cu-Catalyzed domino cyclization for the synthesis of cyclobutane-fused spirotetrahydroquinolines (**This work**)

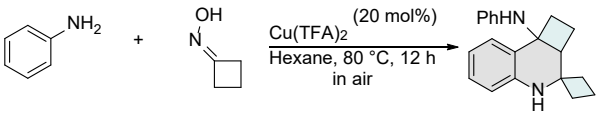


Scheme 1. Synthetic Strategies for the Construction of Spirotetrahydroquinoline (STHQ) Scaffolds.

Results and Discussion

With these considerations in mind, we explored the feasibility of synthesizing cyclobutane-fused spirotetrahydroquinolines (STHQs) through the reaction of aryl amines with cyclobutanone oxime ether under copper catalysis. After extensive optimization of the reaction parameters, the desired product **3aa** was obtained in 92% yield under the following optimal conditions: the reaction between aniline **1a** and cyclobutanone oxime ether **2a** as the model system, hexane as the solvent, and copper(II) trifluoroacetate $Cu(TFA)_2$ as the catalyst (20 mol%) under ambient air at 80 °C for 12 hours; the product **3aa** was isolated by chromatographic purification (Table 1, entry 1). The use of other solvents, including acetonitrile (MeCN), tetrahydrofuran (THF), toluene, acetone and methanol (MeOH), resulted in significantly lower yields of 3aa (Table 1, entry 2). Replacing the $Cu(TFA)_2$ catalyst with other copper sources, such as cuprous chloride (CuCl), cuprous thiocyanate (CuSCN), copper bromide ($CuBr_2$), copper trifluoromethanesulfonate ($Cu(OTf)_2$), and copper powder resulted in diminished reaction efficiency (Table 1, entry 3). When iron(II) sulfate ($FeSO_4$) and Iron trifluoromethanesulfonate ($Fe(OTf)_2$) were used as the catalyst instead of copper(II) trifluoroacetate ($Cu(TFA)_2$), the yields of the product were decreased (Table 1, entries 4 and 5). Using palladium(II) acetate ($Pd(OAc)_2$) as the catalyst provided a moderate yield (Table 1, entry 6). Conducting the reaction at room temperature (r.t.) instead of the optimal elevated temperature resulted in a lower yield (Table 1, entry 7). Increasing the reaction temperature to 100 °C improved the yield, which is slightly higher than the yield at the optimal temperature (Table 1, entry 8).

Table 1. Optimization of reaction conditions[a]



1a **2a** **3aa**

Entry	Deviation from "standard conditions"	Yield of **2a** (%)[b]
1	none	92
2	MeCN, THF, Toluene, Acetone, or MeOH instead of DMSO	20-70
3	CuCl, CuSCN, $CuBr_2$, $Cu(OTf)_2$ or Cu powder instead of $Cu(TFA)_2$	31-60
4	$FeSO_4$ instead of $Cu(TFA)_2$	76
5	$Fe(OTf)_3$ instead of $Cu(TFA)_2$	74
6	$Pa(OAc)_2$ instead of $Cu(TFA)_2$	67
7	r. t.	71
8	100 °C	63

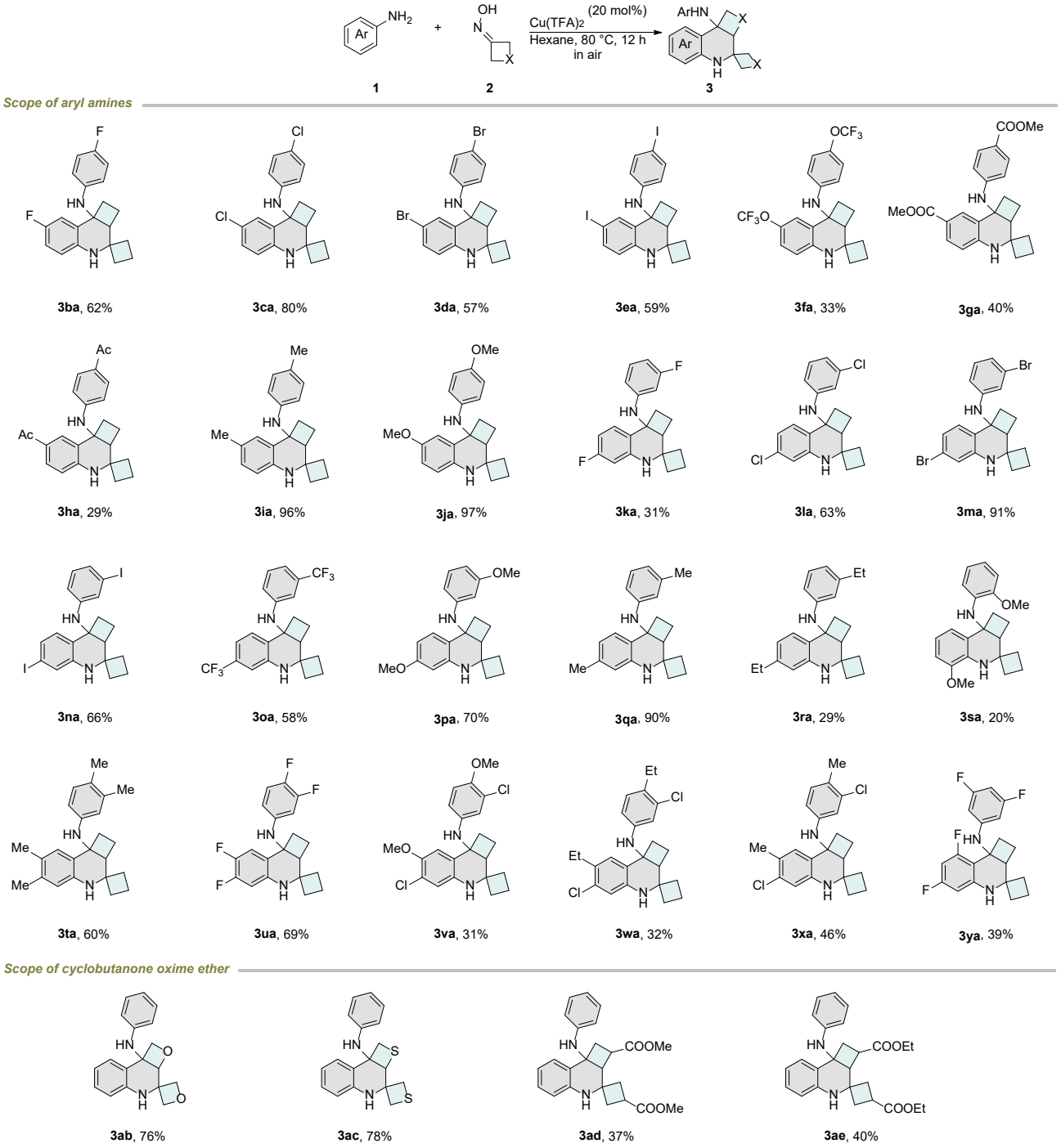
[a] Reaction conditions: aniline **1a** (0.2 mmol), **2a** (0.4 mmol), and $Cu(TFA)_2$ (0.04 mmol) in hexane (2.0 mmol) under air atmosphere, 12 h, 80 °C. [b]Isolated yields after purification by column chromatography.

Having established the optimal reaction conditions, we proceeded to investigate the generality of this Cu-catalyzed system. Initially, a series of anilines bearing diverse substituents were examined, and the results are summarized in Scheme 2. When copper(II) trifluoroacetate was employed as the catalyst, para-halogen-substituted anilines (**1b**–**1e**) demonstrated excellent compatibility with the protocol, affording the desired products in good yields (**3ba**–**3ea**).

However, the introduction of strong electron-withdrawing groups, such as trifluoromethoxy, ester, and acetyl, at the *para* position of the benzene ring (**1f**–**1h**) led to a noticeable decrease in the yields of the corresponding spirotetrahydroquinolines (STHQs) (**3fa**–**3ha**). In contrast, electron-donating groups, including 4-(methyl)aniline (**1i**) and 4-(methoxyl)aniline (**1j**), were well tolerated, delivering the expected products in good yields (**3ia** and **3ja**). Additionally, a variety of *meta*-substituted anilines proved to be suitable substrates for this transformation (**3ka**–**3ra**). However, due to steric hindrance, *ortho*-substituted anilines (**1s**) exhibited significantly lower reactivity, resulting in diminished yields (**3sa**). Notably, disubstituted anilines were also compatible with the protocol, furnishing the desired products in moderate to good yields (**3ta**–**3ya**).

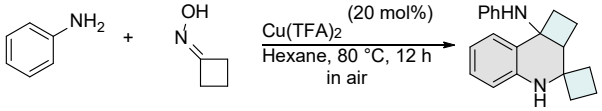
Subsequently, we investigated the scope of cyclobutanones and their analogues in the domino cyclization to access structurally diverse spirotetrahydroquinoline (STHQ) derivatives (Scheme 2). Heterocyclic analogues incorporating oxygen or sulfur atoms within the four-membered ring proved to be compatible substrates, affording cyclo-O/S-containing STHQ derivatives in good yields (**3ab** and **3ac**). Additionally, ester-functionalized cyclobutanones exhibited smooth reactivity with aniline, enabling the synthesis of substituted STHQ motifs in satisfactory yields (**3ad** and **3ae**).

Scheme 2. Substrate Scope.[a]



[a]General reaction conditions: anilines **1** (0.2 mmol), oxime ethers **2** (0.4 mmol), and $Cu(TFA)_2$ (0.04 mmol) in hexane (2.0 mmol) under air atmosphere, 12 h, 80 °C. Isolated yields.

Scheme 3. Scale-up Reaction[a]

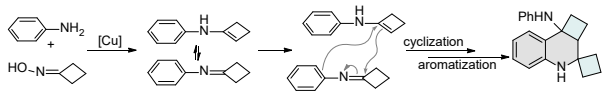


To showcase the practical utility of our Cu-catalyzed spirotetrahydroquinolines (STHQs) formation process, we conducted a 5.0-mmol scale reaction and obtained the target product **3aa** in 82% yield (Scheme 3).

Based on previous reports, a plausible mechanism was proposed. In the presence of a copper catalyst, aniline reacts with cyclobutanone oxime ether to form an imine intermediate, which undergoes

isomerization to generate an enamine intermediate. Subsequently, an intramolecular cyclization occurs between the enamine and imine intermediates, ultimately yielding the final target product through an aromatization process (Scheme 4).

Scheme 4. Proposed Mechanism



Conclusion

In summary, we have developed an efficient and practical copper-catalyzed method for the synthesis of spirotetrahydroquinoline (STHQ) derivatives via the reaction of anilines with cyclobutanone oxime ethers. This protocol offers a straightforward approach to constructing structurally diverse STHQ scaffolds under mild conditions, with broad substrate scope and high functional group tolerance. The optimized reaction conditions, utilizing copper(II) trifluoroacetate as the catalyst and hexane as the solvent, enabled the synthesis of target products in good to excellent yields. Mechanistic studies suggest a catalytic cycle involving the formation of imine and enamine intermediates, followed by intramolecular cyclization and aromatization. The scalability of this method was demonstrated through a gram-scale reaction, highlighting its potential for practical applications in medicinal chemistry and drug discovery.

Supporting Information

Experimental procedures, characterization data for all new compounds, and NMR spectra of products (PDF)

Acknowledgements

We are grateful for the financial support from the China Postdoctoral Science Foundation (2021M692713) and the Natural Science Foundation of Jiangsu Province (BK20210789).

References

1. (a) A. R. Katritzky, S. Rachwal, B. Rachwal, *Tetrahedron* **1996**, *52*, 15031−15070; (b) B. Nammalwar, R. A. Bunce, *Molecules* **2014**, *19*, 204−232; (c) V. Sridharan, P. Suryavanshi, J. C. Menendez, *Chem. Rev*. **2011**, *111*, 7157−7259; (d) I. Muthukrishnan, V. Sridharan, J. C. Menendez, *Chem. Rev*. **2019**, *119*, 5057−5191.
2. (a) N. Goli, P. S. Mainkar, S. S. Kotapalli, K. Tejaswini, R. Ummanni, S. Chandrasekhar, Bioorg. *Med. Chem. Lett*. **2017**, *27*, 1714−1720; (b) V. K. Gore, V. V. Ma, R. Yin, J. Ligutti, D. Immke, E. M. Doherty, M. H. Norman, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3573−3578; (c) D. T. W. Chu, J. Chen, W. Zhang, X. F. Li, J. G. Song, B. Wang, Q. Cong, D. R. James, U.S. Patent 2006/ 0128790 A1, 2006. (d) W. G. Zhong, S. Hitchcock, B. K. Albrecht, M. D. Bartberger, J. Brown, S. C. Chaffee, Y. Cheng, M. Croghan, R. Graceffa, S. Harried, D. Hickman, D. Horne, R. Hungate, T. Judd, M. Kaller, C. Kreiman, D. La, P. Lopez, C. E. Masse, T. Nixey, V. F. Patel, L. Pennington, M. Weiss, Q. F. Xue, B. Yang, H. Monenschein, T. Nguyen, WO Patent 2007061670 A1, 2007.
3. Selected examples for catalytic cyclization: (a) Y. Zhao, Y. Hu, H. Wang, X. Li, B. Wan, *J. Org. Chem*. **2016**, *81*, 4412−4420; (b) L.-Z. Yu, Y. Wei, M. Shi. *Chem. Commun*. 2017, *53*, 8980−8983; (c) D. V. Patil, M. A. Cavitt, P. Grzybowski, S. France. *Chem. Commun*. **2012**, *48*, 10337−10399; (d) L. Liu, C.

Wang, Q. Liu, Y. Kong, W. Chang, J. Li. *Eur. J. Org. Chem*. **2016**, *2016*, 3684−3690; (e) R. Kuppusamy, R. Santhoshkumar, R. Boobalan, H.-R. Wu, C.-H. Cheng. *ACS Catal*. **2018**, *8*, 1880−1883.

4. Selected examples for reductive aminations: (a) A. V. Stepakov, V. M. Boitsov, A. G. Larina, A. P. Molchanov. *Russ. J. Org. Chem*. **2014**, *50*, 389−393; (b) H. Wang, C. Wang, K. Huang, L. Liu, W. Chang, J. Li. *Org. Lett*. **2016**, *18*, 2367−2370; (c) X. Ren, G. Li, J. Huang, W. Wang, Y. Zhang, G. Xing, C. Gao, G. Zhao, J. Zhao, Z. Tang. *Org. Lett*. **2017**, *19*, 58−61; (d) L.-P. Li, X. Cai, Y. Xiang, Y. Zhang, J. Song, D.-C. Yang, Z. Guan, Y.-H. He. *Green Chem*. **2015**, *17*, 3148−3156.

5. Selected examples for photochemical cyclization: (a) W. J. Umstead, O. A. Mukhina, A. G. Kutateladze. *J. Photochem. Photobiol*., A **2016**, 329, 182−188; (b) H. F. Koolman; W. M. Braje; A. Haupt. *Synlett* **2016**, *27*, 2561−2566; (c) G.-Q. Xu; C.-G. Li; M.-Q. Liu; J. Cao; Y.-C. Luo; P.-F. Xu. *Chem. Commun*. **2016**, *52*, 1190−1193.

6. Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3673− 3682.

7. G. Bojack, R. Baltz, J. Dittgen, C. Fischer, J. Freigang, R. Getachew, E. Grill, H. Helmke, S. Hohmann, G. Lange, S. Lehr, F. Porée, J. Schmidt, D. Schmutzler, Z. Yang; J. Frackenpohl. *Eur. J. Org. Chem*. **2021**, *2021*, 3442−3457.

8. L.-L. Qian; Y.-C. Hu; X.-T. Min; S.-N. Yang; B.-X. Shen; B. Wan; Q.-A. Chen. *Chem Catalysis* **2022**, *2*, 2024;

9. A. Shimose, S. Ishigaki, Y. Sato, J. Nogami, N. Toriumi, M. Uchiyama, K. Tanaka, Y. Nagashima, *Angew*. *Chem*. *Int*. *Ed*. **2024**, *63*, No. e202403461.