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Copper-Catalyzed Carbonylative Synthesis of β-Homoprolines from *N*-Fluoro-sulfonamides

Youcan Zhang, Zhiping Yin, and Xiao-Feng Wu*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00227 Read Online

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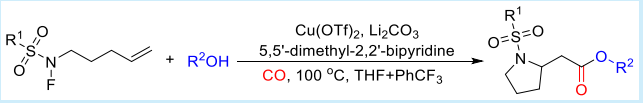
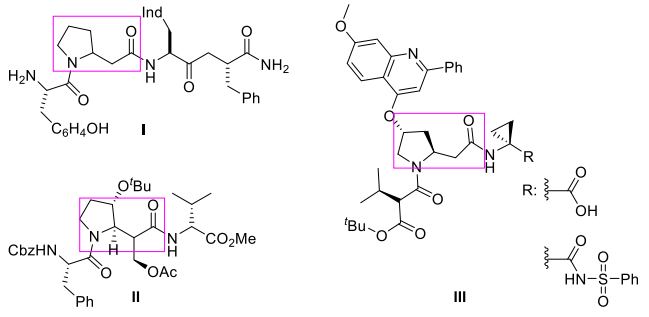
ABSTRACT: A new methodology for the carbonylative transformation of *N*-fluoro-sulfonamides into *N*-sulfonyl-β-homoproline esters has been described. In the presence of a catalytic amount of $Cu(OTf)_2$, a range of β-homoproline derivatives were prepared in moderate to good yield. The reaction proceeds via the intramolecular cyclization and intermolecular carbonylation of a free carbon radical. Notably, this procedure offers the possibility to build potential functionalized bioactive molecules.

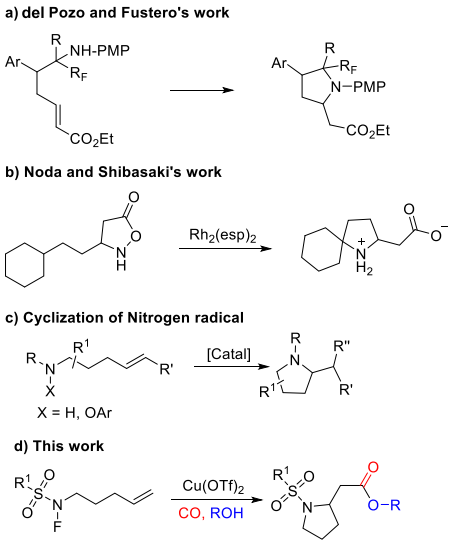


Pyrrolidines are important and valuable functional heterocycles units in the fields of bioactive molecules and natural products.[1] Prolines with a structural element of pyrrolidine, in particular, β-homoproline, are of particular interest due to their special applications in biology and pharmacology.[2] For example, β-homoproline was used in place of proline to produce biologically active homotetrapeptide **I**, which has better affinity toward the μ-opioid receptor and is more resistant to enzymatic hydrolysis (Scheme 1).[3] Usually, β-homoprolines are also used as intermediates to prepare various bioactive molecules,[4] like tripeptide **II**. A new type of HCV NS3 peptidomimetic inhibitor tripeptide **III** has been developed as well.[5] In recent years, it has been confirmed that β-amino acids construct more highly stable secondary structures comparable to their α-amino acid analogs, although they are not susceptible to protease-type hydrolases.[6] The exploration of β-peptides will play an increasingly important role in biomedical research and drug development. Even though many synthetic methods for synthesizing β-amino acid derivatives have been reported,[7] only a few methods are available for synthesizing β-homoproline derivatives.[8] In general, methods like Michael reactions,[8a] dipolar cycloadditions,[8b] Arndt−Eistert homologation,[8c−e] and hydrogenation[8f,g] were applied for constructing β-homoproline derivatives. However, besides their advantages, limitations such as limited substrate expansion, stoichiometric additives, and multistep reactions still restricted their applications. Recently, Fustero, del Pozo, and coworkers reported a novel procedure for the synthesis of diastereomeric fluorinated β-homoproline derivative (Scheme 2, eq a).[9] Noda and Shibasaki's group developed an interesting Rh-catalyzed C−

Scheme 1. Selected Bioactive Homoprolines



Scheme 2. Synthesis of β-Homoproline Derivatives and Our Design



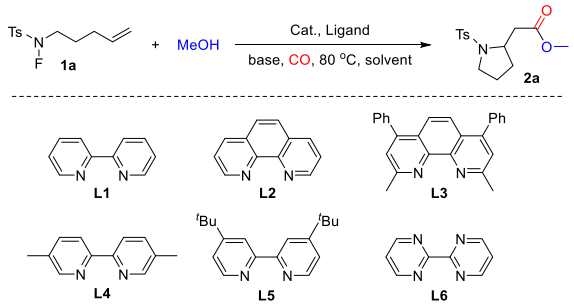
Received: January 16, 2020

H bond activation of isoxazolidin-4-ones,[10] although the substrate scope is limited (Scheme 2, eq b). Therefore, a new method for synthesizing β-homoproline derivatives is still in demand and will be useful for scientists in related areas.

Carbonylation is an effective and important strategy for constructing various compounds with carbonyl functionality; meanwhile, carbon monoxide as a cheap and approachable carbonyl source has been widely applied in synthetic chemistry.[11] We have been attracted by CO chemistry as well and been interested in using CO as a carbonyl source to synthesize various heterocyclic compounds.[11d−f] We envisaged that a low-cost metal-catalyzed carbonylation of *N*-fluoro-sulfonamides to give β-homoproline derivatives might be realized by the intramolecular cyclization and intermolecular carbonylation of free radicals.

Inspired by the previous achievements (Scheme 2, eq c)[12] and to achieve our hypothesis, we chose *N*-fluoro-4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **1a** as the model substrate and MeOH as the nucleophile. Combining the recent research progress of *N*-fluoro-sulfonamides[13] and our previous experience on cheap metal-catalyzed carbonylation,[14] we initiated our study by using $Cu(OTf)_2$ and bipyridine as the catalytic system and Li_2CO_3 as the base under pressure of CO (30 bar) in MeCN at 80 °C. To our delight, we observed the desired β-homoproline ester **2a** in 38% yield (Table 1, entry 1). After comparing different copper catalyst effects, $Cu(OTf)_2$ was found to be the most effective catalyst among these copper catalyst precursors (Table 1, entries 1−4). Different base sources were then tested, including LiOH, K_2CO_3, and pyridine, and the yield of the desired product was decreased in those cases (Table 1, entries 5−7). In the case of LiOH, the decreased yield might be due to the reaction between the target ester and the hydroxide. In the absence of base, no target product was detected (Table 1, entry 8). Then, we examined other various solvents, including THF, $PhCF_3$, and DCE; however, the starting material **1a** could not be better transformed into **2a** (Table 1, entries 9−11). The use of DMAc or DMF as the solvent also lead to a low yield. Delightfully, when the reaction was performed in a mixed solvent of THF/$PhCF_3$ (4:1), a 50% yield of the target product **2a** could be obtained (Table 1, entry 12). Afterward, we turned our attention to explore the ligand effects (Table 1, entries 12−17). A 42% yield of the desired product can be produced with 1,10-phenanthroline used as the ligand, and the reaction efficiency can be improved when it is substituted with a methyl group (Table 1, entries 13 and 14). Improved yields can be obtained when 2,2′-bipyridine is substituted with an alkyl group, and a 56% yield was achieved with **L4** as the ligand (Table 1, entries 15 and 16). However, a decreased yield was obtained when 2,2′-bipyrimidine was applied as the ligand, and the yield of the desired product was further decreased to 28% in the absence of ligand (Table 1, entries 17 and 18). Additionally, we considered adjusting the temperature and the CO pressure of the reaction as well. Satisfactorily, the yield of the target product could be improved to 71%, when the CO pressure was increased to 50 bar (Table 1, entry 19). On the basis of this reaction condition, the reaction yield could be improved to 76% when we changed the temperature to 100 °C (Table 1, entry 20). Subsequently, we continued to increase the CO pressure to 60 bar, and only a small improvement in the reaction outcome was observed (Table 1, entry 21). Finally, we assessed the substrate scope of this reaction with 5 mol % of $Cu(OTf)_2$, 10 mol % of 5,5′-dimethyl-2,2′-bipyridine,

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand + base	solvent	yield (%)[b]
1	$Cu(OTf)_2$	L1 + Li_2CO_3	MeCN	38
2	$Cu(OAc)_2$	L1 + Li_2CO_3	MeCN	32
3	CuI	L1 + Li_2CO_3	MeCN	26
4	CuF_2	L1 + Li_2CO_3	MeCN	28
5	$Cu(OTf)_2$	L1 + LiOH	MeCN	trace
6	$Cu(OTf)_2$	L1 + K_2CO_3	MeCN	35
7	$Cu(OTf)_2$	L1 + pyridine	MeCN	20
8	$Cu(OTf)_2$	L1	MeCN	nd
9	$Cu(OTf)_2$	L1 + Li_2CO_3	THF	46
10	$Cu(OTf)_2$	L1 + Li_2CO_3	$PhCF_3$	44
11	$Cu(OTf)_2$	L1 + Li_2CO_3	DCE	31
12[c]	$Cu(OTf)_2$	L1 + Li_2CO_3	THF + $PhCF_3$	50
13[c]	$Cu(OTf)_2$	L2 + Li_2CO_3	THF + $PhCF_3$	42
14[c]	$Cu(OTf)_2$	L3 + Li_2CO_3	THF + $PhCF_3$	51
15[c]	$Cu(OTf)_2$	L4 + Li_2CO_3	THF + $PhCF_3$	56
16[c]	$Cu(OTf)_2$	L5 + Li_2CO_3	THF + $PhCF_3$	52
17[c]	$Cu(OTf)_2$	L6 + Li_2CO_3	THF + $PhCF_3$	48
18[c,d]	$Cu(OTf)_2$	Li_2CO_3	THF + $PhCF_3$	28
19[c,e]	$Cu(OTf)_2$	L4 + Li_2CO_3	THF + $PhCF_3$	71
20[c,f]	$Cu(OTf)_2$	L4 + Li_2CO_3	THF + $PhCF_3$	76
21[c,f]	$Cu(OTf)_2$	L4 + Li_2CO_3	THF + $PhCF_3$	79 (73)[g]

[a]Reaction conditions: **1a** (0.1 mmol), MeOH (0.1 mL), catalysts (5 mol %), ligands (10 mol %), and base (1 equiv) in solvent (1 mL) at 80 °C for 20 h under CO (30 bar). [b]Yields were determined by GC-FID analysis using *n*-hexadecane as the internal standard. [c]THF/$PhCF_3$ 4:1. [d]80 °C, CO (50 bar). [e]100 °C, CO (50 bar). [f]100 °C, CO (60 bar). [g]Isolated yield. nd = no detection. THF = tetrahydrofuran. DCE = 1,2-dichloroethane.

and 1 equiv of Li_2CO_3 under CO pressure (50 bar) in a mixed solvent of THF/$PhCF_3$ (4:1) at 100 °C.

With the optimized reaction conditions established (Table 1, entry 20), we then explored the scope of this reaction with a range of *N*-fluoro-sulfonamides and alcohols. As shown in Scheme 3, the starting materials of **1a−d** bearing electron-donating or -neutral groups were smoothly converted into the corresponding *N*-sulfonyl-β-homoproline ester products **2a−d** in good yield. The aromatic ring of *N*-fluoro-sulfonamides with no functional group or *ortho*-chloro substitution can be prepared as well, and the desires products **2b** and **2e** were obtained in 70 and 46% yield, respectively. Notably, different alkyl alcohols as nucleophiles including ethanol, propanol, isopropanol, and *n*-butanol, were reacted with **1a**, and the desired products **2f−i** were successfully obtained in moderated yield (51−57%). Furthermore, the alcohol bearing a terminal alkenyl or trifluoromethyl group was well-tolerated as well, forming the desired products **2j−l** in 32−41%. We scaled up the reaction to a 1.0 mmol level under the optimal reaction conditions. To our delight, the desired product **2a** could be prepared in a 60% isolated yield when the reaction of **1a** (1.0

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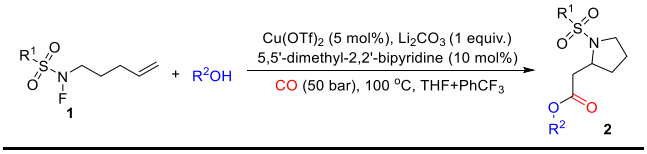
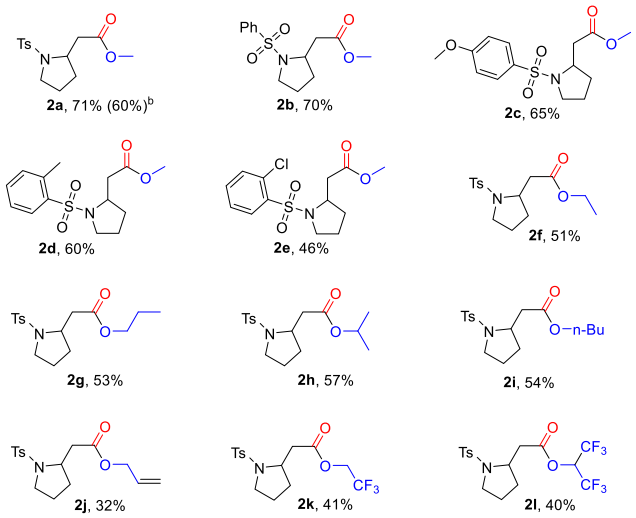
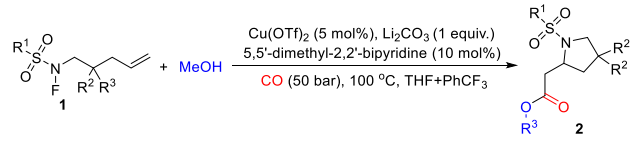
Scheme 3. Scope of *N*-Fluoro-sulfonamides and Alcohols[a]

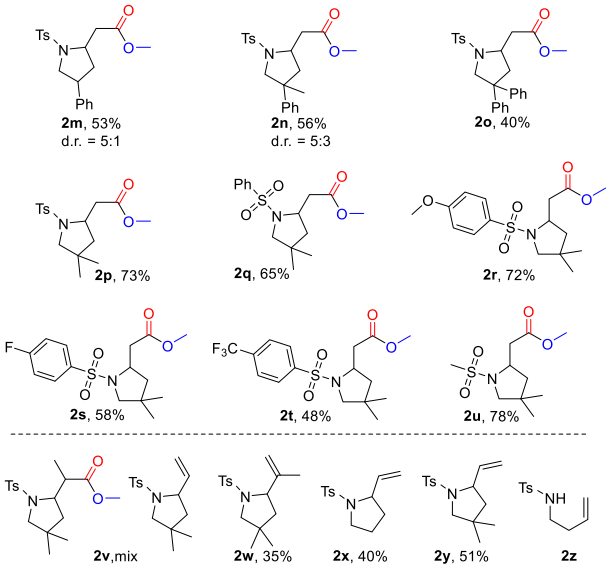




[a]Reaction conditions: **1** (0.2 mmol), ROH (0.2 mL), $Cu(OTf)_2$ (5 mol %), 5,5′-dimethyl-2,2′-bipyridine (10 mol %), and Li_2CO_3 (1.0 equiv) in THF + $PhCF_3$ (2 mL, 4:1) at 100 °C for 20 h under CO (50 bar). [b]**1a** (1.0 mmol), MeOH (1.0 mL), THF + $PhCF_3$ (7 mL, 4:1). Isolated yield.

Scheme 4. Scope of C2-Substituted *N*-Fluoro-sulfonamides[a]



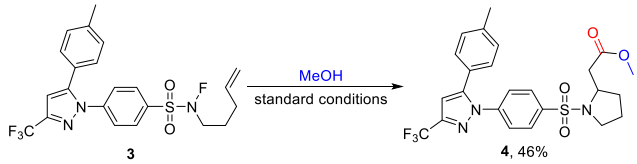


[a]Reaction conditions: **1** (0.2 mmol), ROH (0.2 mL), $Cu(OTf)_2$ (5 mol %), 5,5′-dimethyl-2,2′-bipyridine (10 mol %), and Li_2CO_3 (1.0 equiv) in THF + $PhCF_3$ (2 mL, 4:1) at 100 °C for 20 h under CO (50 bar). Isolated yield.

mmol) and MeOH (1.0 mL) was carried out in 7 mL of a mixed solvent of THF/$PhCF_3$ (4:1).

Subsequently, a range of other *N*-fluoro-sulfonamides was prepared and investigated. These substrates with functional groups in the alkyl branched chain were all transformed smoothly, leading to the desired products in 40−73% yield (Scheme 4, **2m−p**). Additionally, *N*-(2,2-dimethylpent-4-en-1-yl)-*N*-fluoro-sulfonamides with different substitutions on the aromatic ring were tested as well and gave the desired products **2q−t** in moderate to good yield. Interestingly, the product of methyl 2-(4,4-dimethyl-1-(methylsulfonyl)pyrrolidin-2-yl)-acetate **2u** could be formed from the substrate **1n** in good yield. Next, we explored the carbonylation of secondary and tertiary carbon radicals. As the results show in Scheme 4, a mixture of products **2v** from carbonylation and elimination was achieved with a secondary radical intermediate. Only elimination product **2w** was formed with the tertiary carbon radical intermediate. Then, the substrates with different carbon chain lengths (**1q** *N*-(but-3-en-1-yl)-*N*-fluoro-4-methylbenzenesulfonamide, **1r** *N*-(2,2-dimethylhex-5-en-1-yl)-*N*-fluoro-4-methylbenzenesulfonamide, and **1s** *N*-fluoro-*N*-(hex-5-en-1-yl)-4-methylbenzenesulfonamide) were also tested; however, only noncarbonylative cyclization products **2x** and **2y** were detected. Here the two products were obtained via 1,5-proton transfer and then the C−N coupling process.[14] Additionally, no target product was formed, and only the defluorination compound **2z** could be detected by GC-MS from the corresponding *N*-fluoro-sulfonamide. Finally, under our standard reaction conditions, substrate **3** from the biologically important celecoxib can also be successfully reacted and transformed into the desired product **4** in 46% yield (Scheme 5). Moreover, we attempted to remove the tosyl group by SmI_2 but failed.[14c]

Scheme 5. Carbonylation of *N*-Fluoro-*N*-allylcelecoxib



[a]Reaction conditions: **3** (0.2 mmol), MeOH (0.2 mL), $Cu(OTf)_2$ (5 mol %), 5,5′-dimethyl-2,2′-bipyridine (10 mol %), and Li_2CO_3 (1.0 equiv) in THF + $PhCF_3$ (2 mL, 4:1) at 100 °C for 20 h under CO (50 bar). Isolated yield.

On the basis of the above results and literature,[12−15] a possible reaction mechanism is proposed in Scheme 6. Initially, amidyl radical **A** is produced by the Cu^{I}-induced single-electron reduction of **1a** while forming the Cu^{II} species. After an intramolecular cyclization of amidyl radical **A**, a new carbon radical **B** is generated. Then, carbon radical **B** would be captured by CO and Cu^{II} species to give the intermediate **C**. Subsequently, a ligand-exchange procedure of intermediate **C** with ROH occurs to produce the intermediate **D**. Finally, the reductive elimination of intermediate **D** provides the eventual product and the active Cu^{I} species, which is used for the next catalytic cycle.

In summary, a new strategy for the copper-catalyzed intramolecular cyclization and intermolecular carbonylative transformation of *N*-fluoro-sulfonamides has been developed.

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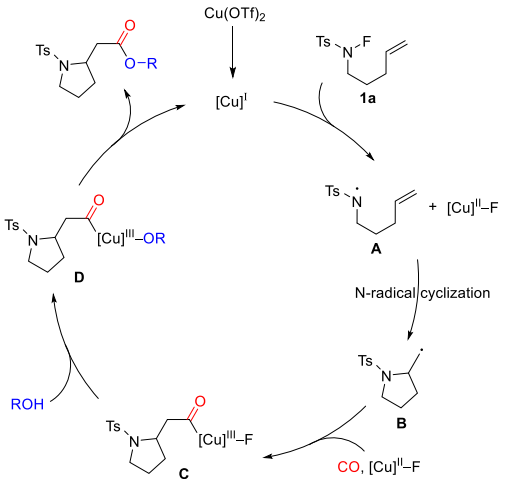
Scheme 6. Proposed Reaction Mechanism



Using low-cost $Cu(OTf)_2$ and bipyridine as the catalytic system, various β-homoproline esters were generated in moderate to good yield. This method provides a new direction for the preparation of β-homoproline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00227.

General comments, general procedure, optimization details, analytic data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xiao-Feng Wu − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock 18059 Rostock, Germany;* orcid.org/0000-0001-6622-3328; Email: xiao-feng.wu@catalysis.de

Authors

Youcan Zhang − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock 18059 Rostock, Germany*

Zhiping Yin − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock 18059 Rostock, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00227

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Chinese Scholarship Council for financial support. The analytical support from Dr. W. Baumann, Dr. C. Fischer, S. Buchholz, and S. Schareina (all in LIKAT) is gratefully acknowledged.

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https://dx.doi.org/10.1021/acs.orglett.0c00227
Org. Lett. XXXX, XXX, XXX−XXX