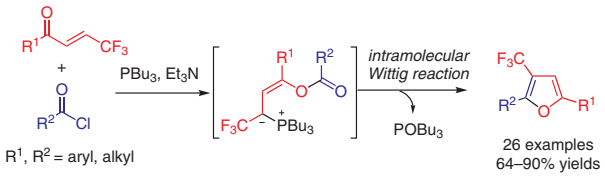
Synlett M. Li, W. Zhou Letter

Transition-Metal-Free Synthesis of Trifluoromethylated Furans via a Bu_3P-Mediated Tandem Acylation–Wittig Reaction

Maizhan Li
Wei Zhou*

International Cooperative Laboratory of Traditional Chinese Medicine Modernization and Innovative Drug Development of Chinese Ministry of Education, College of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, 510632, P. R. of China
weizhou88@jnu.edu.cn



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Abstract A highly efficient nucleophilic addition–*O*-acylation–intramolecular Wittig reaction of β-trifluoromethyl α,β-enones is disclosed. This strategy features mild reaction conditions and provides a practical transition-metal-free method to a set of biologically significant trifluoromethylated furans in high yields with diverse functional groups.

Key words β-trifluoromethyl α,β-enones, Wittig reaction, nucleophilic addition, furans, trifluoromethylated furans

The introduction of trifluoromethyl group into organic molecules has become an important research field in the agrochemical and pharmaceutical industries.[1] The metabolic stability, lipophilicity, and solubility of some drug candidates could be greatly influenced by the trifluoromethyl group due to its special electronic and steric properties.[2] Accordingly, tremendous efforts have been made for the incorporation of these trifluoromethyl moiety in catalytic reactions during last few decades. Efforts in this area could be generally divided into two aspects. The first strategy involve direct trifluoromethylation of organic molecules.[3] A set of trifluoromethylation reagents and catalytic systems (including radical, nucleophilic, and electrophilic approaches) have been reported to realize this target.[4] The second category involves the functionalization of some readily available trifluoromethyl-containing building blocks,[5] such as trifluoromethylated carbonyls, imines, and Michael acceptors.

On the other hand, trifluoromethylated furan and its derivatives are key structural motifs in in many biologically active molecules (Figure 1).[6,7] Over the last few decades, the construction of trifluoromethylated furan skeletons has garnered considerable attention and a set of synthetic methodologies have been well developed. While the direct trifluoromethylation of furans and their derivatives is a step-economical route for the synthesis of these compounds, it suffers from lower selectivity and requirements for higher reaction temperatures and the use of transition-metal catalysts.

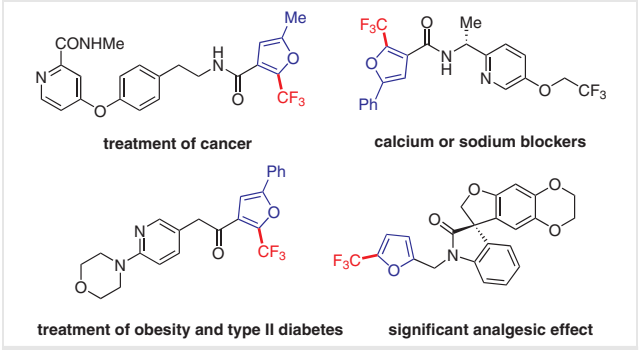
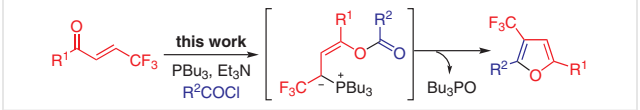


Figure 1 Bioactive molecules featuring a trifluoromethylated furan skeleton

Most recently, β-trifluoromethyl α,β-enones have been employed as versatile synthons in making fluorinated functionalized heterocycles and carbocycles by many research groups.[8] Inspired by these elegant research works and as part of our interest in developing synthetic methods for trifluoromethyl furans from readily available trifluoromethylated building blocks, we speculated that β-trifluoromethyl α,β-enones might undergo a phospha-Michael addition–*O*-acylation–intramolecular Wittig reaction to generate synthetic useful trifluoromethyl-functionalized multisubstituted furans under transition-metal-free conditions (Scheme 1).

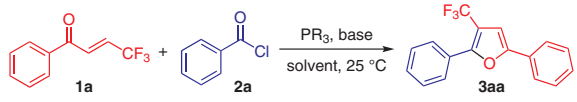


Scheme 1 Bu_3P-mediated tandem acylation–Wittig reaction for the synthesis of trifluoromethylated furans

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Our study was initiated by exploring the triphenylphosphine-mediated reaction of β-trifluoromethyl α,β-enone **1a** and benzoyl chloride **2a** in the presence of triethylamine in dichloromethane at room temperature. The desired trifluoromethylated furan **3aa** was achieved in 6% yield after 0.5 h (Table 1, entry 1). Encouraged by this result, we then moved to screen the reaction conditions for higher chemical yield of **3aa** (Table 1). Further survey of tertiary phosphines revealed that tributyl phosphine with stronger nucleophilicity was the best in terms of reactivity (entries 1–3). Next, a series of solvents were evaluated, and tetrahydrofuran proved to be the most suitable reaction medium for this tandem transformation, and the corresponding trifluoromethylated furan **3aa** was produced in 86% yield (entries 3 and 4–8). Lower chemical yield was observed if this reaction was performed with other organic bases such as DABCO and diisopropylamine (entries 9 and 10). Notably, inorganic bases such as potassium carbonate, potassium *tert*-butoxide, and sodium hydroxide were almost ineffective in this reaction (entries 11–13). Finally, longer reaction time was leading to the formation of furan **3aa** with virtually the same yield (entries 14 and 15).

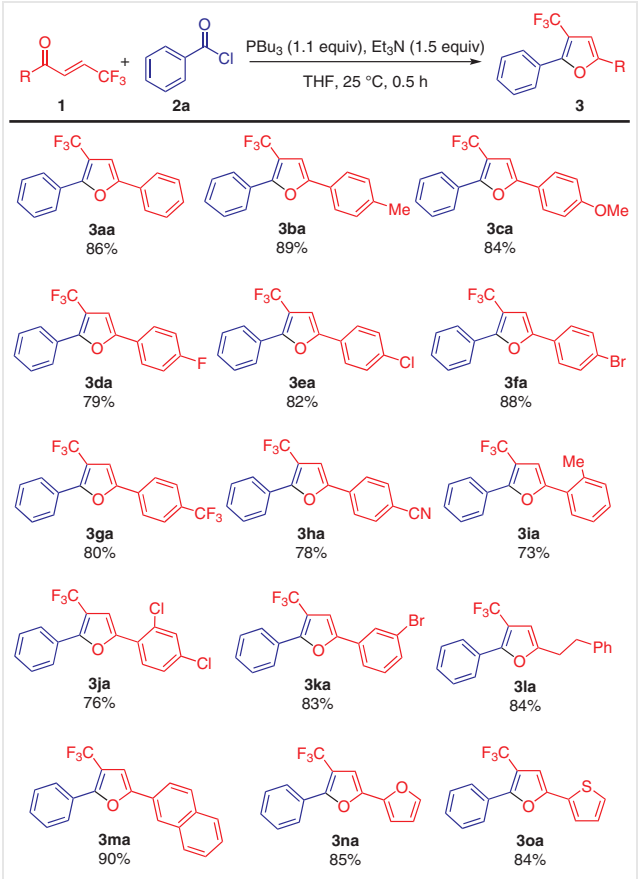
Table 1 Reaction Optimization[a]



Entry	PR_3	Base	Solvent	Time (h)	Yield (%)[b]
1	PPh_3	Et_3N	THF	0.5	6
2	$MePPh_2$	Et_3N	THF	0.5	17
3	PBu_3	Et_3N	THF	0.5	86
4	PBu_3	Et_3N	CH_2Cl_2	0.5	70
5	PBu_3	Et_3N	toluene	0.5	62
6	PBu_3	Et_3N	Et_2O	0.5	71
7	PBu_3	Et_3N	dioxane	0.5	68
8	PBu_3	Et_3N	CH_3CN	0.5	43
9	PBu_3	DABCO	THF	0.5	52
10	PBu_3	*i*-Pr_2NH	THF	0.5	45
11	PBu_3	K_2CO_3	THF	0.5	trace
12	PBu_3	*t*-BuOK	THF	0.5	trace
13	PBu_3	NaOH	THF	0.5	trace
14	PBu_3	Et_3N	THF	1.0	86
15	PBu_3	Et_3N	THF	3.0	85

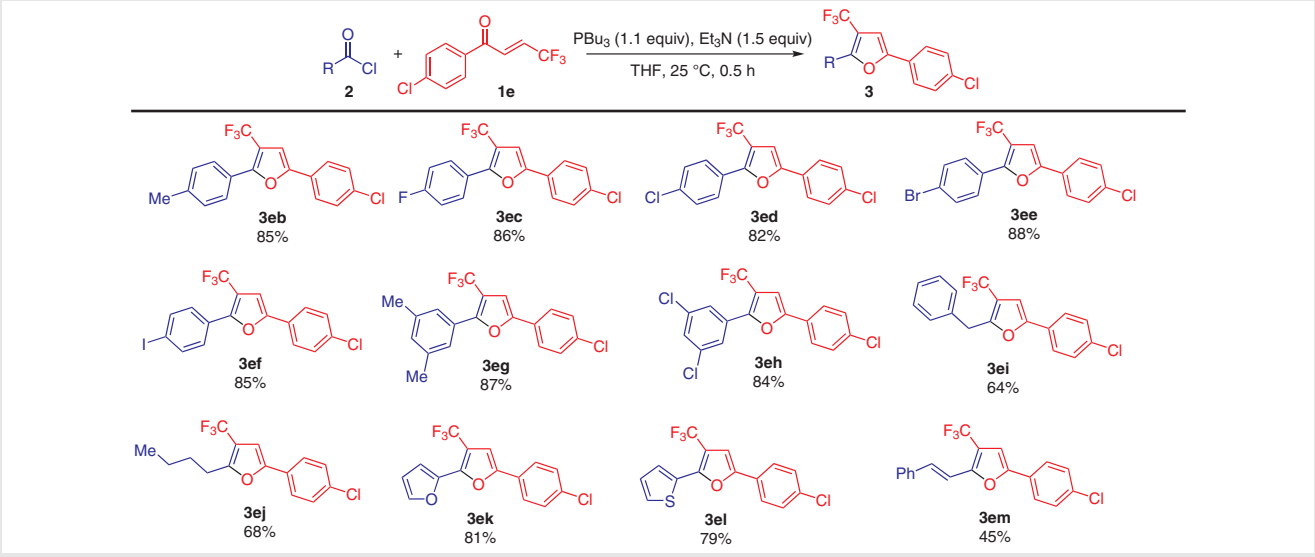
[a] Unless otherwise specified, all reactions were carried out with **1a** (0.2 mmol), **2a** (0.22 mmol), PR_3 (0.22 mmol), and base (0.3 mmol) in solvent (2.0 mL) at 25 °C.
[b] Isolated yield.

With a set of optimal conditions in hand,[9] our efforts concentrated on investigating the scope of this nucleophilic addition–*O*-acylation–intramolecular Wittig reaction of β-trifluoromethyl α,β-enones (Scheme 2). Remarkably, a wide range of β-trifluoromethyl-substituted enones containing electron-rich or electron-poor functional groups were universally worked well with benzoyl chloride **2a**, delivering the multisubstituted trifluoromethylated furan **3aa–ha** in 78–89% yields (Scheme 2). The decreased yields were observed for **3ia** and **3ja** probably due to the steric hindrance from an *ortho* group to the phenyl ring of enone. The tandem annulation reaction of *meta*-substituted α,β-enones **2k** and aliphatic α,β-enones **2l** also produced the desired products **3ka** and **3la** in good yields. Notably, naphthyl- and heteroaryl-containing substrates were also suitable for this reaction system and good yields of **3ma–oa** were attainable.



Scheme 2 Scope of β-trifluoromethyl α,β-enones. *Reagents and conditions*: **1** (0.2 mmol), **2a** (0.22 mmol), PBu_3 (0.22 mmol), and Et_3N (0.3 mmol) in THF (2.0 mL) at 25 °C. Reported yields are for the isolated product.

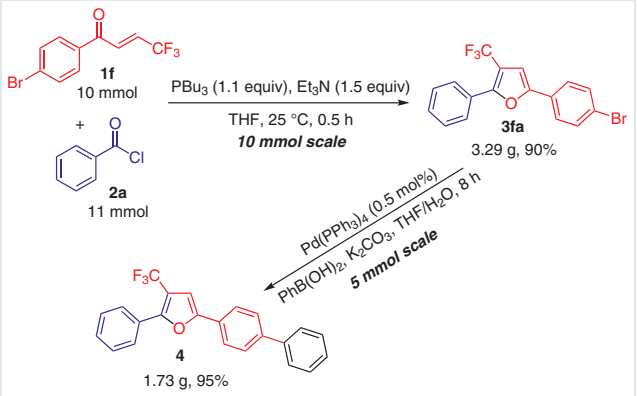
Next, the scope of acyl chloride compounds toward this tandem cyclization reaction was explored. As summarized in Scheme 3, this reaction system demonstrated satisfied functional group tolerance. An electron-donating group such as methyl on the phenyl ring of acyl chloride was well tolerated and the related multisubstituted trifluoromethylated furan **3eb** was attained in 85% yield. Acyl chlorides **2** bearing different halogen atoms (including F, Cl, Br, I) were



Scheme 3 Scope of acyl chloride. *Reagents and conditions*: **1e** (0.2 mmol), **2** (0.22 mmol), PBu_3 (0.22 mmol), and Et_3N (0.3 mmol) in THF (2.0mL) at 25 °C. Reported yields are for the isolated product.

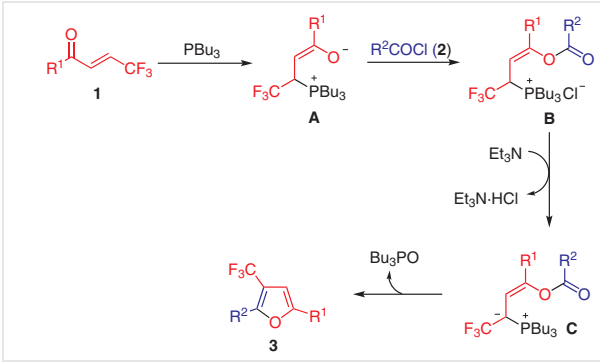
suitable substrates, and highly functionalized trifluoromethylated furans were produced in 82–86% yields. The annulation of 3,5-disubstituted benzoyl chloride also proceeded smoothly and gave **3eg–eh** in good yields. Noteworthy, products **3ei–el** containing alkyl and heteroaryl (like furan and thiophene) substituents were also successfully constructed with up 64–81% yields. Finally, cinnamoyl chloride was also suitable for this reaction system, and the desired **3em** was attained in 45% yield.

Furthermore, a gram-scale phospha-Michael addition–*O*-acylation–intramolecular Wittig reaction of **1f** and **2a** was then performed, which proceeded smoothly under the standard conditions and gave 3.29 g of **3fa** in 90% yield (Scheme 4). Palladium-catalyzed Suzuki coupling reaction of **3fa** with phenylboronic acid was proved to be feasible, and the desired functionalized trifluoromethylated furan **4** was also achieved in gram scale.



Scheme 4 Gram-scale reaction of **1f** with **2a** and Suzuki coupling reaction of **3fa** with phenylboronic acid

Based on previous studies on the phosphine-mediated tandem cyclization–Wittig reaction and the above results,[10] a tentative mechanism for this phospha-Michael addition–*O*-acylation–intramolecular Wittig reaction is shown in Scheme 5. The first step is regioselective nucleophilic addition of Bu_3P toward β-trifluoromethyl α,β-enones leading to the zwitterion intermediate **A**. The intermediate **A** then undergoes acylation with acyl chloride **2** providing intermediate **B**, which is subsequently deprotonated by Et_3N and results in ylide **C**. Finally, trifluoromethylated furan **3** is released through an intramolecular Wittig reaction from ylide **C**.



Scheme 5 Plausible reaction mechanism

In conclusion, we have successfully developed a highly efficient nucleophilic addition–*O*-acylation–intramolecular Wittig reaction of β-trifluoromethyl α,β-enones for the construction of trifluoromethyl-functionalized multisubstituted furans. This strategy features mild and transition-metal-free reaction conditions. In addition, a gram-scale

Wittig reaction of **1f** and **2a** was also showcased, suggesting the high efficiency of this method. Further synthetic studies of other applications of β-trifluoromethyl α,β-enones toward the formation of trifluoromethylated heterocyclic compounds are currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707263.

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(9) **Typical Procedure for the Bu_3P-Mediated Tandem Acylation–Wittig Reaction**

In a 25 mL dry Schlenk tube equipped with a stirring bar, a solution of acyl chloride **2** (1.1 equiv) and Bu_3P (1.1 equiv) in dry THF (1.0 mL) and a solution of β-trifluoromethyl α,β-enone **1** (0.2 mmol) in dry THF (1.0 mL) was added. Subsequently, Et_3N (1.5 equiv) was added to the above reaction solution. The reaction mixture was stirred for 0.5 h at room temperature, the reaction was monitored by TLC (hexane). Thereafter, the solvent was removed by evaporation *in vacuo*, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 100:0 to 40:1) to furnished the desired trifluoromethyl-functionalized multisubstituted furans **3**.

Analytical Data for Compound 3aa

White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79–7.72 (m, 4 H), 7.49–7.41 (m, 5 H), 7.34–7.32 (m, 1 H), 6.89 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.03, 151.90 (q, *J* = 5.00 Hz), 129.46, 129.31, 128.90, 128.67, 128.41, 127.15 (q, *J* = 1.25 Hz), 124.06, 122.91 (q, *J* = 266.25 Hz), 114.29 (q, *J* = 37.50 Hz), 105.27 (q, *J* = 3.75 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –56.41 ppm. HRMS (EI): *m/z* calcd for $C_{17}H_{11}F_3O$ $[M]^+$: 288.0757; found: 288.0753.

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