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Phosphine-catalyzed acyl-transfer of heteroaryl ketones for the construction of *N*-fused heterocycles

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ABSTRACT

An inexpensive phosphine catalyst was used effectively for a transition-metal-free acyl-transfer of *N*-containing heteroaryl ketones for the rapid synthesis of *N*-fused heterocycles. The key pre-aromatic spirocyclic intermediate initialized by the single electron transfer (SET) process of Togni's reagent II promoted by the tertiary phosphine resulted in an intriguing and alternative tactic for the cleavage of C–C bonds. By using inexpensive tertiary phosphine as the catalyst, this skeleton-reorganizing approach of *N*-containing heteroaryl ketones allows a streamlined assembly of complex *N*-fused heterocycles with broad functional group tolerance.

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N-Fused heterocycles are important structural motifs that are diverse and ubiquitous in bioactive natural and non-natural products, drugs, ligands, and functional materials (Fig. 1a) [1–6]. They usually improve the molecular and physiochemical properties and enhance the bioactivities. *N*-Fused heterocycles are present in almost half of the 200 top selling US FDA-approved drug compounds as of 2014 [7]. Therefore, an efficient method to construct *N*-fused heterocycles is in great demand [8–28].

Recently, we developed an intriguing and general method for the synthesis of diverse *N*-fused heterocycles *via* Pd-catalyzed intramolecular acyl-transfer of heteroaryl ketones [9]. Driven by aromatization, the acyl of a heteroaryl ketone can be transferred from a carbon atom to a nitrogen atom to form the corresponding *N*-fused heterocycles. As heteroaryl ketones are stable and simple to prepare, this strategy simplifies the synthesis of *N*-fused heterocycles, which are valuable synthetic intermediates for bioactive compounds but challenging to prepare otherwise. However, the excess loading of noble metals often incurs economic and ecological costs, which prompted us to explore a novel acyl-transfer process. Moreover, achieving the selective C–C bond activation of unstrained heteroaryl ketones under transition-metal-free conditions remains a formidable synthetic challenge [29–34].

In recent years, phosphine-catalyzed reactions have attracted significant attention in the synthetic community. They provide a powerful and metal-free method for diversely functionalized molecule synthesis, eliminating the contamination of metals in organic products [35–43]. Phosphines have been found to achieve outstanding performance in single electron transfer (SET) in the presence of oxidants [44–46]. In particular, tertiary phosphines can react with various iodides through SET processes and generate reactive radical intermediates (Fig. 1b) [47–50]. The excellent ability of phosphines in the SET process motivated us to explore the use of metal-free conditions for the aromatization driven acyl transfer annulation process, which could provide an advantageous alternative to the transition-metal-catalyzed strategy for producing *N*-fused heterocycles modified with trifluoromethyl. To the best of our knowledge, phosphine-catalyzed cleavage of the C–C bond of ketones is challenging and remains unsolved.

To explore this strategy, we initiated a systematic study of the reaction conditions using heteroaryl ketone **1** as a model substrate. The desired trifluoromethyl modified product **2** was isolated in 80% yield using tri(2-furyl)phosphine (TFP, **P1**) and Togni's reagent II *via* phosphine-oxidant charge transfer in dioxane/1,2-dichloroethane (DCE). A control experiment revealed that TFP appears to be critical in this reaction. Tertiary amine DABCO and other phosphines (Table 1, entries 2 and 3), such as tributylphosphine (**P4**) and 1,2-bis(diphenylphosphino)benzene (dppBz, **P6**), were not as effective, and only 31% yield of the product could be observed in the absence of tri(2-furyl)phosphine (Table 1, entry 4), which might be attributed that an electron donor-acceptor (EDA) complex was formed between *N*-containing heteroaryl ke-

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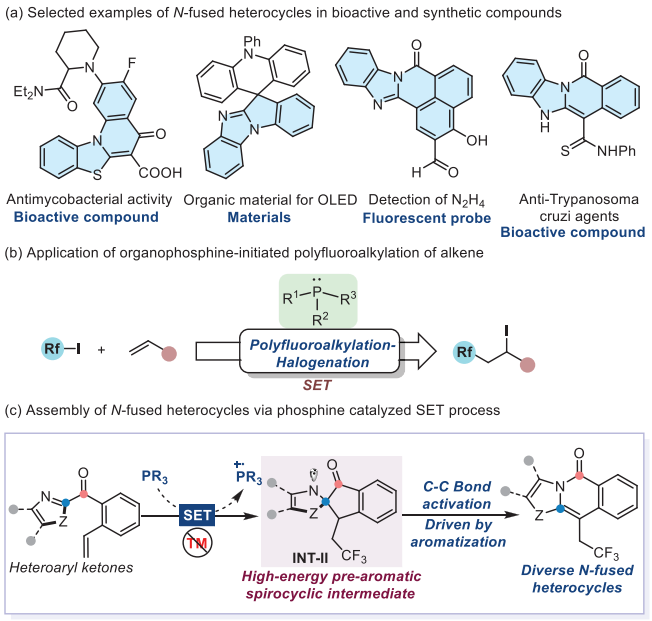
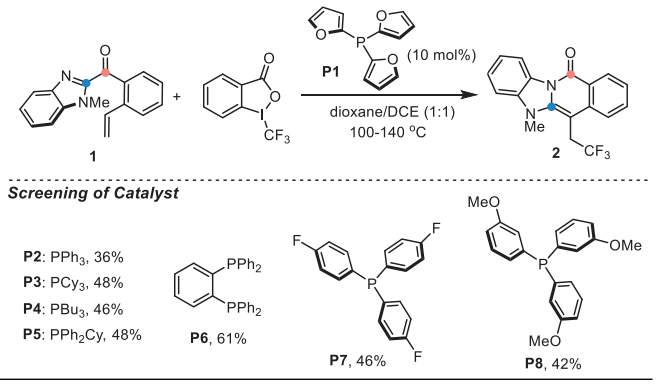


Fig. 1. Examples of important fused-heterocycles and our reaction design.

Table 1
Selected reaction optimization.[a]



Entry	Variation from '*standard condition*'	Yield (%)[b]
1	None	80
2	DABCO instead of TFP	42
3	**P2**-**P8** instead of TFP	36–61
4	Without TFP	31
5	Under air	53
6	In dioxane	64
7	In DCE	50
8	In MeCN	62

[a] Unless otherwise specified, all reactions were carried out using ketone **1** (0.1 mmol) and Togni's reagent II (0.15 mmol, 1.5 equiv.), with 10 mol% tri(2-furyl)phosphine (TFP, **P1**), in dioxane/DCE (0.6 mL, 1:1) at 100 °C for 24 h, and 140 °C for 12 h.
[b] Isolated yields after chromatography.

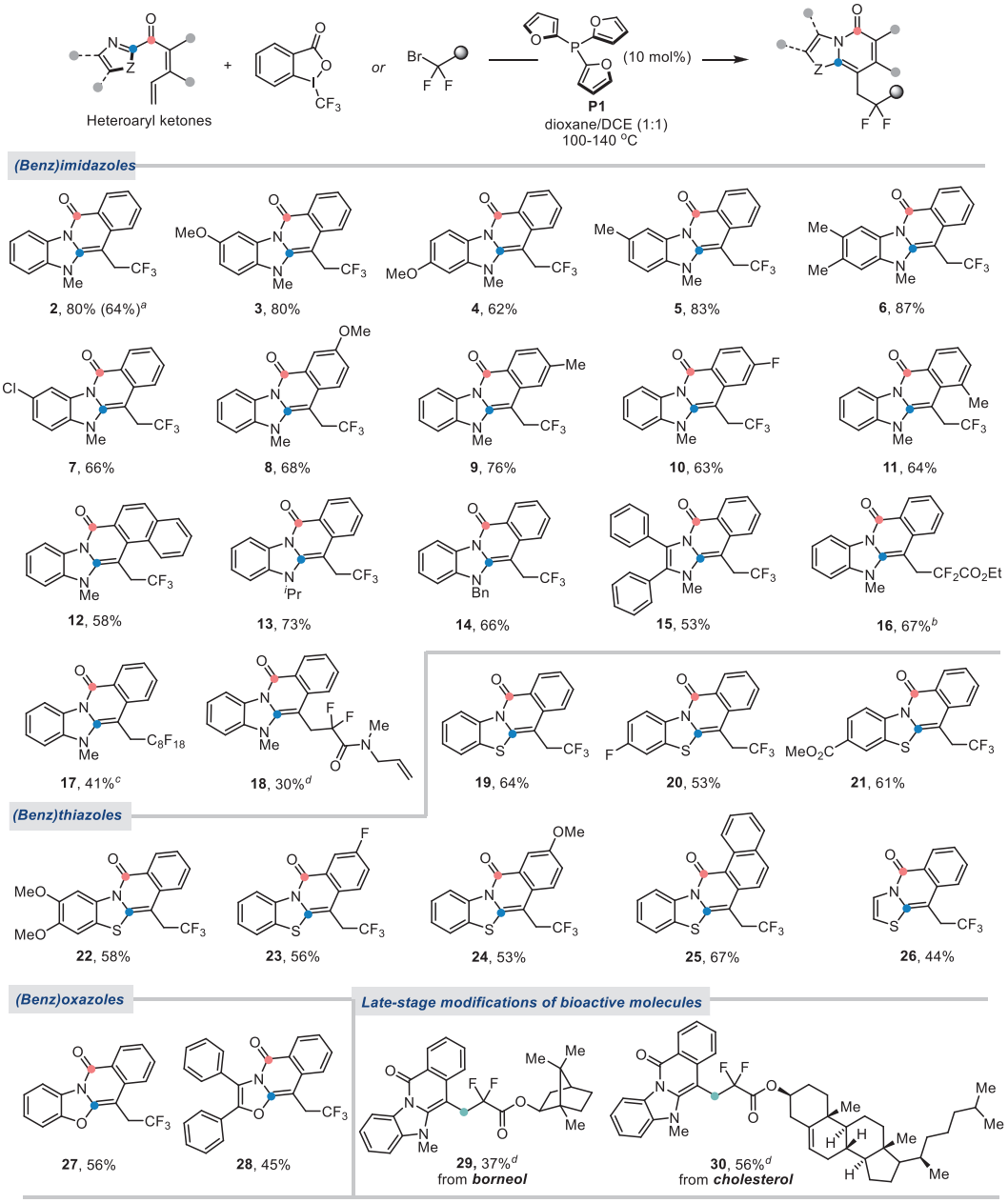
tones (donor) and Togni's reagent II (acceptor) to generate the CF_3 radical [51]. The reaction was not sensitive to oxygen and was promoted smoothly under normal air conditions, although a slightly higher yield was obtained under a N_2 atmosphere (Table 1, entry 5). A survey of different solvents revealed that the individual DCE, dioxane, and MeCN could also give acceptable yields, although lower than that of the mixture (Table 1, entries 6–8). The study of $\cdot CF_3$ sources further suggested that oxidant capacity is essential for the SET process [52], other trifluoromethylation reagents such as Togni's reagent I, Umemoto's reagent and trifluoromethyl thianthrenium triflate were not effective in this process, and only Togni's reagent II is a compatible oxidant that generates phosphinium radical cations and free trifluoromethylcarbon radicals.

With the optimized reaction conditions confirmed, the scope of heteroaryl ketones was examined. As shown in Scheme 1, the reaction exhibits excellent compatibility with heteroaryl ketones and with various *N*-containing heteroaryls, including imidazole (**15**), thiazole (**26**), oxazole (**28**), benzothiazoles (**19**–**25**) and benzoxazole (**27**), all yielding different heterocyclic core fused-ring skeletons. Both electron-rich and electron-deficient substrates, such as methyl (**5**, **6**, **9**, **11**), ether (**3**, **4**, **8**, **22**, **24**), ester (**21**), fluorides (**10**, **20**, **23**), and chlorides (**7**) at different positions, were tolerated. Benzimidazole with isopropyl (**13**) and benzyl (**14**) nitrogen protecting groups were also suitable substrates. Notably, imidazole (**15**), thiazole (**26**), and oxazole (**28**) yielded lower conversions than substrates with more conjugated systems, indicating that aromatization is crucial for promoting the reaction. Remarkably, replacing Togni's reagent II with ethyl bromodifluoroacetate (**16**), perfluoroalkyl iodide (**17**), and bromodifluoroamide (**18**) readily yielded the desired polyfluoroalkyl products. Finally, the merits of the protocol were further manifested by late-stage modifications of borneol (**29**) and cholesterol (**30**), which gave rise to the corresponding products in useful yields, suggesting their potential use in polyfluoroalkyl drug modification.

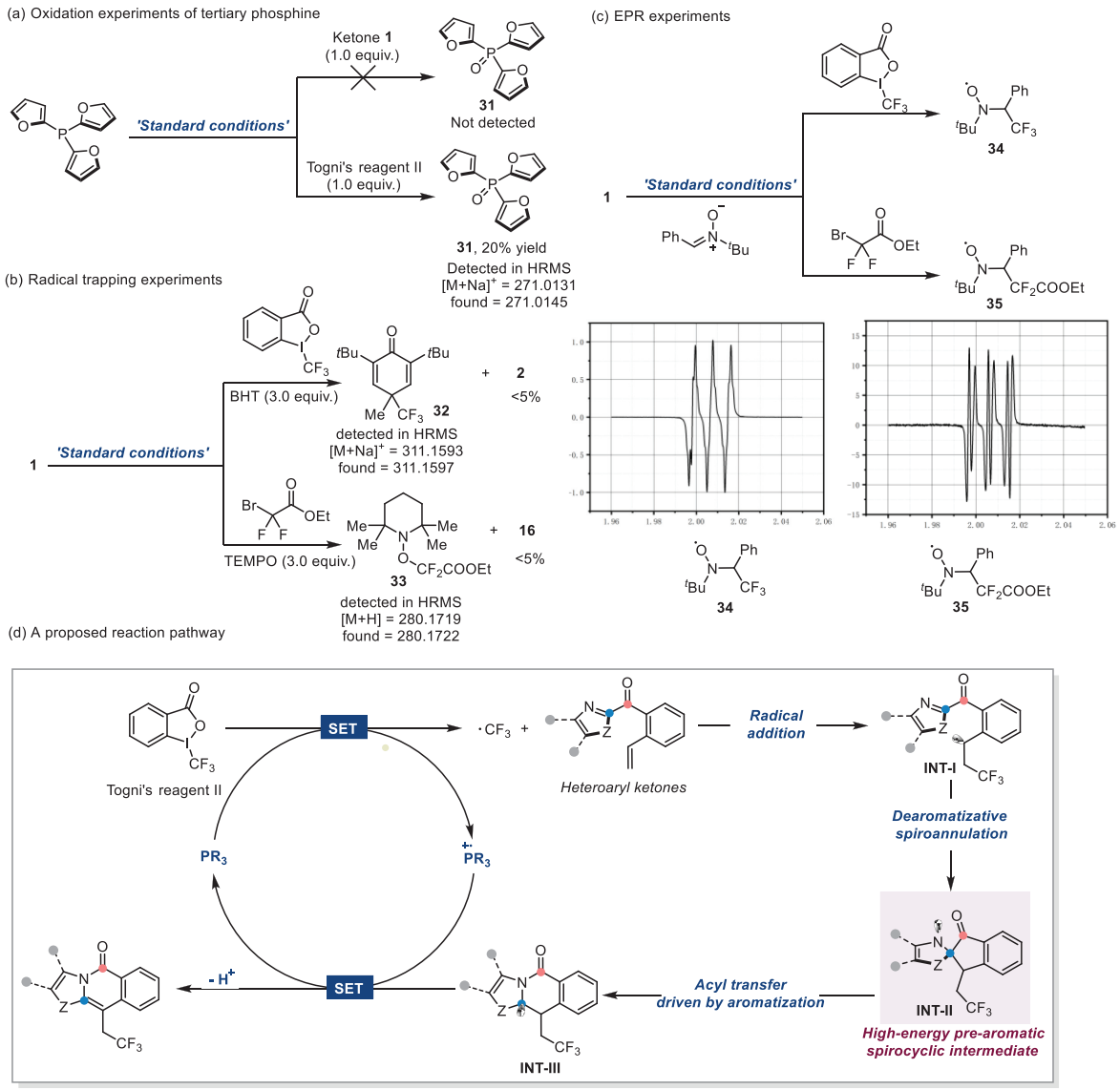
A series of control experiments were performed to investigate the mechanism of the phosphine-catalyzed radical-mediated process. When TFP was used with Togni's reagent II and heteroaryl ketone **1** in a 1:1 ratio at standard conditions and an electrospray ionization mass spectroscopic analysis was performed, it revealed that only tri(furan-2-yl)phosphine oxide **31** was detected in the presence of Togni's reagent II (Scheme 2a). This suggests that only Togni's reagent II can oxidize tertiary phosphine to initiate the generation of CF_3 radicals. Furthermore, a radical inhibition analysis validated the generation of a radial intermediate in the phosphine-initiated SET process (Scheme 2b), which was also confirmed by an electron paramagnetic resonance (EPR) analysis of the reaction between polyfluoroalkyl radicals **34** and **35** (Scheme 2c). The proposed reaction pathway based on the results described above and in previous studies is shown in Scheme 2d. Initially, the use of phosphine as a SET reagent under the oxidation of Togni's reagent II generated the corresponding phosphorus radical cation and CF_3 radical. The CF_3 radical attacks the alkene of heteroaryl ketones, affording a nascent benzyl radical intermediate, **INT-I**, followed by the dearomatizative spirocyclization to form spiro-*N*-radical **INT-II**. The aromatization driven intramolecular acyl transfer of the high-energy intermediate **INT-II** facilitates the formation of stable **INT-III**. Subsequently, single-electron oxidation of the phosphorus radical cation and deprotonation occurred to yield *N*-fused heteroarenes and regenerate the catalyst.

Further studies were conducted to investigate the synthetic utility of *N*-fused heteroarenes (Scheme 3). The bromination of **2** proceeded smoothly to afford **36** in presence of *N*-bromosuccimide (NBS), which allows follow-up fused heterocycle manipulations through cross-couplings. And a deconstruction of *N*-fused heterocycle was observed when treated **2** with *m*CPBA, affording **37** in 41% yield [9].

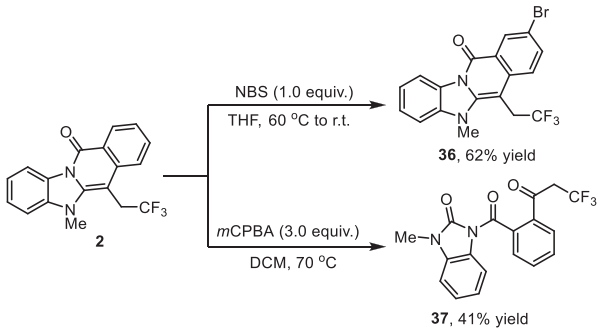
In summary, a transition-metal-free acyl transfer strategy was proved to produce trifluoromethyl modified *N*-fused heteroarenes from *N*-containing heteroaryl ketones. The key SET process of Togni's reagent II promoted by the tertiary phosphine resulted in a low cost and with minimal ecological impact tactic for the cleavage of C–C bonds. This eco-friendly and step-economical method not only offers a robust access to valuable complex *N*-fused heterocyclic systems but also enables late-stage modifications of diverse drug derivatives, thus demonstrating a great potential in heterocyclic drug research.



Scheme 1. Substrate scope for preparing *N*-fused heterocycles. Reaction conditions: ketones (0.1 mmol) and Togni's reagent II (0.15 mmol, 1.5 equiv.), with 10 mol% tri(2-furyl)phosphine (TFP), in dioxane/DCE (0.6 mL, 1:1) at 100 °C for 24 h, and 140 °C for 12 h. Isolated yields after chromatography. [a] The yield for large-scale synthesis with 1.5 mmol of **1**. [b] Using ethyl bromodifluoroacetate (0.15 mmol, 1.5 equiv.) instead of Togni's reagent II at 140 °C for 36 h. [c] Using perfluoroalkyl iodide (0.15 mmol, 1.5 equiv.) instead of Togni's reagent II at 140 °C for 36 h. [d] Using perfluoroalkyl amide or bromodifluoroacetate instead of Togni's reagent II at 140 °C for 48 h.



Scheme 2. Control experiments and proposed mechanism.



Scheme 3. Synthetic applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108529.

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