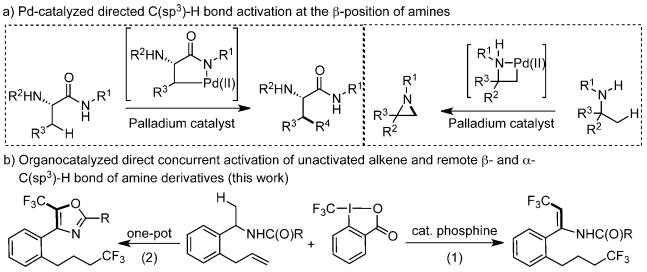
Radical Chemistry

International Edition: DOI: 10.1002/anie.201412310
German Edition: DOI: 10.1002/ange.201412310

Phosphine-Catalyzed Remote β-C–H Functionalization of Amines Triggered by Trifluoromethylation of Alkenes: One-Pot Synthesis of Bistrifluoromethylated Enamides and Oxazoles**

Peng Yu, Sheng-Cai Zheng, Ning-Yuan Yang, Bin Tan, and Xin-Yuan Liu**

Abstract: *An unprecedented phosphine-catalyzed remote β-C–H functionalization of amine derivatives triggered by trifluoromethylation of an alkene with Togni's reagent was disclosed. This reaction proceeded through the highly selective and concomitant activation of an unactivated alkene and the β-C_{sp^3}–H bond of an amine derivative, providing bistrifluoromethylated enamides in excellent yields with good regio-, chemo-, and stereoselectivity. Furthermore, the newly developed one-pot protocol provides a facile and step-economical access to valuable trisubstituted 5-(trifluoromethyl)oxazoles. Mechanistic studies showed that this reaction may initiate with a novel phosphine-catalyzed radical trifluoromethylation of unactivated alkene via a phosphorus radical cation.*



Scheme 1. Catalytic functionalization of C–H bonds at the β position of amine.

The increasing importance of trifluoromethyl nitrogen-rich compounds for the synthesis of interesting pharmaceuticals and biologically active molecules[1] has inspired considerable effort to develop expedient methods for C–CF_3 bond formation.[2] Among the most direct approaches for the construction of C–CF_3 bonds is the trifluoromethylation of alkenes by using Togni's reagent as the CF_3 radical source in the presence of transition metal complexes or organic oxidants as external initiators through a single-electron-transfer (SET) process.[3] In our study on the trifluoromethylation of alkenes,[4] we recently reported the approach of using a radical trifluoromethylation of an olefin to trigger an intramolecular 1,5-H radical shift and further C–O bond formation adjacent to amide with a Cu catalyst.[4f] Based on this mode of activation, we became interested in developing a novel redox-neutral process involving simultaneous remote functionalization of the β-C_{sp^3}–H bond of an amine derivative and unactivated alkene (Scheme 1b, path 1). Noteworthy is that selective functionalization of the β-C_{sp^3}–H bond of amines remains a formidable synthetic challenge.[5] To address this issue, the group of Yu[5a,b] as well as other research groups[5c–e] have elegantly demonstrated arylation, olefination, and alkylation at the β position of amino acid precursors by employing Pd-catalyzed amine-directed C–H activation (Scheme 1a). Alternatively, Gaunt and co-workers have championed the use of a four-membered-ring cyclopalladation pathway to activate the β-C_{sp^3}–H bond of amines (Scheme 1a).[5f] Despite these significant achievements in the field of transition metal catalysis, the exploration of alternative, mechanistically distinct catalytic systems for the β-C_{sp^3}–H bond functionalization of amines, especially with concomitant activation of other unactivated group and selective installation of different functional groups into organic compounds under metal-free conditions, has never been reported (Scheme 1b). However, our proposed reaction was rather challenging because of the presence of three unactivated structures including unactivated olefin and two α and β-C_{sp^3}–H bonds of amine and difficulties in simultaneously controlling the regio-, chemo-, and stereoselectivity associated with the highly reactive CF_3 radical intermediate[3] in the current reaction system.

Given the established capacity of ammonium/phosphorus radical cations to rapidly undergo a variety of reactions, which are most generally formed in situ from simple tertiary amine/phosphine through SET in the presence of various oxidants,[6] we hypothesized that such compounds in combination with Togni's reagent could concurrently generate the CF_3 radical and ammonium/phosphorus radical cations through autoxidation. To our knowledge, this mode of simple organic base as the catalyst to activate Togni's reagent via a radical cation intermediate toward direct trifluoromethylation of unactivated alkene has not been reported.[7] Herein, we describe the first successful development of an unprecedented organophosphine-catalyzed remote β-C_{sp^3}–H bond functionalization of amine derivatives triggered by trifluoromethylation of unactivated alkenes with Togni's reagent involving the concurrent incorporation of two CF_3 groups into the alkene and the remote β-C_{sp^3}–H bond of amine in one step

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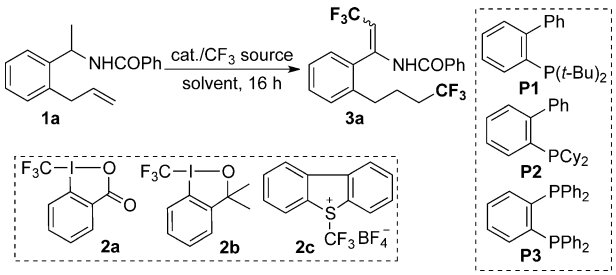
[**] Financial support from the National Natural Science Foundation of China (grant numbers 21302088 and 21302087) and the National Basic Research Program of China (2013CB834802) is greatly appreciated.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201412310.

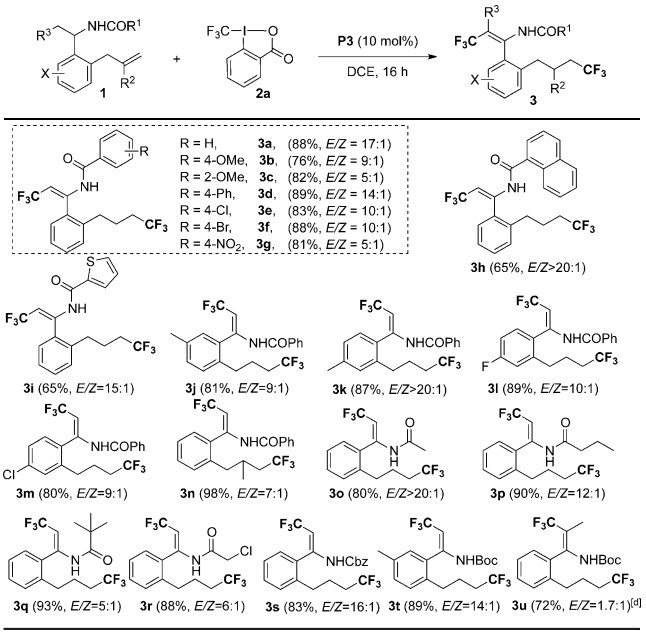
(Scheme 1b, path 1). It is noteworthy that this reaction is an advantageous alternative to the transition-metal-catalyzed β-C_{sp^3}–H bond functionalization of amine derivatives assisted by a nitrogen-based directing group.[5] Most importantly, this transformation through a sequential phosphine-catalyzed bistrifluoromethylation followed by intramolecular cyclization in a one-pot version, provides a convenient and step-economical access to diverse trisubstituted 5-(trifluoromethyl)oxazoles (Scheme 1b, path 2); such structural motifs are important components of various biologically active natural products and medicinal compounds.[8]

We initiated these investigations by examining the reaction of *N*-(1-(2-allylphenyl)ethyl)benzamide **1a** with Togni's reagent **2a**[3a,9] as the model reaction (Scheme 2, Table S1 in



Scheme 2. Initially investigated catalysts and CF_3 sources.

Table 1: Substrate scope of alkenyl *N*-ethyl-amides.[a,b,c]



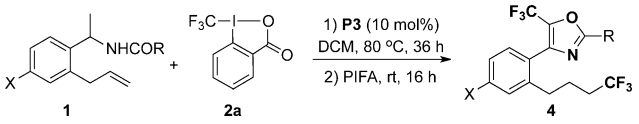
[a] Reaction conditions: **1** (0.2 mmol), Togni's reagent **2a** (2.2 equiv), DCE (2.0 mL) at 80–100 °C for 16 h under argon. [b] Yield of the isolated product. [c] *E*/*Z* ratio was determined by ^{19}F NMR spectroscopy. [d] 56 h reaction time. Cbz = carboxybenzyl, Boc = *tert*-butyloxycarbonyl.

the Supporting Information). The use of DABCO as the catalyst in EtOAc promoted the sequential unactivated alkene/remote β-C_{sp^3}–H bond difunctionalization reaction of **1a** to afford the bistrifluoromethylated product **3a** in 71% yield as a 6:1 mixture of *E*/*Z* isomers (Table S1, entry 1). Based on these findings, we also screened other tertiary amines and organic solvents and found that DABCO as the catalyst in dichloroethane (DCE) gave the best result with 93% yield as a 3:1 mixture of *E*/*Z* isomers. To further improve the *E*/*Z* selectivity, we changed the tertiary amines to various phosphines as the catalyst and found that the use of 10 mol% of bisphosphine such as 1,2-bis(diphenylphosphino)benzene (dppBz) (**P3**) under otherwise identical conditions resulted in a significantly increased *E*/*Z* selectivity of up to 17:1 with 88% yield. Notably, a control experiment demonstrated that the reaction did not occur in the absence of organocatalyst under the standard conditions.

We next investigated the substrate scope of alkenyl *N*-ethyl-amide with diverse substituents (Table 1). A variety of substrates **1b**–**1g**, bearing electron-donating or electron-withdrawing groups on the aryl ring at the α position of the amide group consistently afforded **3b**–**3g** in good yields with good *E*/*Z* selectivity. The introduction of a naphthyl or thienyl group was compatible with this protocol to form **3h** or **3i** in 65% yield with excellent *E*/*Z* selectivity. In addition, substituents including methyl (**1j**, **1k**), fluoro (**1l**), and chloro (**1m**) groups at the different positions were compatible to afford **3j**–**3m** in 80–89% yield with excellent *E*/*Z* selectivity. Further studies show that the geminal-disubstituted alkene **1n** also underwent this reaction to furnish the corresponding product **3n** in 98% yield with 7:1 *E*/*Z* ratio. Interestingly, the use of alkyl groups at the α position of amides did not affect the product yield and *E*/*Z* selectivity. Several substituents, such as methyl (**1o**), *n*-propyl (**1p**), and *tert*-butyl (**1q**) as the alkyl moiety were well-tolerated. Even 2-chloro-acetamide remained intact in the reaction and the product **3r** was obtained in 88% yield as a 6:1 mixture of *E*/*Z* isomers. The configuration of **3r** was determined to be *E* by X-ray analysis (Figure S1).[10] A variety of functional groups including Cbz (**1s**) and Boc (**1t**) were also found to be compatible with the current reaction system, affording **3s** and **3t** in 83% and 89% yield, respectively, with excellent *E*/*Z* selectivity. Furthermore, when alkenyl *N*-*n*-propyl-amide **1u** was used as substrate, the product **3u** was obtained in 72% yield with 1.7:1 *E*/*Z* ratio.

Trisubstituted 5-(trifluoromethyl)oxazoles have been used as important building blocks in pharmaceutically and agrochemically relevant molecules.[8] However, convergent one-step or one-pot methods to prepare such skeletons are rare, and often require the use of highly reactive species or 2,4-disubstituted oxazole precursors with consequent structural limitations.[8e,f] We reasoned that oxidative cyclization of trifluoromethyl enamides **3** with an appropriate oxidant may afford polysubstituted oxazoles.[11] To further simplify the reaction protocol, we investigated the possibility of the combination of two distinct reaction sequences to a one-pot process with minimal extra procedures. After systematic optimization of different reaction parameters, including oxidant, additive, solvent, and temperature (Table S2), a simple one-pot procedure was realized. Compound **1a** was efficiently converted into **3a** in the presence of dppBz (**P3**) (10 mol%) in DCM under otherwise identical conditions, followed by an oxidative cyclization with [bis(trifluoroacet-

Table 2: Reaction scope.[a]

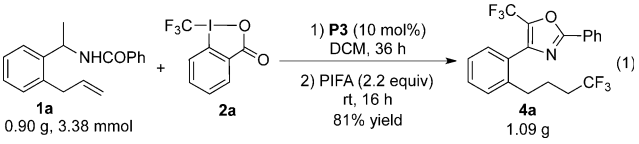


Entry	R	X	Product	Yield [%][b]
1	Ph	H	**4a**	73
2	4-MeOC$_6$H$_4$	H	**4b**	76
3	4-BrC$_6$H$_4$	H	**4f**	63
4	1-naphthyl	H	**4h**	46
5	2-thienyl	H	**4i**	78
6	Ph	Me	**4k**	70
7[c]	Ph	Cl	**4m**	60
8[d]	Me	H	**4o**	66
9	ClCH$_2$	H	**4r**	74

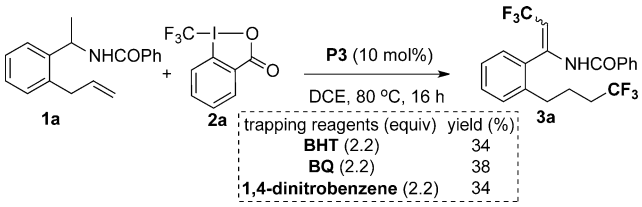
[a] Reaction conditions: **1** (0.1 mmol), **2a** (2.2 equiv), **P3** (10 mol%), 80 °C; PIFA (2.2 equiv) was added after first step. [b] Yield of the isolated product. [c] The reaction temperature was 40 °C for the second step. [d] PIFA (5.0 equiv) was added in two portions in the second step for 24 h at 60 °C.

oxy)iodo]benzene] (PIFA) at room temperature to afford **4a** in 73% yield (Table 2, entry 1). A series of substrates containing electron-donating, or -withdrawing aryl groups (naphthyl, thienyl, alkyl) at the α position of the amide group, and even those containing different functional groups on the aryl rings were well tolerated to afford **4a**–**4r** in 46–78% yields (Table 2). It is encouraging to note that the present process is a rather general protocol for the one-pot synthesis of trisubstituted oxazoles from simple alkenyl *N*-ethyl-amides through simultaneous functionalization of three sequential C_{sp^2}–H, C_{sp^3}–H, and C_{sp^2}–H bonds and selective installation of different functional groups with remarkable precision under metal-free conditions, which is clearly complementary to the previous oxidative cyclization of enamides.[11]

To further evaluate the practicality of such process, the reaction was carried out on a gram scale. There was almost no influence on the chemical yield (81% yield) [Eq. (1)], indicating this protocol should be potential for large-scale chemical production of trisubstituted 5-(trifluoromethyl)oxazoles.

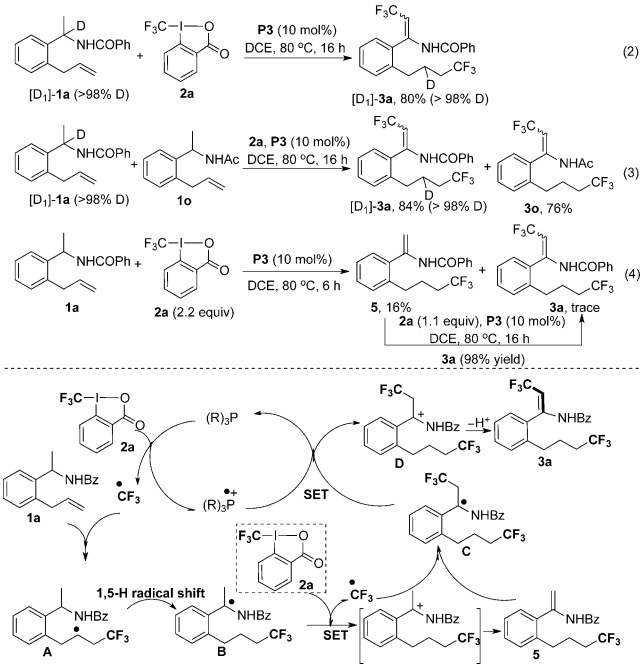


To gain more insights into the reaction mechanism, a series of control experiments was performed. Initially, ^{31}P NMR analysis showed a remarkable downfield shift after the interaction of dppBz (**P3**) and Togni's reagent **2a** in a 1:10 ratio at 80 °C for 16 h (Figure S2c). By comparison, the sample containing **P3** and substrate **1a** showed no chemical shift as compared with that of **P3** (Figure S2b). These results clearly indicated that the phosphine catalyst possibly would not provide significant activation of unactivated alkenes, but only activate Togni's reagent to generate the CF_3 radical intermediate. Furthermore, we also performed electrospray ionization mass spectroscopic analysis (ESI-MS) of a solution of PPh_3 and **2a** in a 1:1 ratio in DCE under air. The spectrum (Figure S3) shows the characteristic signals corresponding to $P(O)Ph_3$ at *m*/*z* 279.0974 ($[P(O)Ph_3+H]^+$) as well as the 2-iodobenzoate ion at *m*/*z* 246.9130, suggesting that Togni's reagent **2a** can oxidize the tertiary phosphine under the reaction conditions. Additionally, to validate the original design of the present radical tandem process involving a phosphine-initiated single-electron transfer, radical trapping experiments were also conducted by employing 2,6-di-*tert*-butyl-4-methylphenol (BHT), benzoquinone (BQ), and 1,4-dinitrobenzene. The reaction could be significantly inhibited by these reagents, suggesting that a SET process is involved in this reaction (Scheme 3).



Scheme 3. Radical trapping experiments.

With regard to a 1,5-H radical shift, the reaction of deuterium-substituted [D_1]-**1a** was performed under the standard conditions and the deuterium at the carbon adjacent to the nitrogen atom completely shifted to the β position of the alkene in [D_1]-**3a** [Eq. (2), Scheme 4]. Next, a crossover experiment involving equimolar amounts of [D_1]-**1a** and **1o** showed no incorporation in [D_1]-**1a** and **1o** [Eq. (3)]. These



Scheme 4. Control experiments and proposed mechanism.

results indicated that the current reaction proceeded with an intramolecular 1,5-H radical shift process. To further investigate the reaction mechanism in detail, we examined the reaction of **1a** with 2.2 equiv of **2a** at 80 °C for 6 h, which could afford enamide **5** in 16 % yield along with most of **1a** recovered. Subsequent reaction of **5** with **2a** with **P3** catalyst gave the final product in 98 % yield [Eq. (4)],[12] which clearly indicated that the reaction should proceed via an intermediate enamide.

On the basis of the results described above and previous studies,[4f] a proposed pathway is depicted in Scheme 4. Initially, the use of phosphine as a SET reagent for the reduction of **2a** would generate the corresponding phosphorus radical cation and CF_3 radical. The CF_3 radical attacks alkene **1a** affording a nascent α-CF_3-alkyl radical intermediate **A**, followed by 1,5-H radical shift to generate a lower energy amide-stabilized radical **B**, with subsequent single-electron oxidation from **2a** and deprotonation, to simultaneously afford enamide intermediate **5** and CF_3 radical. Next, the attack of enamide **5** with the CF_3 radical generates intermediate **C**, followed by single-electron oxidation from the phosphorus radical cation and then deprotonation, to give **3a**. However, phosphine as the dual catalyst to initiate two distinct catalytic cycles including the formation of enamide **5** through a 1,5-H radical shift triggered by trifluoromethylation of alkene and of the resultant enamide **5**[12] under the current reaction conditions, could not be excluded at the present stage. Therefore, rigorous investigations are necessary to unambiguously elucidate the exact mechanism.

In summary, we have developed the first phosphine-catalyzed tandem radical process enabling the highly selective and concomitant functionalization of alkene and the remote β-C_{sp^3}–H bond of amine derivatives, which provides facile access to bistrifluoromethylated enamides in excellent yields with good regio-, chemo-, and stereoselectivity under mild and metal-free conditions. Furthermore, the newly developed one-pot protocol from alkenyl *N*-ethyl-amides by simultaneous functionalization of three sequential C_{sp^2}–H, C_{sp^3}–H, and C_{sp^2}–H bonds provides a facile and step-economical access to valuable trisubstituted 5-(trifluoromethyl)oxazoles, thus demonstrating great potential in synthetic and medicinal chemistry.

Keywords: 1,5-H radical shift · alkenes · radical chemistry · trifluoromethylation · β-C–H functionalization

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 4041–4045
Angew. Chem. **2015**, *127*, 4113–4117

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Received: December 23, 2014
Published online: February 18, 2015

