



# Enantioselective $\alpha$ -C-H functionalization of amides with indoles triggered by radical trifluoromethylation of alkenes: Highly selective formation of C—CF<sub>3</sub> and C—C bonds



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## ABSTRACT

A dual copper/chiral phosphoric acid-catalyzed asymmetric tandem remote C(sp<sup>3</sup>)-H/unactivated alkene functionalization reaction triggered by radical trifluoromethylation of unactivated alkenes for the concomitant construction of C—CF<sub>3</sub> and C—C bonds was described. This approach provided an efficient method for the synthesis of valuable chiral trifluoromethylated indole derivatives with excellent regio-, chemo-, and good enantioselectivity.

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## 1. Introduction

The increasing importance of chiral CF<sub>3</sub>-containing azaheterocycles in pharmaceuticals and agrochemicals has inspired synthetic chemists' interest in the development of new catalytic asymmetric methods for their synthesis [1]. Trifluoromethyl radical-initiated functionalization of unactivated alkenes has been intensively investigated, providing a reliable and robust avenue towards CF<sub>3</sub>-containing compounds [2]. However, few such methodologies are able to deliver these CF<sub>3</sub>-containing products in an enantioselective manner. In this context, we recently reported highly enantioselective radical 1,2-aminotrifluoromethylation of alkenes using a Cu(I)/chiral phosphoric acid dual-catalytic system, affording diverse chiral CF<sub>3</sub>-containing pyrrolidines [3]. Additionally, our group has recently also developed an asymmetric radical tandem unactivated alkene/C—H bond difunctionalization reaction via a 1,5-H atom transfer process for the synthesis of highly enantioenriched *N,O*-aminals using alcohols as nucleophiles (Scheme 1A) [4]. In order to expand the scope of applicable

nucleophiles and thus enhance the synthetic utility of the latter methodology, we set out to explore other nucleophilic candidates, such as indole. Chiral indole-containing compounds are widespread heterocyclic compounds in nature and exist ubiquitously in biologically active natural products and pharmaceutical compounds [5], and their enantioselective synthesis is no doubt one of the most extensive research areas.

On the basis of our continuous interest in the area of asymmetric radical difunctionalization of alkenes [3] and previous work [4,6], we herein report a successful example of a tandem process involving radical trifluoromethylation of alkenes to trigger an intramolecular 1,5-H atom transfer and further an enantioselective C—H functionalization/Friedel-Crafts alkylation reaction [7] with indole as the nucleophile using a copper/Brønsted acid catalytic system. The mild reaction conditions conveniently and economically give rise to a broad range of useful chiral CF<sub>3</sub>-containing indole derivatives with good regio-, chemo-, and enantioselectivity (Scheme 1B).

## 2. Results and discussion

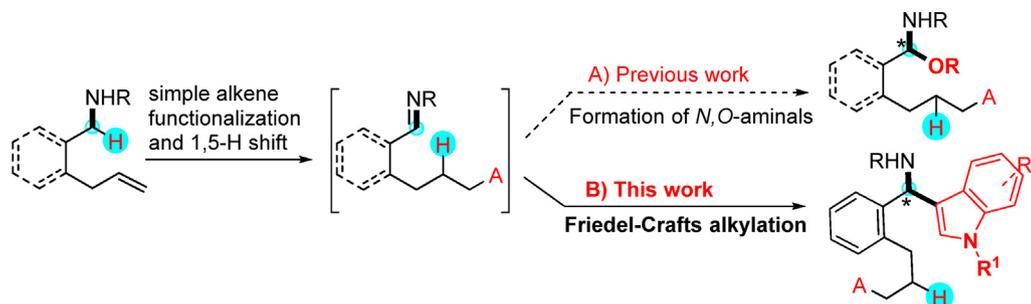
Inspired by our recent work on the synthesis of enantioenriched *N,O*-aminals using alcohols as nucleophiles [4][4a], we began by choosing the *N*-(2-allylbenzyl)benzamide (**1a**), 1-benzyl-1H-indole (**2a**), and commercially available Togni's reagent (**3a**) [8] as the

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## Enantioselective simple alkene/remote C-H difunctionalization:



**Scheme 1.** Enantioselective catalytic functionalization of C—H bond adjacent to heteroatoms based on radical 1,5-H shift.

model substrate for the optimization of reaction conditions. To our delight, the reaction of **1a** with **2a** and **3a** in a 1:1.2:1.2 mol ratio was initially carried out using CuI as the catalyst in EtOAc at 60 °C under argon conditions, affording the desired product **4a**, along with 61% yield (Table 1, entry 1). Encouraged by this result, several reaction parameters were further investigated to improve the reaction efficiency. CuI was found to be most beneficial for the reaction to give the corresponding product after screening a range of copper(I) catalysts (entries 2–5). Next, screening of the reaction solvents revealed DCM was optimal to give **4a** in 76% yield (entries 6–11), suggesting an obvious solvent effect for the current reaction. Switching the CF<sub>3</sub> reagents from Togni's reagent **3a** to Togni's reagent **3b** or Umemoto's reagent **3c** dramatically decreased the yields, revealed that **3a** was the best CF<sub>3</sub> source for this tandem

process (entries 12, 13). Afterward, examination of the molar ratio of **1a** to **2a** revealed an optimum ratio (**1a:2a**=1:1.2) in this reaction (entry 6), whereas inferior results were displayed by increasing this ratio (entries 14–15). Under the optimal radical conditions, about 17% NMR yield of complicated byproducts containing trifluoromethylated *N*-benzylindole **2a** was detected because poor regioselectivity was observed in the direct radical trifluoromethylation of indoles without any substitution at the 3 and 4 positions in previous report [9]. Although both the electron-rich indoles and alkenes present highly reactive with trifluoromethyl radical, the reason for predominance of **4a** over the side product is possibly the maintenance of the intact aromaticity in trifluoromethylation of alkenes of **1a** compared with the detriment of aromaticity in the trifluoromethylation of **2a**. Finally, no desired product was observed without copper catalyst (entry 16), suggesting that copper catalyst played an important role in this system.

**Table 1**  
Optimization of the condition.<sup>a</sup>

Entry	[Cu]	Solvent	Yield (%) <sup>b</sup>
1	CuI	EtOAc	61
2	CuCN	EtOAc	57
3	CuSCN	EtOAc	51
4	Cu(CH <sub>3</sub> CN) <sub>4</sub> BF <sub>4</sub>	EtOAc	– <sup>c</sup>
5	CuTc	EtOAc	– <sup>c</sup>
<b>6</b>	<b>CuI</b>	<b>DCM</b>	<b>76</b>
7	CuI	DCE	73
8	CuI	1,4-dioxane	36
9	CuI	CH <sub>3</sub> CN	57
10	CuI	THF	13
11	CuI	Toluene	16
12 <sup>d</sup>	CuI	DCM	51
13 <sup>e</sup>	CuI	DCM	12
14 <sup>f</sup>	CuI	DCM	66
15 <sup>g</sup>	CuI	DCM	60
16	– <sup>h</sup>	DCM	– <sup>c</sup>

<sup>a</sup> Reaction conditions: **1a** (0.05 mmol), **2a** (1.2 equiv), Togni's reagent **3a** (1.2 equiv), Cu source (20 mol%), solvent (0.5 mL), 60 °C, Ar.

<sup>b</sup> Yield based on <sup>19</sup>F NMR analysis of the crude product.

<sup>c</sup> Product was not detected.

<sup>d</sup> Togni's reagent **3b** was used.

<sup>e</sup> Umemoto's reagent **3c** was used.

<sup>f</sup> 1.7 equiv of **2a** was used.

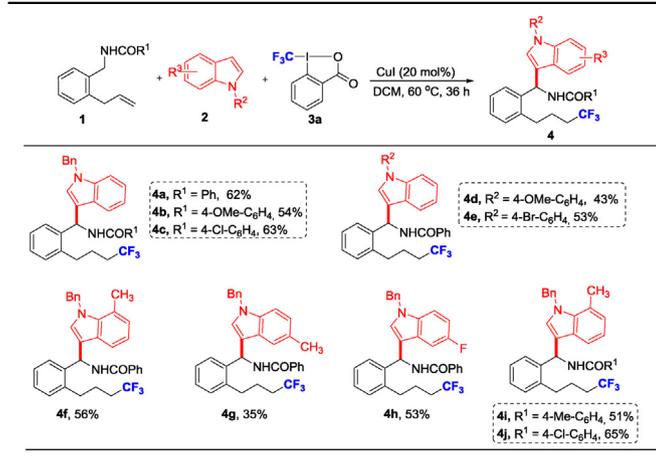
<sup>g</sup> 2.2 equiv of **2a** was used.

<sup>h</sup> No Cu catalyst. CuTc = copper(I)-thiophene-2-carboxylate.

With the optimized reaction conditions in hand, we then commenced to evaluate the generalization of this transformation and found a broad range of other *N*-(2-allylbenzyl)amide substrates are suitable to the present transformation (Table 2). A number of substituents, including Me, MeO, and Cl groups, on the aromatic ring alpha to the amide carbonyl group, were well-tolerated, affording the corresponding products **4b**, **4c**, **4i** and **4j** in moderate yields, respectively. Notably, the *para*-substituted *N*-benzyl indole substrates with various substituents (R<sup>2</sup>) on the phenyl ring were good for the transformation to give the desired products **4d** and **4e** in 43% and 53% yields, respectively. Furthermore, several diversely functionalized 1-benzyl-1H-indoles, containing either electron-donating or electron-withdrawing groups at different positions on the benzene ring, have been tested in the reaction with *N*-(2-allylbenzyl)benzamide **1a**, **1c** and **1d**, respectively, furnishing the corresponding products **4f–4j** in moderate to good yields.

Encouraged by our recent success in enantioselective C—H bond functionalization triggered by radical trifluoromethylation of unactivated alkenes [4][4a] and inspired by enantioselective Friedel-Crafts reaction of indoles with imines by a chiral phosphoric acid (CPA) [7], we became particularly interested in the asymmetric unactivated alkene/C—H bond difunctionalization reaction for the concomitant construction of C—CF<sub>3</sub> and C—C bonds in the presence of a cooperative catalyst system composed of a copper catalyst and chiral phosphoric acid. In light of the described results, our investigation commenced with the reaction of *N*-(2-allylbenzyl)benzamide (**1a**) with benzyl-1H-indole (**2a**) and Togni's reagent (**3b**) using a copper/Brønsted acid cooperative catalytic system. Gratifyingly, the reaction proceeded smoothly to deliver the desired product **5a** in 43% yield with 80% ee in the presence of CuCN and (*R*)-**A1** at room temperature (Table 3, entry 1). Encouraged by this result, we next screened different

**Table 2**  
Substrate scope of amides and indoles.<sup>a,b</sup>



<sup>a</sup> All of the reactions were conducted on a 0.2 mmol scale.

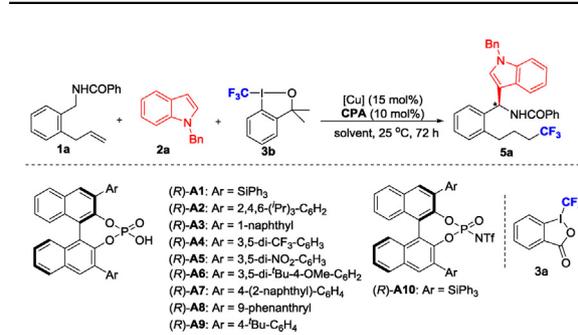
<sup>b</sup> Isolated yields based on 1.

combinations of various BINOL-based CPAs and copper salts (entries 2–18) in different solvents and found out that the dual catalyst comprising CuSCN (15 mol%) and (*R*)-**A1** (10 mol%) was the best one, delivering the desired product **5a** in the 55% yield and 76% ee (entry 18). Examination of a variety of the freshly dried molecular sieves (MS) revealed that use of molecular sieves as an additive to minimize the water content in the reaction system did not affect the reaction efficiency and enantioselectivity (entries 23–25). It is noteworthy that changing the CF<sub>3</sub> reagent from **3b** to **3a** resulted in a remarkable increase in the enantioselectivity (88% ee) in the presence of 5 Å molecular sieves (entry 26), which was in sharp contrast to our previous work [4][4a], revealing that 2-iodobenzoic acid which was generated from the reaction system, did not affect the enantioselective reaction catalyzed by CPAs in the current reaction system.

Under the optimized conditions, the substrate scope was examined. First, *N*-(2-allylbzyl)amide and indole substrates bearing various substituents were surveyed. As illustrated in Table 4, a wide variety of substrates were well-tolerated, irrespective of the electronic nature and position of substituents, furnishing the corresponding chiral CF<sub>3</sub>-containing indole products in moderate to good yields with good enantioselectivities. Aryl amides with Cl, Me and MeO groups on the aromatic ring adjacent to the amide group, were readily accommodated, affording products **5b**, **5c** and **5h** in moderate yields with good enantioselectivities. Notably, the *para*-substituted *N*-benzyl indole substrates with various substituents (R<sup>2</sup>) on the phenyl ring underwent the reaction smoothly to deliver the expected products **5d** and **5e** in moderate yields with 85% and 80% ee, respectively. Furthermore, several diversely functionalized 1-benzyl-1H-indoles, were also suitable for this transformation to furnish the desired products **5f–5i** in moderate yields with good enantioselectivities. The absolute configuration of **5a** was determined to be *S* referred to our previous report [4][4a].

To gain some mechanistic insights into the reaction, radical inhibition experiments of **1a** were performed by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), benzoquinone and 1,4-dinitrobenzene under the standard conditions, respectively (Scheme 2). The yield of **5a** was significantly decreased, where the TEMPO-CF<sub>3</sub> adduct was formed in 41% yield for the reaction in the presence of TEMPO. Together with previous studies on radical trifluoromethylation of

**Table 3**  
Screening of reaction conditions.<sup>a</sup>



Entry	[Cu]	CPA	Solvent	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	CuCN	( <i>R</i> )- <b>A1</b>	EtOAc	43	80
2	CuCN	( <i>R</i> )- <b>A2</b>	EtOAc	50	54
3	CuCN	( <i>R</i> )- <b>A3</b>	EtOAc	48	8
4	CuCN	( <i>R</i> )- <b>A4</b>	EtOAc	27	0
5	CuCN	( <i>R</i> )- <b>A5</b>	EtOAc	trace	– <sup>d</sup>
6	CuCN	( <i>R</i> )- <b>A6</b>	EtOAc	trace	– <sup>d</sup>
7	CuCN	( <i>R</i> )- <b>A7</b>	EtOAc	27	0
8	CuCN	( <i>R</i> )- <b>A8</b>	EtOAc	25	41
9	CuCN	( <i>R</i> )- <b>A9</b>	EtOAc	37	23
10	CuCN	( <i>R</i> )- <b>A10</b>	EtOAc	56	23
11	CuI	( <i>R</i> )- <b>A1</b>	EtOAc	40	77
12	CuBr	( <i>R</i> )- <b>A1</b>	EtOAc	trace	– <sup>d</sup>
13	CuCl	( <i>R</i> )- <b>A1</b>	EtOAc	trace	– <sup>d</sup>
14	CuTc	( <i>R</i> )- <b>A1</b>	EtOAc	30	75
15	CuOAc	( <i>R</i> )- <b>A1</b>	EtOAc	26	78
16	Cu(CH <sub>3</sub> CN) <sub>4</sub> PF <sub>6</sub>	( <i>R</i> )- <b>A1</b>	EtOAc	trace	– <sup>d</sup>
17	Cu(CH <sub>3</sub> CN) <sub>4</sub> BF <sub>4</sub>	( <i>R</i> )- <b>A1</b>	EtOAc	15	0
18	CuSCN	( <i>R</i> )- <b>A1</b>	EtOAc	55	76
19	CuSCN	( <i>R</i> )- <b>A1</b>	DCM	59	75
20	CuSCN	( <i>R</i> )- <b>A1</b>	DCE	60	67
21	CuSCN	( <i>R</i> )- <b>A1</b>	THF	trace	– <sup>d</sup>
22	CuSCN	( <i>R</i> )- <b>A1</b>	CH <sub>3</sub> CN	trace	– <sup>d</sup>
23 <sup>e</sup>	CuSCN	( <i>R</i> )- <b>A1</b>	EtOAc	70	75
24 <sup>f</sup>	CuSCN	( <i>R</i> )- <b>A1</b>	EtOAc	39	76
25 <sup>g</sup>	CuSCN	( <i>R</i> )- <b>A1</b>	EtOAc	79	75
26 <sup>h</sup>	CuCN	( <i>R</i> )- <b>A1</b>	EtOAc	81	82
27 <sup>h</sup>	CuI	( <i>R</i> )- <b>A1</b>	EtOAc	82	80
28 <sup>h</sup>	<b>CuSCN</b>	( <i>R</i> )- <b>A1</b>	<b>EtOAc</b>	<b>76</b>	<b>88</b>

<sup>a</sup> The reactions were conducted with 0.05 mmol **1a**, 1.7 equiv **3b**, 1.2 equiv **2a**, 15 mol% Cu source and 10 mol% CPA in 0.5 mL solvent for 3 days.

<sup>b</sup> Determined by <sup>19</sup>F NMR spectroscopy using PhCF<sub>3</sub> as an internal standard.

<sup>c</sup> Determined by chiral HPLC analysis.

<sup>d</sup> Not determined.

<sup>e</sup> 40 mg of 3 Å molecular sieve was added.

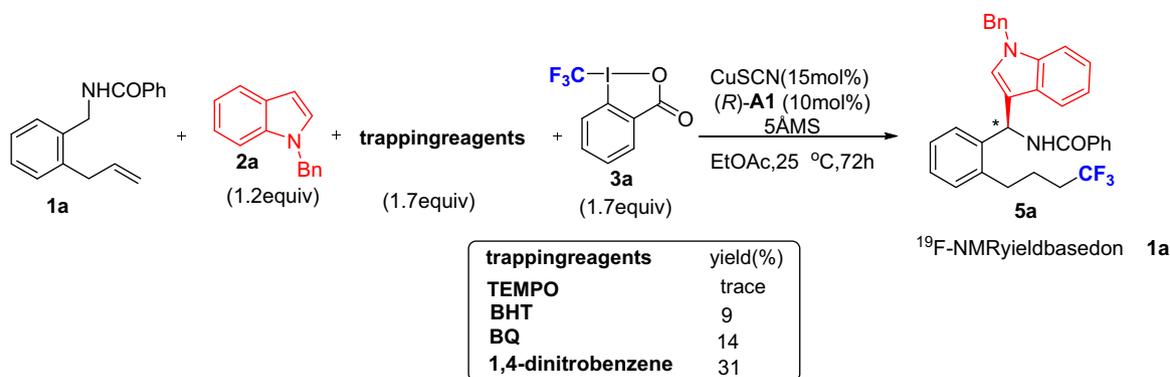
<sup>f</sup> 40 mg 4 Å molecular sieve was added.

<sup>g</sup> 40 mg 5 Å molecular sieve was added.

<sup>h</sup> Togni's reagent **3a** and 40 mg 5 Å molecular sieve were added.

alkenes, the results reveal that the CF<sub>3</sub> radical is likely involved in the current reaction [2].

The mechanisms are proposed for the current reaction system (Scheme 3) on the basis of the present observations and the literature reports [6]. First, a CF<sub>3</sub> radical is generated from the reaction of Togni reagent **3a** with copper(I) and the chiral phosphoric acid (CPA). Subsequently, addition of CF<sub>3</sub> radical to alkene produces the high-energy radical intermediate **A** [4], which abstracts a proximal hydrogen atom [10] adjacent to the nitrogen atom of the amide, generating a radical intermediate **B** [11] via 1,5-H atom transfer process [4,10]. Afterward, **B** was oxidized through single-electron oxidation (SET) to give the *N*-acyl imine intermediate **C**. Finally, the addition of *N*-benzyl indole to *N*-acyl imine **C** via intermediate **D** [12] through enantioselective Friedel-Crafts reaction [7] in the presence of a chiral phosphoric acid, affords the final product **5** with good enantioselectivity.



Scheme 2. Control experiments in the presence of radical scavengers.

### 3. Conclusions

In conclusion, we have successfully developed an enantioselective tandem process to realize concomitant formation of two new C—CF<sub>3</sub> and C—C bonds by remote functionalization of C(sp<sup>3</sup>)-H bonds adjacent to an amide, triggered by radical trifluoromethylation of unactivated alkenes. The overall process serves as an efficient and simple approach for straightforward access to diversely valuable enantioenriched trifluoromethylated indole derivatives in moderate to good yields and with excellent regioselectivity, chemoselectivity, and good enantioselectivity using a copper/Brønsted acid cooperative system.

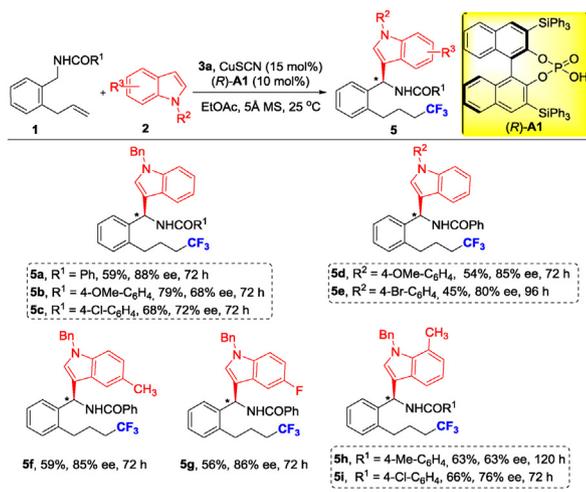
### 4. Experimental

#### 4.1. Synthetic procedures and spectral data for indoles

*N*-(2-Allylbenzyl)benzamide (**1**) were synthesized according to the procedures [4]. 1-benzyl-1*H*-indole (**2**) were synthesized according to the procedures [13].

To a flame-dried Schlenk tube equipped with a magnetic stir bar were added **1** (0.2 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv), Togni's reagent **3a** (75.8 mg, 0.24 mmol, 1.2 equiv) and CuI (7.6 mg, 0.04 mmol, 0.2 equiv). The tube was evacuated and backfilled with Ar for three times, and then solvent (EtOAc, 2.0 mL) was added *via*

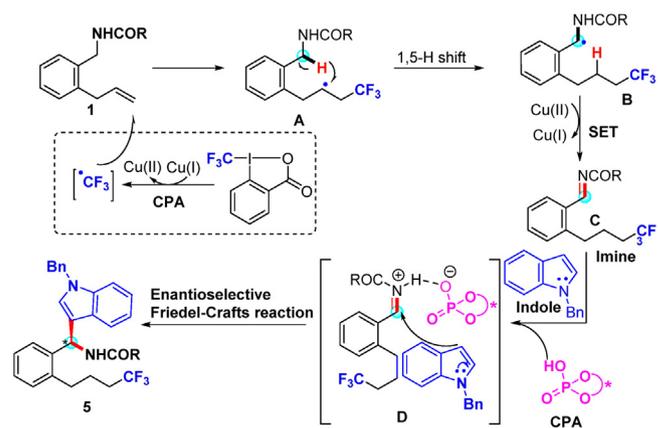
**Table 4**  
Substrate scope of amides and indoles.<sup>a,b,c</sup>



<sup>a</sup> All of the reactions were conducted on a 0.1 mmol scale.

<sup>b</sup> Isolated yields based on **1** are shown.

<sup>c</sup> The ee values were determined by HPLC analysis.



Scheme 3. Mechanistic proposal.

syringe. The tube was stirred at 60 °C for 36 h. After reaction completed the reaction solution was concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography (petroleum ether/DCM = 1/1) to give the corresponding indole products.

To a flame-dried Schlenk tube equipped with a magnetic stir bar were added **1** (0.1 mmol, 1.0 equiv), **2** (0.12 mmol, 1.2 equiv), Togni's reagent **3a** (53.7 mg, 0.17 mmol, 1.7 equiv), (*R*)-**A1** (8.6 mg, 0.01 mmol, 0.10 equiv) and CuSCN (1.8 mg, 0.015 mmol, 0.15 equiv). The tube was evacuated and backfilled with Ar for three times, and then solvent (EtOAc, 1.0 mL) were added *via* syringe. The tube was stirred at 25 °C. After reaction completed the reaction solution was concentrated *in vacuo* and the crude residue was purified by silica gel column chromatography (petroleum ether/DCM = 1/1) to give the corresponding indole products.

#### 4.2. Experiments for mechanistic studies

##### 4.2.1. Control experiments in the presence of radical scavengers

Under argon, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with amide substrate **1a** (0.05 mmol, 1.0 equiv), CuSCN (0.9 mg, 0.0075 mmol, 15 mol%), chiral phosphoric acid (**A1**) (4.3 mg, 0.005 mmol, 10 mol%), Togni's reagent **2a** (26.9 mg, 0.085 mmol, 1.7 equiv), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 13.3 mg, 0.085 mmol, 1.7 equiv) or 2,6-di-*tert*-butyl-4-methylphenol (BHT, 18.7 mg, 0.085 mmol, 1.7 equiv), or 1,4-benzoquinone (BQ, 9.2 mg, 0.085 mmol, 1.7 equiv), or 1,4-dinitrobenzene (14.3 mg, 0.085 mmol, 1.7 equiv) and EtOAc (0.50 mL) at 25 °C, the sealed tube was then stirred at 25 °C for 72 h. PhCF<sub>3</sub> (internal standard, 0.05 mmol, 1.0 equiv) was added to

the reaction mixture. Yield was based on  $^{19}\text{F}$  NMR analysis of the crude product.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.jfluchem.2017.03.008>.

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