Enantioselective α-C-H functionalization of amides with indoles triggered by radical trifluoromethylation of alkenes: Highly selective formation of C—CF₃ and C—C bonds

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A dual copper/chiral phosphoric acid-catalyzed asymmetric tandem remote C(sp²)-H/unactivated alkene functionalization reaction triggered by radical trifluoromethylation of unactivated alkenes for the concomitant construction of C—CF₃ 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 CF₃-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 CF₃-containing compounds [2]. However, few such methodologies are able to deliver these CF₃-containing products in an enantioselective manner. In this context, we recently reported highly enantiospecific radical 1,2-aminationotrifluoromethylation of alkenes using a Cu(1)/chiral phosphoric acid dual-catalytic system, affording diverse chiral CF₃-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 enantiospecific 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 CF₃-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:

\[
\text{NHR} \quad \text{(simple alkene functionalization and 1.5-H shift)} \quad \text{complex} \quad \text{B) This work} \\
\text{A)} \quad \text{Formation of N,O-aminals} \quad \text{Friedel-Crafts alkylation}
\]

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 Cul 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. Cul 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 CF₃ 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 CF₃ 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 indoles 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.

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 (R²) 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)benzamides 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—CF₃ 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/Bromsted 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

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**Table 1. Optimization of the condition.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu</td>
<td>EtOAc</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>CuCN</td>
<td>EtOAc</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>CuSCN</td>
<td>EtOAc</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Cu(CH₃CN)₄BF₄</td>
<td>EtOAc</td>
<td>_–*</td>
</tr>
<tr>
<td>5</td>
<td>CuTC</td>
<td>EtOAc</td>
<td>_–*</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>DCM</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>Cu</td>
<td>DCE</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>Cu</td>
<td>1,4-dioxane</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>Cu</td>
<td>CH₂CN</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>Cu</td>
<td>THF</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>Cu</td>
<td>Toluene</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>Cu</td>
<td>DCM</td>
<td>51</td>
</tr>
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<td>14</td>
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<td>Cu</td>
<td>DCM</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>_–*</td>
<td>DCM</td>
<td>_–*</td>
</tr>
</tbody>
</table>

* 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.
* Yield based on [19F] NMR analysis of the crude product.
* Product was not detected.
* Togni’s reagent 3b was used.
* Umemoto’s reagent 3c was used.
* 1.7 equiv of 2a was used.
* 2.2 equiv of 2a was used.
* No Cu catalyst. CuTC = copper(1)-thiophene-2-carboxylate.
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 CF₃ 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-allylbenzyl)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 CF₃-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 (R²) 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-CF₃ adduct was formed in 41% yield for the reaction in the presence of TEMPO. Together with previous studies on radical trifluoromethylation of alkenes, the results reveal that the CF₃ 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 CF₃ radical is generated from the reaction of Togni reagent 3a with copper(I) and the chiral phosphoric acid (CPA). Subsequently, addition of CF₃ radical to alkenes 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-aryl 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.
3. Conclusions

In conclusion, we have successfully developed an enantioselective tandem process to realize concomitant formation of two new C–CF₃ and C–C bonds by remote functionalization of C(sp³)-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/Bronsted acid cooperative system.

4. Experimental

4.1. Synthetic procedures and spectral data for indoles

N-(2-allyl)benzylbenzamide (1) were synthesized according to the procedures [4], 1-benzyl-1H-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 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 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 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-piperidinoloxyl (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. PhCF₃ (internal standard, 0.05 mmol, 1.0 equiv) was added to
the reaction mixture. Yield was based on $^{19}F$ 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.

References


