# <u>LETTERS</u>

## Amide Groups Switch Selectivity: C–H Trifluoromethylation of $\alpha,\beta$ -Unsaturated Amides and Subsequent Asymmetric Transformation

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**(5)** Supporting Information

**ABSTRACT:** The first direct C–H  $\beta$ -trifluoromethylation of unsubstituted or  $\alpha$ -alkyl-substituted  $\alpha_{,\beta}$ -unsaturated carbonyl compounds under metal-free conditions was realized with excellent regio- and stereoselectivity as well as a very broad substrate scope. Both olefinic and allylic trifluoromethylation products are accessible with high selectivities by altering the



substrate substitutions. The resultant olefinic products, namely (E)- $\beta$ -trifluoromethyl (CF<sub>3</sub>)  $\alpha$ , $\beta$ -unsaturated hydroxamic acid derivatives, served as acceptors in organocatalytic asymmetric Michael addition reactions to give hydroxamic acid derivatives bearing a chiral CF<sub>3</sub>-substituted stereocenter with high enantioselectivities.

ydroxamic acid derivatives with functional substituents are structural motifs found in a number of interesting pharmaceuticals and biologically active molecules.<sup>1</sup> The stereoselective introduction of trifluoromethyl groups in these therapeutically important organic motifs at a specific site may give rise to significant changes in the chemical and physical properties of a potential drug candidate owing to improved solubility and lipophilicity properties.<sup>2,3</sup> However, the stereoselective synthesis of chiral trifluoromethylated hydroxamic acids has been much less explored and remains a very important and extremely challenging task for practitioners of chemical and pharmaceutical synthesis. To address this demand and as part of our continued interest in the area of trifluoromethylation<sup>4</sup> and asymmetric catalysis,<sup>5</sup> we envisaged that a two-step sequential synthetic strategy comprising the direct C–H  $\beta$ -trifluoromethylation of  $\alpha_{\beta}$ -unsaturated hydroxamic acid derivatives with a CF<sub>3</sub> source and enantioselective organocatalytic Michael addition of nucleophiles to the resulting  $\beta$ -trifluoromethylated compounds could yield the desired chiral trifluoromethylated hydroxamic acid scaffold in a stereocontrolled manner (Scheme 1).

#### Scheme 1. Our Strategy for the Synthesis of Desired Chiral Trifluoromethylated Hydroxamic Acid Scaffold



Despite the recent great advances in the direct C–H trifluoromethylation of various types of organic molecules,<sup>2,6</sup> the C–H trifluoromethylation of electron-deficient alkenes has been proven as an attractive but underexploited strategy for providing easy access to trifluoromethylated  $\alpha_{\eta}\beta$ -unsaturated carbonyls.<sup>6b,7</sup>

In this regard,  $Loh^{8a}$  and  $Besset^{8b}$  have independently developed a Cu-catalyzed or -mediated elegant C–H  $\beta$ -trifluoromethylation of  $\alpha$ -substituted acrylamides to furnish preferably the Z isomers via the possible involvement of the directing group in the formation of the C–CF<sub>3</sub> bond (Scheme 2a). In contrast, Bi et al. has successfully demonstrated Cu-

#### Scheme 2. Direct C–H Trifluoromethylation of Electron-Deficient Alkenes



catalyzed C–H  $\alpha$ -trifluoromethylation of  $\beta$ -substituted  $\alpha_{,\beta}$ unsaturated carbonyl compounds (Scheme 2b).<sup>9</sup> While these reports stand out as pioneering efforts, limitations such as the required substitution at the  $\alpha$ - or  $\beta$ -position of a double bond to efficiently control  $\alpha$ - or  $\beta$ -site selectivity and E/Z selectivity and the need for a metal catalyst or mediator have left great potential for further development. For example, the direct C–H trifluoromethylation of unsubstituted  $\alpha_{,\beta}$ -unsaturated carbonyl compounds has no report and remains an unmet challenge due to the selectivity issues including the regioselectivity ( $\alpha$ - or  $\beta$ -site) and stereoselectivity (E/Z isomers) based on the previously reported methods.<sup>8,9</sup> An additional disadvantage of the reported methods is the difficulty in controlling the reaction pattern in the

Received: October 20, 2014 Published: November 10, 2014 direct C-H  $\beta$ -trifluoromethylation of  $\alpha$ -alkyl-substituted  $\alpha$ , $\beta$ unsaturated carbonyl compounds, thereby affording both an olefinic and allylic trifluoromethylation product with low selectivity.<sup>8</sup> Therefore, the development of a promising and mechanistically distinct strategy for the direct C-H  $\beta$ trifluoromethylation of unsubstituted or  $\alpha$ -alkyl-substituted  $\alpha,\beta$ -unsaturated carbonyl compounds with high selectivity especially under metal-free conditions would be highly interesting (Scheme 2c) not only from the viewpoint of the synthetic versatility of such trifluoromethylated products<sup>10</sup> but also from the mechanistic point of view. We herein present the details of our studies. Significantly, E isomers of  $\beta$ -trifluoromethylation are accessed with high selectivities under metalfree conditions, which provide a useful alternative to the known transition metal catalyzed methods.<sup>8,9</sup> Furthermore, the judicious choice of the amide groups of  $\alpha$ -alkyl substituted acrylamides can completely switch the reaction pattern from an olefinic to allylic trifluoromethylation product with high efficiency (Scheme 2c).

Our investigation commenced with the reaction between 1a and Togni's reagent<sup>11</sup> 2 in the presence of catalytic or substoichiometric amounts of different copper salts Cul, CuBr, or CuCl with various organic solvents, based on recent reports on the direct C-H  $\beta$ -trifluoromethylation of  $\alpha_{,\beta}$ -unsaturated carbonyls.<sup>8,9</sup> Not surprisingly, all of the reactions gave a complex result under these conditions, presumably due to low reactivity and the difficulty in controlling both regioselectivity and E/Zselectivity (Table S1, entries 1 and 2). Inspired by recent work concerning the direct trifluoromethylation reactions with  $nBu_4NI$  as an initiator,<sup>12</sup> we chose  $nBu_4NI$  (10 mol %) as the catalyst in the presence of NaHCO<sub>3</sub> (2 equiv) in CH<sub>3</sub>CN to activate this reaction, and we found that the expected  $\beta$ trifluoromethylation E isomer could be obtained in 14% yield with high selectivity (Table S1, entry 3). Encouraged by this result, we then screened different amounts of nBu<sub>4</sub>NI as an initiator revealing 1.5 equiv of *n*Bu<sub>4</sub>NI as being optimal to give 3a in 71% yield (Table S1, entry 8). Among the different organic solvents examined, CH<sub>3</sub>CN gave the best results (Table S1, entries 8-11). We then investigated the effect of different additives and found that the yield of the reaction marginally improved to 83% with high regioselectivity and up to almost complete stereoselectivity with the use of NaOAc (2 equiv) as the base (Table S1, entry 12).

With the optimized reaction conditions in hand, various unsubstituted  $\alpha_{\beta}$ -unsaturated hydroxamic acid derivatives 1b-1h were reacted with 2 to examine the generality of this protocol (Scheme 3). By switching the cyclopentyl substituent bound to the N atom ( $\mathbb{R}^1$  group in the substrate) to the cyclohexyl (1b), linear aliphatic (1c-1e), branched aliphatic (1f and 1g), and phenethyl (1h) group, the reaction also proceeded smoothly to give the corresponding desired products 3b-3h in good yields in excellent regio- and stereoselectivity. To further investigate the scope of application, we tested the use of more challenging  $\alpha$ methyl  $\alpha_{\beta}$ -unsaturated hydroxamic acid derivatives as substrates, since the mixtures of Z-selective-olefinic and allylic trifluoromethylation products were observed in previous Cucatalyzed  $\beta$ -trifluoromethylations of  $\alpha$ -alkyl acrylamides.<sup>8</sup> We are delighted to find that, under the standard conditions, various  $\alpha$ methyl  $\alpha$ , $\beta$ -unsaturated hydroxamic acids with different aliphatic substituents on the N atom could be exclusively transformed into the corresponding olefinic  $\beta$ -trifluoromethylation 3i-3l as a single thermodynamical *E* isomer in good yields.

Encouraged by the aforementioned C–H  $\beta$ -trifluoromethylation reaction of  $\alpha_{,\beta}$ -unsaturated hydroxamic acid derivatives, we





<sup>*a*</sup>Conditions: 1 (0.2 mmol), 2 (0.4 mmol),  $nBu_4Nl$  (0.3 mmol), NaOAc (0.4 mmol), MeCN (3 mL). <sup>*b*</sup> NaHCO<sub>3</sub> was used as the base.

next turned our attention to expand the substrate scope to acrylamides (Scheme 4). Under the standard conditions, the





expected E-isomer 3m was obtained in 57% yield with high selectivity when unsubstituted N,N-diisopropylacrylamide 1m was used as the substrate. In addition, reactions of 2 with different types of acrylamides were also carried out. The  $\alpha$ - or  $\beta$ substituted acrylamides, including those having a methyl group at the  $\alpha$ - or  $\beta$  position, gave the corresponding products **3n** and **3o** in 70% and 53% yields, respectively. This contrasts with the formation of similar  $\beta$ -trifluoromethylation products in relatively lower yields (especially in 19% yield for  $\alpha$ -alkyl derivative) in the presence of 1.1 equiv of CuI with excess amounts of TFA (trifluoroacetic acid) and N-methylforamide as the additives at 120 °C.<sup>8b</sup> It should be noted that this process has also been applied to the use of substituted  $\alpha$ ,  $\beta$ -unsaturated imides as a viable substrate. For example, different types of unsubstituted,  $\alpha$ or  $\beta$ -substituted imides including pyrrolidinone (1p, 1q, and 1t), oxazolidinone (1r), and acyclic imide (1s) were well-tolerated, giving the corresponding products 3p-3t as single geometrical isomers in moderate to good yields. It is encouraging to note that the present process is a rather general reaction that can be extended to a wide range of synthetically important functional groups. The structure of 3r was determined by X-ray

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crystallographic analysis, and the configuration of other products was determined in reference to **3r**.

It is interesting to note that the current protocol could be extended to sterically bulky acrylamides as a viable substrate with a complete switch of the reaction pattern while under the reaction conditions identical to those of  $C-H \beta$ -trifluoromethylation detailed above (Scheme 5). Thus, the reaction of **2** with **1u** 

#### Scheme 5. Allylic Trifluoromethylation



or **1v** in the presence of  $nBu_4NI$  (1.5 equiv) under the standard conditions proceeded selectively and afforded only the allylic trifluoromethylation products **3u** and **3v** in 85% and 87% yields, respectively (Scheme 5). Most importantly, the product yields did not have a significant influence when the amount of  $nBu_4NI$  was reduced from 1.5 to 0.3 equiv. Furthermore, changing the substituent of the double bond in **1w** from a methyl to butyl group gave **3w** in 68% yield. These results indicate that substituents on acrylamide can switch the reaction pattern and that a more bulky amide group makes the allylic trifluoromethylation more favorable due to their extremely sterically and electronically distinct inherent properties as compared to general amide groups as shown in Scheme 4.

Based on the above experimental results and the mechanistic investigation on aryltrifluoromethylation of activated alkenes with  $nBu_4NI$  as the initiator previously reported by Nevado et al.,<sup>12a</sup> a plausible mechanism for our methodology is depicted in Scheme 6, which involves the generation of the highly

#### Scheme 6. Proposed Mechanism



electrophilic species **A** from the reaction of  $nBu_4NI$  with Togni's reagent **2**, followed by addition of activated alkene **1** and elimination to give intermediate **B**, with subsequent deprotonation of the resulting carbocation **B**, which leads to the desired product **3**. However, an alternative mechanism involving the CF<sub>3</sub> radical intermediate cannot be ruled out at the present stage.<sup>12b</sup> The high stereoselectivity of this olefinic trifluoromethylation may arise from the steric interaction between the CF<sub>3</sub> and amide group, in which the CF<sub>3</sub> substituent is directed away from the amide group to give the single thermodynamical *E* isomer.

To further demonstrate the synthetic utility of the methodology and considering the fact that chiral trifluoromethyl hydroxamic acid derivatives are pharmaceutically important,<sup>2</sup> we explored the organocatalytic asymmetric Michael additions<sup>13</sup> of nitromethane to (E)- $\beta$ -trifluoromethyl  $\alpha_{,\beta}$ -unsaturated hydroxamic acid derivatives in the presence of a bifunctional organocatalyst, although no example of such a scenario has been reported to date presumably due to their inherent low electrophilicity. Inspired by the recent reports<sup>14,15</sup> that a pyrrolidinone, oxazolidinone, or pyrazole moiety of  $\alpha_{\beta}$ unsaturated imides is demonstrated in the thiourea-catalyzed Michael reaction via multiple H-bonding interactions, we envisioned that hydroxamic acid derivatives might have a similar interaction with such a catalyst for suitable reactivity and stereoinduction. After optimization of the reaction conditions with several bifunctional organocatalysts, the reaction proceeded smoothly with cinchona-alkaloid-thiourea  $(I)^{16}$  and provided the corresponding products 4a-4e in good yields with excellent enantioselectivity albeit with long reaction times (5 days) (Scheme 7). The absolute configuration of the products 4a-4e

### Scheme 7. Enantioselectivie Michael Addition of Nucleophiles to Trifluoromethylatated Acrylamides<sup>a</sup>



<sup>*a*</sup>Reaction conditions: **3** (0.1 mmol),  $CH_3NO_2$  (0.5 mmol), malononitrile (0.3 mmol), toluene (0.2 mL). <sup>*b*</sup> Microwave (MV) assisted at 40 °C for 12 h. <sup>*c*</sup> MV assisted at 100 °C for 1 h. <sup>*d*</sup> 10 mol % of catalyst at 0 °C for 2 d.

was determined to be *R* by chiroptical methods and X-ray crystallographic analysis (Figures S1 and S2, Supporting Information). To shorten the reaction times, we subjected the organocatalytic reaction to microwave irradiation.<sup>18</sup> For product **4a**, the chemical yield can be increased to 78% without significant loss of the enantioselectivity within only 12 h. In contrast, the disappointing results for product **4c** suggested that the temperature and the substrate might have a significant influence on the optical purity. Furthermore, the reaction of an (*E*)- $\beta$ -trifluoromethyl  $\alpha_{,\beta}$ -unsaturated pyrrolidinone with nitrome-thane or malononitrile with I or Takemoto's catalyst<sup>19</sup> (II) gave the desired product **4f** or **4g** in excellent yields with good enantioselectivity.<sup>17</sup> This is interestingly in contrast with the moderate enantioselectivity in the asymmetric reaction with an (*E*)- $\beta$ -trifluoromethyl  $\alpha_{,\beta}$ -unsaturated oxazolidinone.<sup>15b</sup>

In summary, we have successfully developed the first direct C– H  $\beta$ -trifluoromethylation of unsubstituted or  $\alpha$ -alkyl-substituted  $\alpha,\beta$ -unsaturated carbonyl compounds with excellent regio- and stereoselectivity as well as a very broad substrate scope under metal-free conditions. Interestingly, both olefinic and allylic trifluoromethylation products are accessed with high selectivities by altering the amide groups of  $\alpha$ -alkyl substituted acrylamides. Moreover, it is the first example involving (*E*)- $\beta$ -trifluoromethyl  $\alpha,\beta$ -unsaturated hydroxamic acid derivatives as acceptors in organocatalytic asymmetric Michael addition reactions. Mechanistic studies and further synthetic applications of this reaction are under investigation in our laboratory.

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ASSOCIATED CONTENT

#### **S** Supporting Information

Experimental procedures, characterization of all new compounds, Table S1, Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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