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Copper(I)-Catalyzed Enantioselective Intramolecular Aminotrifluoromethylation of *O*-Homoallyl Benzimidates

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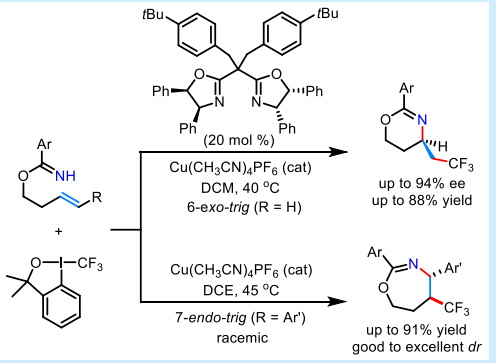
Supporting Information

ABSTRACT: In the present paper, the Cu(I)-catalyzed intramolecular aminotrifluoromethylation of *O*-homoallyl benzimidates with Togni reagent **I** was reported. *O*-Homoallyl benzimidates equipped with terminal alkenes produced chiral 1,3-oxazines with high enantioselectivity in the presence of a chiral BOX ligand, and racemic tetrahydro-1,3-oxazepines were obtained in high yields from internal alkene derivatives with a monoprotected amino acid additive under similar conditions.



The direct functionalization of alkenes is an efficient route to synthesize complex organic architectures with valuable functional groups.[1] In this regard, trifluoromethylation of alkenes has attracted considerable attention due to the unique physical and biological properties of molecules carrying a trifluoromethyl group (CF_3).[2−7] In particular, the trifluoromethylative intramolecular difunctionalization of alkenes provides a streamlined synthesis of CF_3-carrying heterocycles, which are widely used in pharmaceutical, agrichemical, and materials science research.[8] Since the pioneer works of Buchwald,[9a,10a] Sodeoka,[11a] and Liu,[11b] a broad range of unactivated alkenes equipped with pendant nucleophilic groups, such as carboxylic acid, amine, urea, amide, and oxime, have been transformed into CF_3-containing heterocycles in racemic or enantioselective fashion (Scheme 1A).[9−12] However, despite these achievements, the enantioselective trifluoromethylation of alkenol substrates remains challenging due to the weak affinity of hydroxyl group to transition metals. In 2017, Liu et al.[13] first reported the enantioselective intramolecular oxytrifluoromethylation of geminal-substituted alkenol derivatives using a chiral phosphoric acid ligand (Scheme 1B). We have been interested in functionalization of aliphatic alcohols via a radical relay strategy[14] and found that the imidate group can serve as directing group as well as amine source to yield oxazolines with high yield and regioselectivity.[14a] Therefore, it can be speculated that this strategy is also amenable for the functionalization of alkenol substrates. In the present work, the Cu(I)-catalyzed intramolecular aminotrifluoromethylation of *O*-homoallyl benzimidate derivatives[15] with Togni reagent **I** (serving as the CF_3 source) is reported.[16] In the presence of a chiral BOX ligand,[17] CF_3-containing chiral 1,3-oxazines were obtained with high enantioselectivity from terminal alkene derivatives in a *6-exo-trig* fashion, and CF_3-carrying racemic tetrahydro-1,3-oxazepines were derived from 1-aryl *O*-homoallyl-benzimidates with the *N*-Ac-Trp-OH additive followed by the *7-endo-trig* pathway under similar reaction conditions (Scheme 1C).

We commenced our study with functionalization of *O*-homoallyl benzimidate **1** using Togni reagent **I** as CF_3 source and $Cu(CH_3CN)_4PF_6$ as catalyst in DCE (dichloroethane) at 45 °C (initial conditions, Table 1). The reaction without any ligand or additive gave trace amounts of 1,3-oxazine **2**, and most of the starting material was recovered (Table 1, entry 1). The addition of chiral phosphoric acid ligands (**L1**, **L2**) or monoprotected amino acid (**L4**) accelerated the reaction, but all gave racemic product. It was observed that addition of chiral BOX ligand **L5** produced **2** with moderate yield and enantiometric excess (ee). Moreover, an increase in the steric hindrance of the C4 substituent caused a diminishing trend in enantioselectivity (**L5**−**L8**). The diphenyl-substituted BOX ligand **L10** generated **2** with improved yield and ee. An increase in the steric hindrance of the substituent at the bridge carbon of BOX manifested improvements in both yield and ee, and 4-*t*Bu-benzyl-substituted **L12** was optimal, giving **2** in 64% yield and 73% ee (see the SI for more screening conditions and synthesis of chiral BOX ligands). The following inferences were made from examination of other reaction parameters: (1) Replacement of DCE with DCM and a decrease in reaction temperature to 40 °C gave better results (entries 5 and 6). (2) Addition of *o*-(3′,5′-di-*tert*-butylphenyl)benzoic acid (3′,5′-*t*Bu-*o*PBA) was beneficial for both conversion and enantiose-

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Scheme 1. Copper-Catalyzed Trifluoromethylative Intramolecular Difunctionalization of Alkene

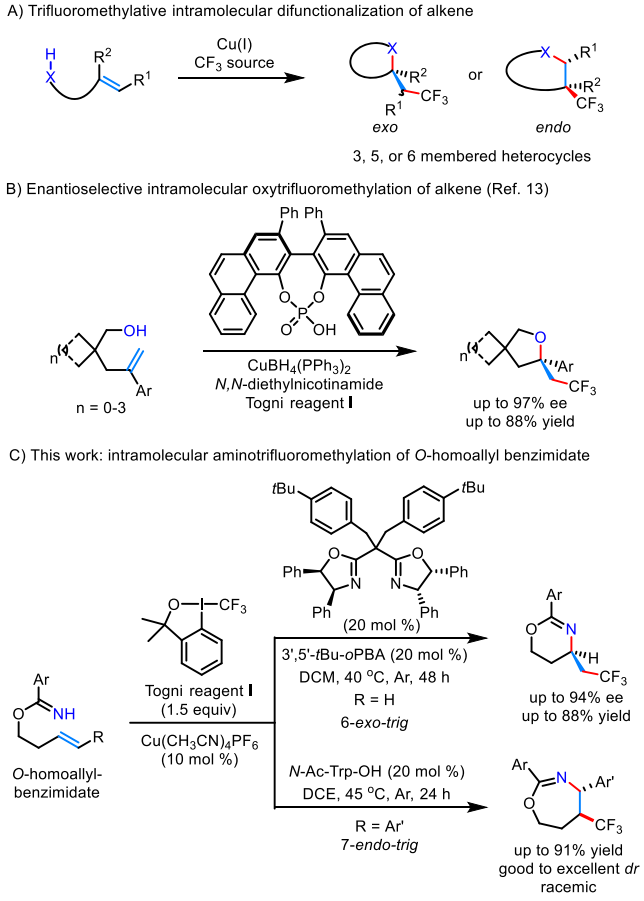
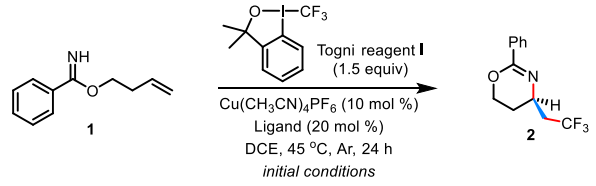
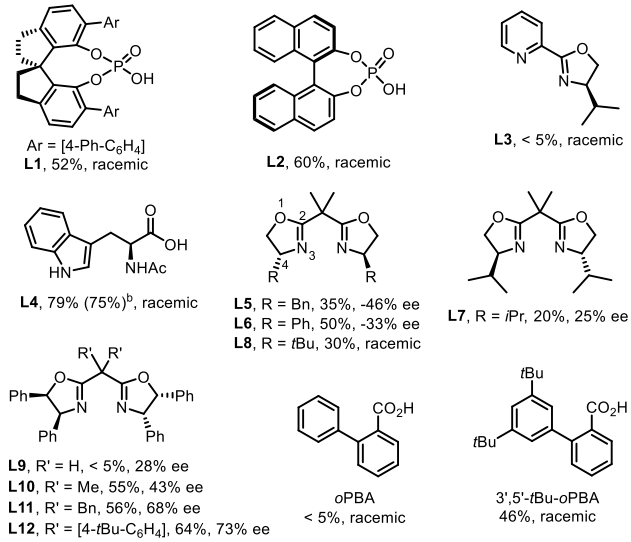


Table 1. Enantioselective Intramolecular Aminotrifluoromethylation of 1 with Togni Reagent I



entry	change from initial conditions	yield of **2**[a] (%) (ee, %)
1	no ligand	<5
2	**L12**	64 (73)
3	**L12**, DCE → AcOEt	45 (57)
4	**L12**, DCE → $CHCl_3$	31 (80)
5	**L12**, DCE → DCM	75 (77)
6	**L12**, DCE → DCM, 45 → 40 °C	70 (82)
7	**L12**, DCE → DCM, 45 → 35 °C	54 (81)
8	**L12**, DCE → DCM, 45 → 40 °C, *o*PBA (20 mol %)	50 (69)
9	**L12**, DCE → DCM, 45 → 40 °C, 3′,5′-*t*Bu-*o*PBA (20 mol %)	84 (92)
10	**L12**, DCE → DCM, 45 → 40 °C, 3′,5′-*t*Bu-*o*PBA (20 mol %), 24 → 48 h (conditions A)	90 (92)/ 81 (92)[b]
11	Togni reagent **I** → Togni reagent **II**	30 (84)[c]

Ligands & additives (under initial conditions):



[a]Yields are based on ^{1}H NMR analysis of reaction mixture with 1,1,2,2-tetrachloroethane as internal standard on a 0.1 mmol scale. The enantioselectivity was determined by chiral HPLC analysis of the crude reaction mixture. [b]Isolated yield on a 0.1 mmol scale. [c]Change from conditions A.

lectivity and produced **2** with 92% ee (entries 9 and 10), whereas with 3′,5′-*t*Bu-*o*PBA alone formed racemic **2** in 46% yield. (3) Togni reagent **II** generated moderate ee with low conversion under optimal conditions (entry 11).

With the optimized conditions in hand, we explored the substrate scope of the Cu-catalyzed enantioselective intramolecular aminotrifluoromethylation reaction. As shown in Scheme 2, *O*-homoallyl benzimidates with electron-donating or electron-withdrawing groups on the phenyl ring proceeded well under conditions A, giving CF_3-containing 2-aryl-1,3-oxazines in good yields and ee (**3**−**11**). Halogen atoms were well tolerated and provided a versatile path for further transformation. Substrate with a *gem*-dimethyl substituent generated the desired product with high ee and low conversion (**12**). 2-Aryl-substituted alkene substrate failed to produce satisfying results, and a trace amount **13** was obtained with 27% ee. However, racemic **13** was obtained in 63% yield under conditions B with 20 mol % of of *N*-Ac-Trp-OH as additive.[18] The trichloroacetimidate analogue of **1** was not compatible with this enantioselective intramolecular aminotrifluoromethylation reaction, leaving most of starting material unconsumed.

The reaction of benzimidate substrates equipped with 1,2-disubstituted alkene were investigated under conditions A. Interestingly, with 1-aryl-substituted *O*-homoallyl benzimidates, 7-membered tetrahydro-1,3-oxazepines were obtained in low yield without any enantioselectivity (Scheme 3, **15** and **16**). Tetrahydro-1,3-oxazepines are widely used in medicinal chemistry and material science; however, very few methods have been developed for their synthesis.[19] It was disappointing that no improvement in enantioselectivity was observed under the conditions evaluated (see the SI for detailed information). However, racemic 2-aryltetrahydro-1,3-oxazepines were obtained with improved yields and moderate to excellent diastereoselectivity under conditions B (**15**−**17**). It is worth noting that both substrates equipped with *E* and *Z* alkenes gave the cyclized product **16** with identical stereochemistry.[20] 1,1-Diaryl-substituted substrates resulted in relatively higher yields (**18**, **19**), whereas 1,1-dialkyl-substituted substrate only furnished 35% yield (**20**).

Some control reactions were carried out to probe the mechanism. As shown in Scheme 4A, when a radical scavenger (TEMPO or BHT) was added into the reaction of **1** under conditions A or B, the reaction was dramatically inhibited, and

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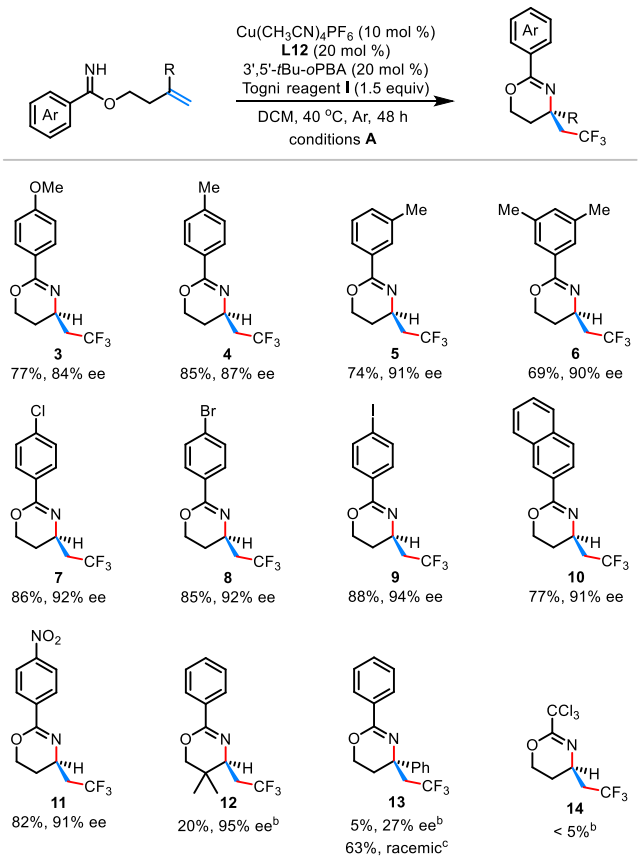
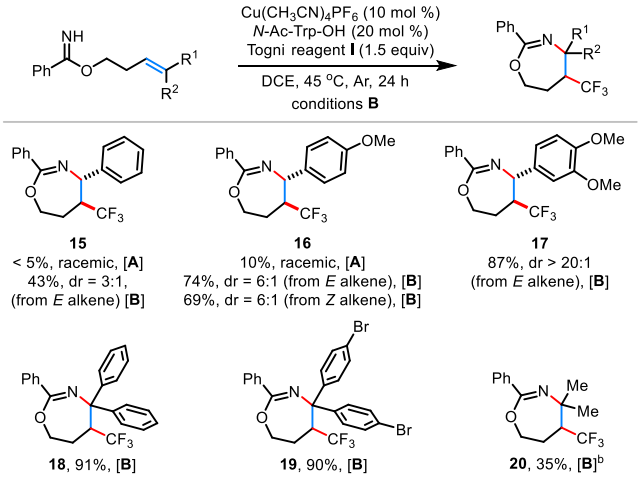
Scheme 2. Substrate Scope of the Cu-Catalyzed Enantioselective Intramolecular Aminotrifluoromethylation Reaction[a]



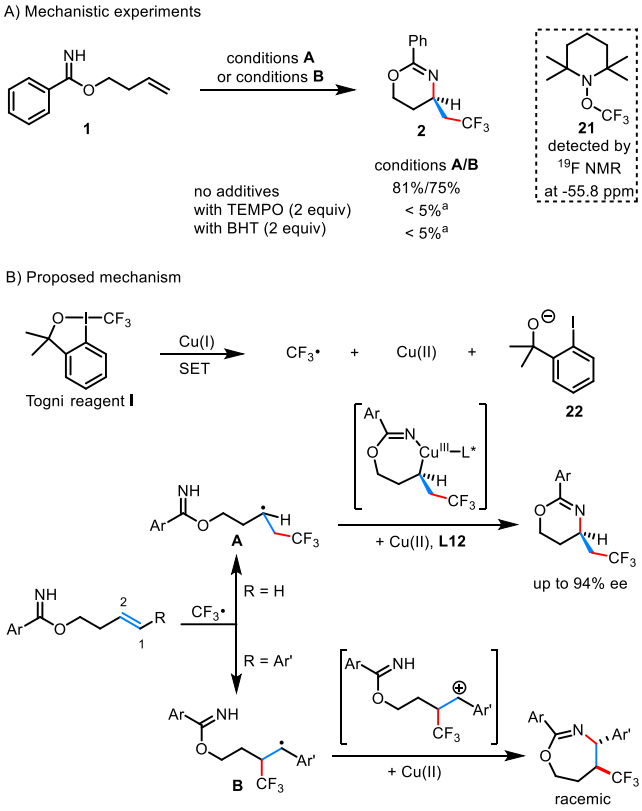
[a]All yields are based on isolated product on a 0.1 mmol scale. The enantioselectivity was determined by chiral HPLC analysis. [b]Most starting material was unconsumed; only a small amount of hydrolyzed byproduct was detected. [c]Conditions B: $Cu(CH_3CN)_4PF_6$ (10 mol %), Togni reagent **I** (1.5 equiv), *N*-Ac-Trp-OH (20 mol %), in DCE at 45 °C, 24 h.

Scheme 3. Synthesis of CF_3 Carrying Tetrahydro-1,3-oxazepine.[a]



[a]All yields are based on isolated product on a 0.1 mmol scale. [b]About 60% of starting material was unconsumed; only a trace amount of hydrolyzed byproduct was detected.

Scheme 4. Mechainsm Study



[a]Yields are based on ^{1}H NMR analysis of reaction mixture with 1,1,2,2-tetrachloroethane as internal standard on a 0.1 mmol scale. Most of **1** was unconsumed. [b]TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; BHT, 2,6-di-*tert*-butyl-4-methylphenol.

the corresponding trifluoromethyl-captured product **21** was detected as the major product (based on the ^{19}F NMR analysis; see the SI for detailed information). Therefore, these results indicated the radical nature of the intramolecular amino trifluoromethylation reaction.

Based on the results of the present study and previous reports,[9a,c,10a,11c] a possible mechanism for the Cu-catalyzed enantioselective intramolecular aminotrifluoromethylation reaction is proposed in Scheme 4B. Togni reagent **I** first reacts with Cu(I) through single-electron transfer (SET) followed by the homolytic cleavage of the I-CF_3 bond, generating $CF_3^\bullet$ radical species and Cu(II) along with an anion species **22**, which serves as base in the following transformation. There might be two possible pathways for the addition of trifluoromethyl radical with alkene: with terminal alkene (R = H), $CF_3^\bullet$ added at the terminal position and generated a secondary carbon centered radical **A**. Radical **A** was then captured by **L12**-ligated Cu(II) in a enantioselective fashion to form a Cu(III) intermediate. Reductive elimination of the Cu(III) intermediate produced chiral 1,3-oxazines with high ee and regenerated the Cu(I) catalyst. With 1-aryl-substituted *O*-homoallyl benzimidates, $CF_3^\bullet$ preferentially attacks the C2 position and generated a stabilized benzylic radical B. Radical B was oxidized by Cu(II) to a secondary carbocation intermediate and regenerated Cu(I) catalyst. Finally, the carbocation intermediate was intramolecularly attacked by the benzimidate motif to produce racemic tetrahydro-1,3-oxazepines.

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In summary, the Cu(I)-catalyzed intramolecular amino trifluoromethylation of *O*-homoallyl-benzimidate with Tongi reagent **I** (serving as the CF_3 source) is presented.[21] The newly developed procedure represents an efficient route to synthesize CF_3-containing heterocycles from readily available homoallylic alcohols and aryl nitriles. For monosubstituted terminal alkene substrates, enantioenriched 2-aryl-1,3-oxazines with high ee were obtained in the presence of a chiral BOX ligand, whereas for 1-aryl-substituted internal alkene substrates, racemic 2-aryltetrahydro-1,3-oxazepines with high yield and good to excellent diastereoselectivity were formed in the presence of the *N*-Ac-Trp-OH additive.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01552.

Additional experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Most *O*-homoallylbenzimidates we tested can give racemic 2-aryl-1,3-oxazine products in good yields under conditions B; e. g., both **4** and **8** were isolated in 81% yield.
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(20) No *E*/*Z* isomerization of the starting material recovered from partial conversion reaction under the conditions B was observed.
(21) Other types of alkenol imidates are not compatible with the current reaction conditions. *O*-Homoallyl acetimidate and benzimidate made from 4-penten-1-ol failed to give any detectable product, leaving most of the starting material unconsumed. *O*-Allyl benzimidates are prone to undergo Overman rearrangement under the standard conditions; thus, no intramolecular aminotrifluoromethylation product was obtained.

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