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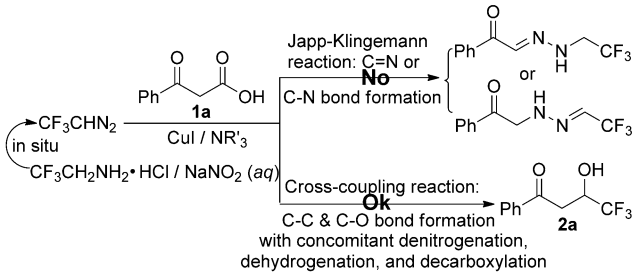
Synthetic Methods

Copper-Catalyzed One-Pot Denitrogenative–Dehydrogenative–Decarboxylative Coupling of β-Ketoacids with Trifluorodiazoethane: Facile Access to Trifluoromethylated Aldol Products

Heng-Ying Xiong, Zhen-Yan Yang, Zhen Chen, Jun-Liang Zeng, Jing Nie, and Jun-An Ma*[a]

Abstract: A novel copper-catalyzed one-pot cross-coupling of β-ketoacids with in situ generated trifluorodiazoethane has been developed. This reaction provides a direct and efficient method, in which one C–C bond and one C–O bond were formed in a carbenoid center with concomitant denitrogenation–dehydrogenation–decarboxylation, to afford trifluoromethylated aldol products. In several preliminary experiments, good to high enantioselectivities were also obtained.



Scheme 1. Observations from the reaction of β-ketoacid 1a with 2,2,2-trifluorodiazoethane.

The incorporation of fluorinated moieties into organic molecules has become an important requirement for pharmaceutical, agrochemical, and material synthesis.[1] One of the most common and attractive approaches is to exploit readily accessible fluorinated building blocks in a multi-step process towards more complex small molecules. A particularly useful example is 2,2,2-trifluorodiazoethane, CF_3CHN_2, a valuable reagent available to the organic chemists.[2] The development of new synthetic methods that use this fluorinated C2-synthon has been the subject of recent research.[3] As a continuation of our interest in this area,[4] we hoped to explore the Japp–Klingemann reaction[5,6] between β-ketoacids and trifluorodiazoethane. It was expected that an alkylhydrazone product would be obtained from the initial decarboxylative condensation of β-ketoacid **1a** with trifluorodiazoethane. To our surprise, the unexpected aldol product **2a** was obtained from the reaction of β-ketoacid **1a** with trifluorodiazoethane and no related Japp–Klingemann products were observed (Scheme 1). Herein we report this new one-pot transformation involving denitrogenative–dehydrogenative–decarboxylative coupling of β-ketoacids and trifluorodiazoethane. The notable features of this reaction are its operational simplicity, inexpensive catalyst, easily accessible starting materials, and mild reaction conditions. Additionally, a highly enantioselective catalytic cross coupling that constructs one C–C and one C–O bond in a carbenoid center with exceptional enantioselectivities was accomplished.

We began our studies by evaluating the reaction of 3-oxo-3-phenylpropanoic acid **1a** with the stock solution of CF_3CHN_2 in dichloromethane using triethylamine as the base at room temperature. No product was obtained after 24 h and a significant amount of acetophenone, generated through decarboxylative protonation of **1a**, was recovered. The lack of reactivity may be explained by the weak electrophilic ability of CF_3CHN_2. Therefore, we turned our attention to the use of various Lewis acid catalysts. With CuI as the catalyst, the unexpected aldol product **2a** was obtained in 10% yield. The structure of **2a** was further confirmed by means of X-ray crystallographic analysis (see the Supporting Information).[7] To improve the reaction yield, it was envisioned that water might be favorable toward bringing about carbenoid center hydroxylation. On the basis of previous elegant reports by the Carreira group,[3d–i] we evaluated the in situ generation of CF_3CHN_2 from the corresponding amine with $NaNO_2$ in aqueous media. The results are summarized in Table 1. To our delight, the yield of **2a** could be increased to 35% (entry 1). The use of other copper complexes resulted in a slight lower yield (entries 2–5). The solvent was found to have an important effect on the reactivity (entries 6–11). Among the solvents tested, the mixed solvent system was found to be the best choice for this cross-coupling reaction (entry 10). Evaluation of other organic bases led to finding that 8-diazabicyclo[5.4.0]undec-7-ene (DBU) was the most promising additive for the model reaction (entries 12–14). A lower

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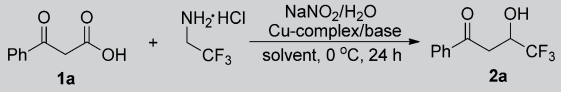
Table 1. Screening optimal reaction condition.[a]



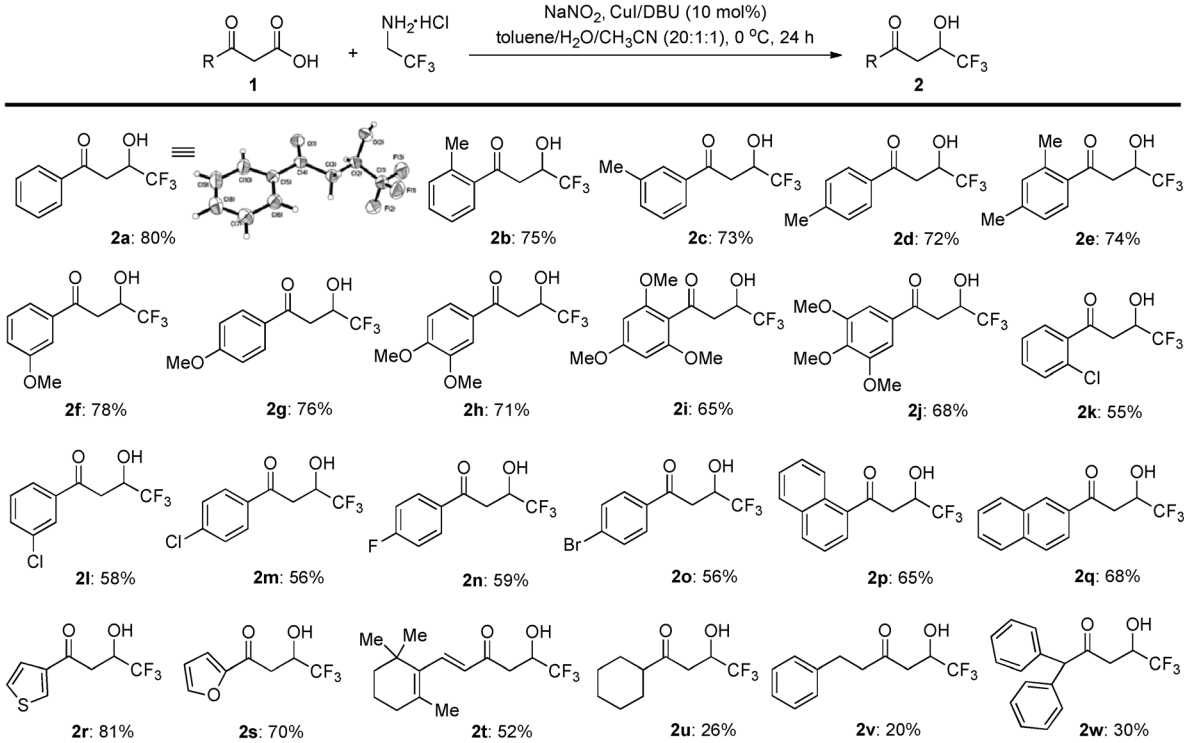
	CuX_n/base [mol%]	Solvent	Yield [%][b]
1	CuI/Et_3N (10)	CH_2Cl_2/H_2O (20:1)	35
2	CuBr/Et_3N (10)	CH_2Cl_2/H_2O (20:1)	23
3	CuCl/Et_3N (10)	CH_2Cl_2/H_2O (20:1)	26
4	CuOTf/Et_3N (10)	CH_2Cl_2/H_2O (20:1)	30
5	$Cu(OTf)_2/Et_3N$ (10)	CH_2Cl_2/H_2O (20:1)	26
6	CuI/Et_3N (10)	THF, Et_2O, CH_3CN, or DMF/H_2O (20:1)	0
7	CuI/Et_3N (10)	toluene/H_2O (20:1)	56
8	CuI/Et_3N (10)	toluene/THF/H_2O (20:1:1)	55
9	CuI/Et_3N (10)	toluene/CH_3CN/H_2O (10:1:1)	71
10	CuI/Et_3N (10)	toluene/CH_3CN/H_2O (20:1:1)	76
11	CuI/Et_3N (10)	toluene/CH_3CN/H_2O (30:1:1)	70
12	CuI/DMAP (10)	toluene/CH_3CN/H_2O (20:1:1)	69
13	CuI/DABCO (10)	toluene/CH_3CN/H_2O (20:1:1)	70
14	CuI/DBU (10)	toluene/CH_3CN/H_2O (20:1:1)	80
15	CuI/DBU (5)	toluene/CH_3CN/H_2O (20:1:1)	67
16[c]	CuI/DBU (10)	toluene/CH_3CN/H_2O (20:1:1)	65

[a] Reactions conducted on 0.2 mmol scale of **1a**: CuX_n (5–10 mol%), organic base (5–10 mol%), $CF_3CH_2NH_2$·HCl (4.0 equiv), $NaNO_2$ (4.0 equiv), and H_2O (0.2 mL) in solvent (4 mL) at 0 °C for 24 h. [b] Isolated yields. [c] $CF_3CH_2NH_2$·HCl (2.0 equiv). DMAP: 4-(*N*,*N*- dimethylamino)pyridine; DABCO: 1,4-diazabicyclo[2.2.2] octane.

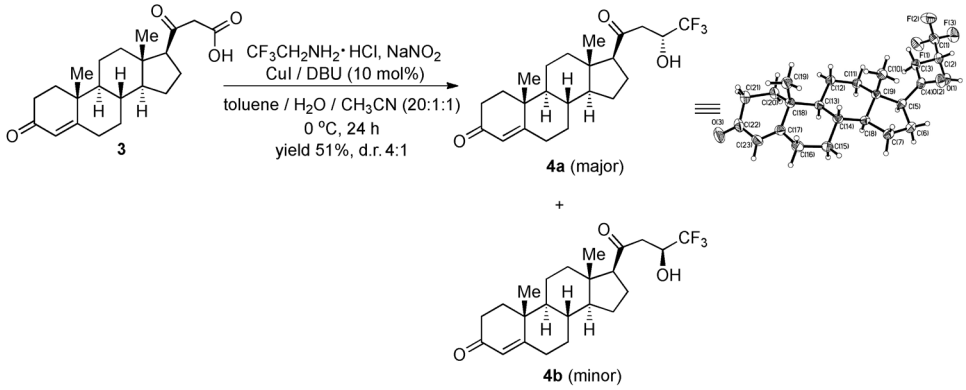
catalyst loading reduced the reaction yield (entry 15). In addition, the use of an excess of the $CF_3CH_2NH_2$·HCl reagent was essential for the high efficiency of this cross-coupling reaction. Reducing the loading of $CF_3CH_2NH_2$·HCl to two equivalents resulted in much lower yield of **2a** (entry 16).

With these interesting results in hand, we next investigated the scope of this catalytic cross coupling under the optimal reaction conditions (Table 1, entry 14) with a series of β-ketoacids. As shown in Scheme 2, the cross-coupling of the in situ generated CF_3CHN_2 with β-aryl-substituted β-ketoacids bearing electron-neutral and -donating groups at the aromatic ring furnished the corresponding products **2a–j** in good yields. When β-aryl-β-ketoacids containing electron-withdrawing substituents were used, the desired products **2k–o** were obtained in moderate yields. 1-Naphthyl-, 2-naphthyl-, 3-thiophenyl-, and 2-furanyl-substituted β-ketoacids were also found to be good substrates, delivering the aldol products **2p–s** in 65–81% yields. In addition, β-ionone based β-ketoacid was subjected to this cross-coupling reaction under the same conditions, and the corresponding product **2t** was obtained in 52% yield without any detectable quantities of the cyclopropanation byproducts despite the presence of olefin moieties in the reactant. Unfortunately, β-alkyl-substituted β-ketoacids were poor substrates under the current conditions, providing the cross-coupling products **2u–w** in lower yields. We also attempted to optimize the reactions with β-alkylketoacids by decreasing the temperature and increasing the amount of trifluoroethanamine hydrochloride, but still could not improve the product yields.

To use this copper-catalyzed, one-pot cross coupling for the modification of biologically interesting compound, we tested the reaction of progesterone-derived β-ketoacid **3** with the in situ generated CF_3CHN_2 under our standard conditions (Scheme 3). The reaction provided a 4:1 mixture of diastereo-



Scheme 2. The substrate scope of copper-catalyzed cross-coupling of β-ketoacids **1a** with the in situ generated CF_3CHN_2.

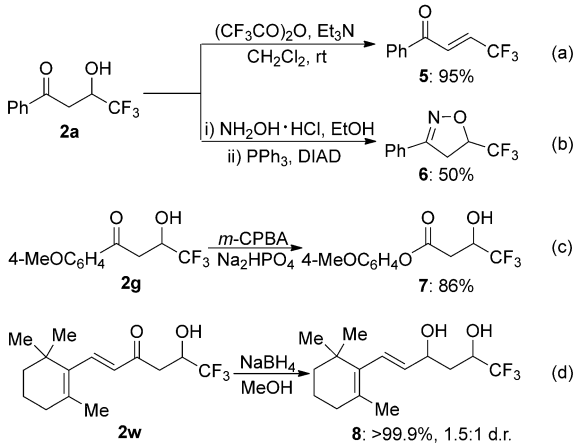


Scheme 3. Copper-catalyzed cross-coupling of progesterone-derived β-ketoacid **3** with the in situ generated CF_3CHN_2.

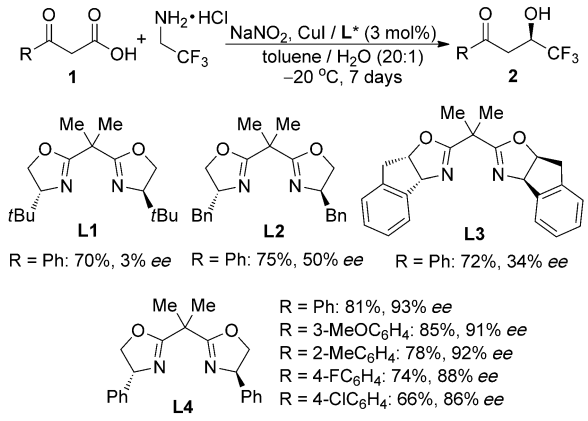
As a successive study, the enantioselective version of the described cross-coupling reaction using chiral bis(oxazoline) ligands was also disclosed (Scheme 5). The model reaction occurred in low yield (18%) when performed with 12 mol% of (*R*,*R*)-*t*Bu-bis(oxazoline) **L1**, possibly due to its secondary role as a base to promote a competing decarboxylation of β-ketoacid. Accordingly, a 1:1 ratio of CuI/**L1** (3 mol%) was used, and as expected, the yield was increased to 70%. Preliminary optimization of the other reaction conditions (including chiral ligands **L1**–**4**, solvent, temperature, and time; see the Supporting Information) led to the discovery that the best results were obtained when the reaction was performed in toluene and water at −20 °C in the presence of (*R*,*R*)-Ph-bis(oxazoline) **L4** (81% yield, 93% *ee*). Furthermore, several other cross-coupling products were also obtained in respectable yields (66–85%) with high enantioselectivities (86–93% *ee*).[8]

mers **4a** and **b** in 51% overall yield, and both diastereomers were readily separated by flash chromatography. Furthermore, the single stereoisomer of **4a** proved to be crystalline, allowing the determination of the absolute configuration of the newly formed stereogenic center by means of X-ray crystallographic analysis (see the Supporting Information).[7]

The cross-coupling products **2** are also versatile synthetic intermediates and can be readily transformed into other highly functionalized organofluorine compounds. For example, direct treatment of 4,4,4-trifluoro-3-hydroxy-1-phenylbutan-1-one **2a** with $(CF_3CO)_2O$ and Et_3N at room temperature gave rise to the corresponding trifluoromethylated enone **5** in excellent yield (Scheme 4a). Oximation of **2a** with $NH_2OH{\cdot}HCl$ in EtOH, and subsequent ring-closing afforded 5-(trifluoromethyl)-4,5-dihydroisoxazole **6** in 50% yield (Scheme 4b). The Baeyer–Villiger oxidation of **2g** using *m*-chloroperoxybenzoic acid (*m*-CPBA) and Na_2HPO_4 gave 4,4,4-trifluoro-3-hydroxybutanoate **7** in 86% yield (Scheme 4c). Also, direct reduction of **2w** with $NaBH_4$ in MeOH delivered the trifluoromethylated diol **8** in quantitative yield (Scheme 4d). These interesting results indicate that the present protocol provides a reliable and rapid approach for the construction of diverse CF_3-containing molecules.

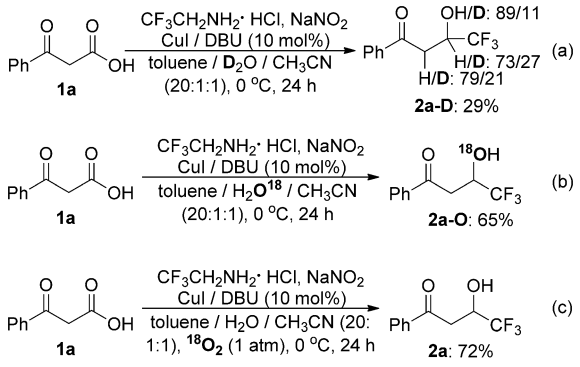


Scheme 4. Further transformation of the cross-coupling products.

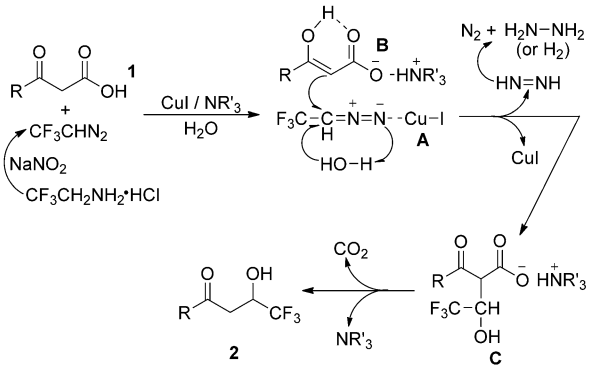


Scheme 5. Catalytic enantioselective cross-coupling reaction.

To gain some preliminary understanding of the mechanism, we performed the following isotopic labeling experiments under the standard reaction conditions. Reaction **1a** with the in situ generated 2,2,2-trifluorodiazoethane in the presence of D_2O delivered the cross-coupling product in 29% yield upon isolation (Scheme 6a). The deuterated products were detected by ^1H NMR spectroscopy as anticipated. Meanwhile, in the presence of ^{18}O-labeled water, it was found that the ^{18}O-label was also effectively incorporated into the corresponding product (Scheme 6b). Accordingly, we conducted one control experiment, and did not observe any incorporation of the ^{18}O label in the product when $^{18}O_2$ were used as an oxidant at atmospheric pressure (Scheme 6c). These experimental results showed that water can indeed transfer an oxygen atom into the cross-coupling product under copper catalysis.



Scheme 6. Isotopic labeling and control experiments.



Scheme 7. Proposed mechanism.

On the basis of the preliminary results described above and previous studies,[9] we proposed the reaction mechanism as outlined in Scheme 7. Initially, the copper complex **A** is formed by the reaction of the in situ generated trifluorodiazoethane with copper salt. Meanwhile, the amine bonds to the β-ketoacid **1** (in its enol form) through a salt bridge to give intermediate **B**. Subsequently, the intermediate **B** attacks the complex **A** and terminates with water to form the addition intermediate **C**, with the regeneration of the catalyst and the release of diazene. Diazene rapidly undergoes a disproportionation reaction to form nitrogen gas and hydrazine (or H_2).[10] The subsequent step is decarboxylation and release of the amine additive of **C**, thus giving rise to the final cross-coupling product **2**. However, the detailed mechanism of this cross-coupling reaction remains to be elucidated.

In conclusion, we have developed a novel copper-catalyzed cross coupling of β-ketoacids with in situ generated 2,2,2-trifluorodiazoethane under mild reaction conditions. During this transformation, one C–C and one C–O bond are constructed in a carbenoid center with concomitant denitrogenation, dehydrogenation, and decarboxylation. This one-pot synthetic protocol enables the efficient preparation of a variety of trifluoromethylated aldol adducts, which are versatile synthetic intermediates toward other useful building blocks. In several preliminary experiments, good to high enantioselectivities were also obtained. Application of 2,2,2-trifluorodiazoethane in cross-coupling reactions will open up a novel way to access the diversity of trifluorodiazoethane chemistry. Further investigation of the reaction mechanism, as well as full development of the enantioselective copper-catalyzed cross-coupling are ongoing in our laboratory and will be reported in due course.

Acknowledgements

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Keywords: 2,2,2-trifluorodiazoethane · decarboxylation · dehydrogenation cross-coupling reaction · enantioselectivity · β-ketoacids

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[10] Although all attempts to use phthalaldehyde for the trapping of hydrazine failed, hydrazine was not excluded as the byproduct involved in this process.

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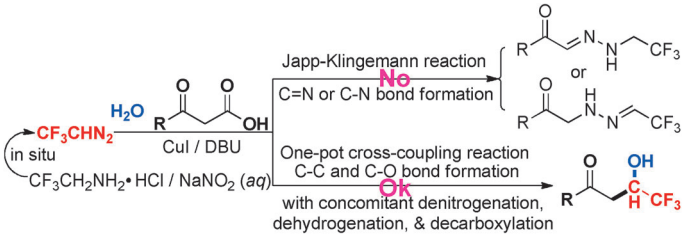

Unexpected aldol: A novel copper-catalyzed one-pot cross-coupling of β-ketoacids with in situ generated trifluorodiazoethane has been developed. This reaction provides a direct and efficient method, in which one C–C and one C–O bond were formed in a carbenoid center with concomitant denitrogenation–dehydrogenation–decarboxylation, to afford trifluoromethylated aldol products (see scheme; DBU = 1,8-diazabicycloundec-7-ene).