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A Direct Intermolecular Cross-Benzoin Type Reaction: N-Heterocyclic Carbene-Catalyzed Coupling of Aromatic Aldehydes with Trifluoromethyl Ketones

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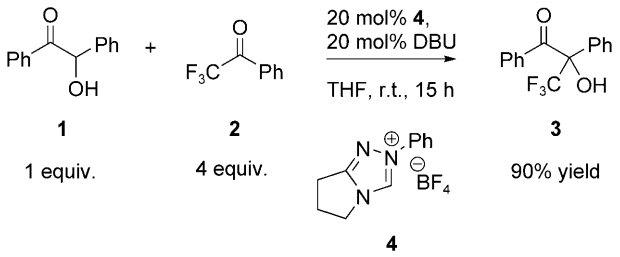
Abstract: A direct intermolecular cross-benzoin-type condensation catalyzed by an N-heterocyclic carbene has been developed. The cross-coupling of commercially available aromatic aldehydes and trifluoromethyl ketones results in α-hydroxy-α-trifluoromethyl ketones bearing a quaternary stereocenter with excellent chemoselectivity and good to excellent yields.

Keywords: cross-benzoin reaction; N-heterocyclic carbenes; organocatalysis; trifluoromethyl substitution; umpolung

In their pioneering and historic paper on the benzoyl compounds of 1832[1] Wöhler and Liebig not only started the chemistry of aromatic compounds, such as benzaldehyde, benzoic acid, benzoyl chloride and benzamide, but also reported the cyanide-catalyzed (bitter almond oil) formation of benzoin, which in a sense can be seen as the start of organocatalysis. Since these early days of organic chemistry, the cyanide- and later carbene-catalyzed coupling of two aldehyde molecules to form the corresponding α-hydroxy ketones (benzoin, acyloin) has been investigated extensively.[2]

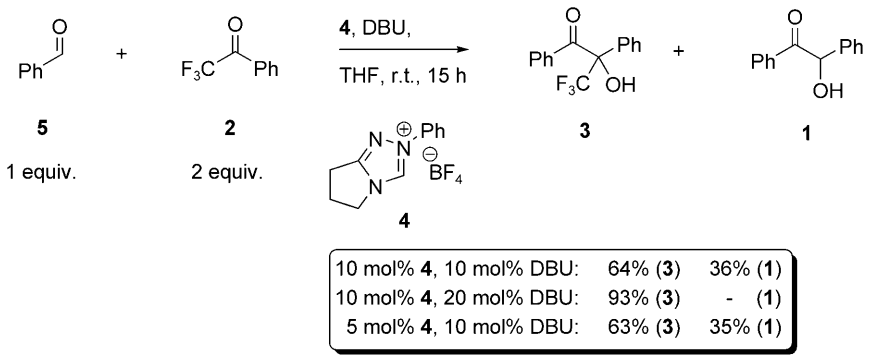
Although significant progress has been made with enantioselective and *intramolecular* versions in recent years,[3] there still are limitations in the *intermolecular* coupling of two different aldehydes and of aldehydes with ketones. In these cases the outcome is typically a mixture of all possible symmetrical and unsymmetrical acyloins, with the chemoselectivity strongly depending on the relative thermodynamic stability of the corresponding products.[4] In order to overcome this problem several research groups have made excellent contributions by developing enzymatic approaches[5] or utilizing acylsilanes[6] and acylphosphonates[7] as acyl anion equivalents in cyanide-catalyzed transformations. In addition, very recently Scheidt et al. reported intermolecular cross-acyloin reactions by fluoride-promoted addition of *O*-silylthiazolium salts.[8] However, to the best of our knowledge, there is no precedent for a direct organocatalytic *intermolecular* coupling of aldehydes with ketones, which we would like to report in this communication.

Based on our mechanistic proposal for the Stetter reaction, which relies on a reversible formation of the benzoin product prior to the Stetter product formation,[9] we envisaged to use benzoins as masked aldehyde equivalents.[10] To our delight, benzoin (**1**) in combination with an excess of trifluoroacetophenone (**2**) as reactive electrophilic ketone component led chemoselectively to the crossed acyloin product **3** in high yield, employing 20 mol% of the bicyclic triazolium salt **4**[11] as precatalyst in the presence of 20 mol% DBU in THF at room temperature (Scheme 1).



Scheme 1. Intermolecular cross-benzoin test reaction.

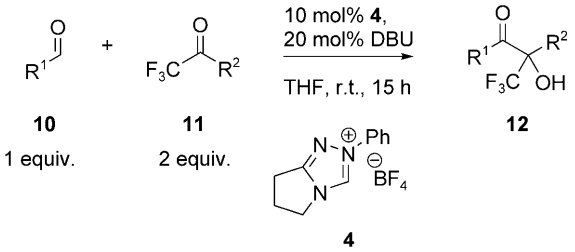
Since the crossed acyloin product **3** containing a tertiary alcohol seemed to be energetically preferred relative to benzoin (**1**) a simpler and more practical version of this concept would be to employ the aldehyde component directly in this transformation (Scheme 2). Under the reaction conditions given (10 mol% carbene precursor **4** and 10 mol% DBU), it was indeed possible to obtain the cross-coupled product **3** in 64% yield beside 36% of the homo-coupled benzoin. By simply employing an excess of DBU the formation of benzoin could be avoided and the cross-coupling improved to 93% yield which may be due to



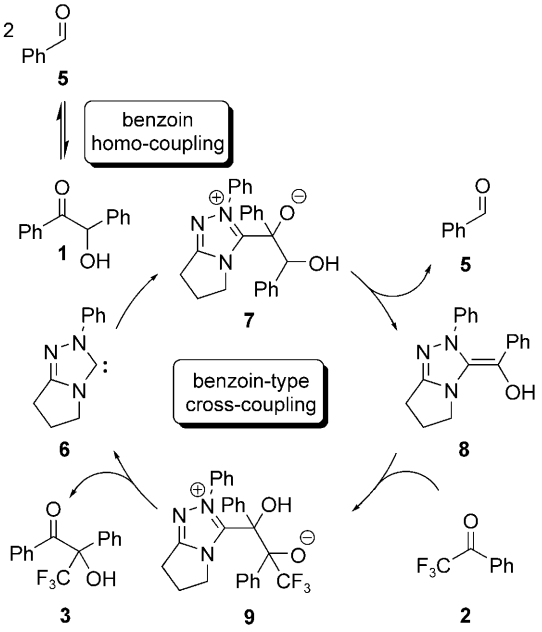
Scheme 2. NHC-catalyzed direct intermolecular cross-benzoin reaction.

the generation of more triazolylidene catalyst under these reaction conditions. Of note, a decrease of catalyst loading (5 mol%) in combination with an excess of DBU (10 mol%) resulted in a lower yield of α-hydroxy-α-trifluoromethyl ketone **3** (63%). The reversible nature of the benzoin condensation under the present reaction conditions (Scheme 1) and our previous mechanistic insights into the Stetter product formation[9] led us to the assumption that two coupled catalytic cycles are involved in this transformation (Scheme 3).

Initially, benzoin (**1**) is formed rapidly and reversibly prior to the formation of the cross-coupling product **3**. Next, initiated by a nucleophilic attack of the NHC-catalyst **6** at the carbonyl function of benzoin, the 1,2-adduct **7** is formed. This in turn eliminates benzaldehyde (**5**) to result in the formation of the Breslow intermediate **8**, which attacks trifluoroacetophenone (**2**) leading to the tetrahedral intermediate **9**. An intramolecular proton transfer and elimination of the α-hydroxy-α-trifluoromethyl ketone **3** returns the catalyst. Next we examined the substrate scope and various aromatic as well as heteroaromatic aldehydes **10** were tested for their reactivity with aromatic trifluoromethyl ketones **11** (Scheme 4). As is shown in



Scheme 4. Direct intermolecular cross-benzoin type reaction under optimized conditions.

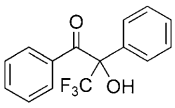
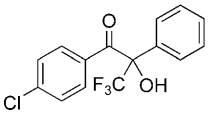
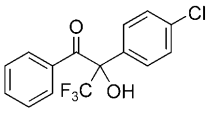
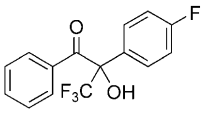
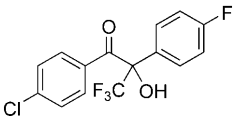
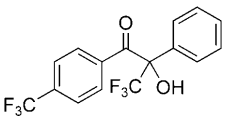
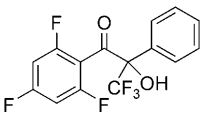
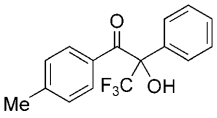
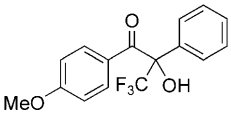
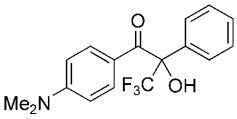
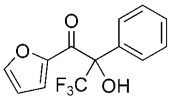
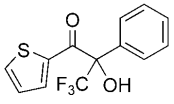


Scheme 3. Coupled catalytic cycles in the formation of the crossed benzoin-type products **3**.

Table 1, the reaction works well for all tested substrates, providing the crossed hydroxy ketones **12a–l** in good to excellent yields (64–99%). Aldehydes and ketones bearing an electron-withdrawing group (entries 2–6) gave slightly better yields (88–92%, except entry 7[12]), than electron-rich aldehydes (entries 8–10) (66–84%). Of note, heteroaromatic aldehydes such as 2-furfural and 2-thiophenaldehyde (entries 11 and 12) resulted in excellent yields (91–99%).

In summary, we have developed a first NHC-organocatalyzed method for the direct cross-coupling of aromatic aldehydes and trifluoromethyl ketones in good to excellent yields. The resulting trifluoromethyl-substituted α-hydroxy ketones bearing a quaternary stereocenter are useful synthetic building blocks and valuable pharmaceutical intermediates. Extension of the substrate scope as well as development of an enantioselective version of this protocol are currently being investigated in our laboratories.

Table 1. Substrate scope for the direct intermolecular cross-benzoin type reaction.

Entry	R^1	R^2	Product	Yield[a] [%]
1	Ph	Ph	**12a** 	93
2	4-Cl-C_6H_4	Ph	**12b** 	88
3	Ph	4-Cl-C_6H_4	**12c** 	89
4	Ph	4-F-C_6H_4	**12d** 	89
5	4-Cl-C_6H_4	4-F-C_6H_4	**12e** 	90
6	4-CF_3-C_6H_4	Ph	**12f** 	92
7	2,4,6-F_3-C_6H_2	Ph	**12g** 	64
8	4-Me-C_6H_4	Ph	**12h** 	81
9	4-MeO-C_6H_4	Ph	**12i** 	84
10	4-Me_2N-C_6H_4	Ph	**12j** 	66
11	2-furyl	Ph	**12k** 	99
12	2-thienyl	Ph	**12l** 	91

[a] Yield of the isolated analytically pure product.

Experimental Section

General Procedure for the Intermolecular Crossed Benzoin Reaction

In a dry, argon-flushed Schlenk tube precatalyst **4** (27 mg, 0.1 mmol, 10 mol%), DBU (30 mg, 0.2 mmol, 20 mol%), aldehyde **10** (1 mmol) and trifluoromethyl ketone **11** (2 mmol) were dissolved in absolute THF (3 mL). After stirring for 15 h at room temperature, the reaction mixture was loaded directly on to a column and purified *via* flash chromatography on silca gel (pentane/diethyl ether = 9:1) to yield the corresponding α-hydroxy-α-trifluoromethyl ketone **12** as a colorless solid or yellow oil.

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[12] Of note, the reaction seems to be sensitive to aldehydes carrying a substituent in *ortho*-position. A reaction of 2-chlorobenzaldehyde with **2** afforded the corresponding 1-(2-chlorophenyl)-3,3,3-trifluoro-2-hydroxy-2-phenylpropan-1-one in 34% yield.

