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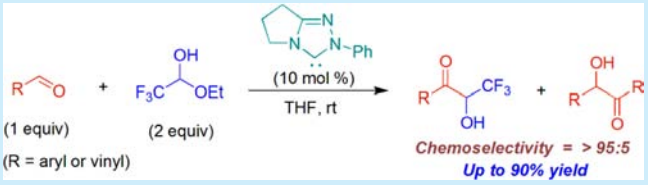
N-Heterocyclic Carbene Catalyzed Highly Chemoselective Intermolecular Crossed Acyloin Condensation of Aromatic Aldehydes with Trifluoroacetaldehyde Ethyl Hemiacetal

Bandaru T. Ramanjaneyulu, Sriram Mahesh, and Ramasamy Vijaya Anand*

Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Sector 81, Knowledge City, S. A. S. Nagar, Manauli (PO), Punjab − 140306, India

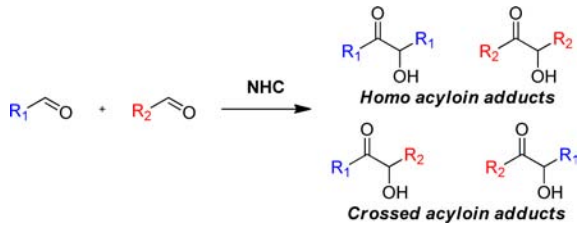
Supporting Information

ABSTRACT: A highly chemoselective intermolecular crossed acyloin condensation between aromatic aldehydes and trifluoroacetaldehyde ethyl hemiacetal has been developed under mild reaction conditions using *N*-heterocyclic carbene as a catalyst. A wide range of aromatic aldehydes bearing electron-withdrawing and -donating substituents underwent a smooth transformation to their corresponding trifluoromethyl containing acyloin derivatives in moderate to good yields.



The distinctive reactivity of *N*-heterocyclic carbenes (NHCs) has been well investigated for the intermolecular homodimerization of aldehydes (Benzoin and acyloin condensation).[1] Nevertheless, the intermolecular cross benzoin or acyloin condensations remain challenging due to a mismatch between the reactivity of aldehyde and the coupling partner (usually another aldehyde). Choosing the right coupling partner is a crucial task in the crossed acyloin reaction; otherwise, the reaction would lead to four different acyloins including two homodimerized products (Scheme 1).

Scheme 1. General Crossed Acyloin Condensation



In order to execute the cross-benzoin/acyloin reaction chemoselectively, the coupling partner must be chosen in such a way that it must not react with the NHC, and at the same time its reactivity toward Breslow intermediate[2] must be more than that of the aldehyde. In line with this concept, many successful reports have appeared in the literature for the asymmetric intramolecular benzoin reaction[1,3] as well as the inter-/intramolecular Stetter reaction.[1,4] However, only a handful of reports are available for the intermolecular crossed acyloin type reactions. The first intermolecular crossed acyloin condensation was reported by the Stetter group.[5] This seminal report was followed by Inoue's contribution, which deals with the cross coupling of aliphatic aldehydes with formaldehyde.[6] Later, Glorius developed a competent approach for the highly chemoselective hydroxymethylation of aldehydes.[7] Müller and co-workers reported an enantioselective cross-benzoin reaction through enzymatic cross-coupling of aromatic aldehydes using ThDP-dependent benzaldehyde lyase (BAL).[8] Independent reports by Glorius[9] as well as Zeitler and Connon[10] display that high levels of chemoselectivity could be achieved by introducing a substitution, especially chloro or bromo, at the *ortho* position of aromatic aldehydes. Yang's group has demonstrated that the choice of NHC is the crucial factor for switching the regioselectivity in crossed acyloin condensation.[11] Recently, Gravel reported a highly chemoselective cross-benzoin reaction using morpholinone or piperidinone derived triazolium NHC as a catalyst.[12] The Scheidt group has developed fluoride mediated desilylative coupling of *O*-silyl thiazolium carbinols with aliphatic aldehydes leading to crossed acyloins.[13]

In addition, Enders' group has developed an NHC catalyzed chemoselective cross-benzoin reaction of aldehydes with trifluoromethyl ketones.[14] Johnson's group reported a regiospecific cross silyl benzoin reaction using trimethysilyl ketones as donors.[15] Apart from these methods, a few other protocols were also reported for the chemoselective cross-benzoin-type reaction, where α-keto esters[16] or imines[17] were used as acceptors.

While working on NHC catalyzed transformations, we envisioned that the chemoselectivity in the intermolecular crossed acyloin/benzoin reaction could be enhanced if an "aldehyde equivalent" is used as a coupling partner instead of another aldehyde. Herein we report a highly chemoselective intermolecular crossed acyloin reaction of aromatic aldehydes using trifluoroacetaldehyde ethyl hemiacetal [$CF_3CH(OH)$-

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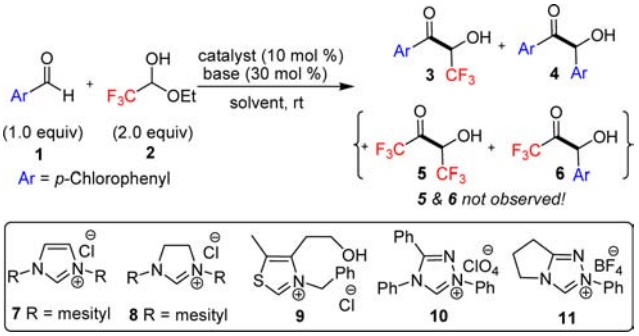
OEt] as an aldehyde equivalent (coupling partner). Although $CF_3CH(OH)OEt$ has been reconnoitered as an aldehyde equivalent in a few other transformations,[18] it has not been explored yet in acyloin condensation. We were particularly interested in $CF_3CH(OH)OEt$ because, unlike other hemiacetals, it is highly stable and commercially available (as 90% aq. solution). Moreover, this hemiacetal introduces the trifluoromethyl group in the acyloin product, which could be easily transformed to pharmaceutically important trifluoromethyl containing heterocycles or drugs.[19]

The optimization studies were carried out using *p*-chlorobenzaldehyde (**1**) and a variety of NHC precursors (**7**−**11**) under different reaction conditions (Table 1). Initially,

Table 1. Catalyst Screen and Optimization[a]

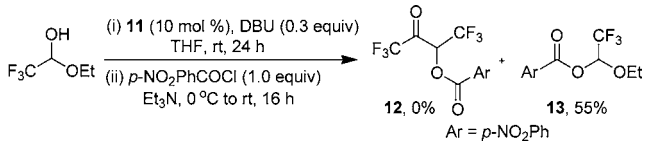


entry	catalyst	base	solvent	time [h]	3:4[b]	yield 3 [%][c]
1	**7**	DBU	THF	24	>95:5	7
2	**8**	DBU	THF	15	–	0
3	**9**	DBU	THF	15	73:27	22
4	**10**	DBU	THF	24	>95:5	33
5	**11**	**DBU**	**THF**	**4**	>95:5	**90**
6	**11**	K^tOBu	THF	6	>95:5	68
7	**11**	Cs_2CO_3	THF	6	>95:5	76
8	**11**	Et_3N	THF	8	>95:5	62
9	**11**	DBU	DCM	26	>95:5	40
10	**11**	DBU	DME	10	>95:5	80
11	**11**	DBU	DMF	10	>95:5	82
12	**11**	DBU	1,4-dioxane	12	>95:5	82

[a]Reaction conditions: 0.15 M of **1** in solvent. Use of 2 equiv of **2** with respect to **1** was found to be optimal. [b]Ratio determined by ^1H NMR analysis of the crude mixture after workup. [c]Isolated yield. rt = 23−26 °C.

we carried out an experiment using **7** as a catalyst (entry 1) and the anticipated crossed acyloin adduct **3** was formed only in 7% yield. Indeed, this result was encouraging because the crossed acyloin product **3** was formed in a chemoselective manner, albeit the yield was quite low. Screening of other NHCs **9** and **10** did not give promising results, as a considerable amount of **4** was obtained and/or the yield of **3** was low (entries 3 and 4). Intriguingly, when the reaction was performed using NHC **11** as a catalyst and DBU as a base, the desired crossed acyloin **3** was obtained in 90% yield with high chemoselectivity (entry 5). Further optimization studies were performed using **11** as a catalyst by altering the base or solvent (entries 6−12). But in all those cases, the yield of the desired product was inferior when compared to entry 5. A noteworthy observation was that the other possible products **5** and **6** were not formed under the reaction conditions. The acyloins **5** and **6** are possible only if trifluoroacetaldehyde is produced during the reaction. To have a better understanding of this observation, an experiment was carried out in which $CF_3CH(OH)OEt$ was subjected to self-acyloin condensation using **11** as a catalyst followed by esterification with *p*-nitrobenzoyl chloride under basic conditions (Scheme 2). Interestingly, in this case, the acyloin ester

Scheme 2. Control Experiment with $CF_3CH(OH)OEt$



12 was not observed; instead the acetal ester **13** was isolated in 55% yield. This experiment suggests that $CF_3CH(OH)OEt$ does not decompose to trifluoroacetaldehyde under the reaction conditions, which also explains why **5** and **6** were not observed in any of the reaction conditions tried (Table 1).[20]

Having optimized conditions in hand (entry 5, Table 1), we shifted our attention in evaluating the substrate scope. As shown in Scheme 3, a wide range of aromatic aldehydes were treated with $CF_3CH(OH)OEt$ under standard reaction conditions. In all cases, the expected crossed acyloin adducts were obtained in moderate to good yields with high levels of chemoselectivity (>95:5). A general observation was that the yields of products in the cases of electron-rich aldehydes (**14b**−**14d**) were found to be a bit inferior when compared to those of electron-poor aldehydes (**14e**−**14i**). Interestingly, in the cases of halo- and dihalo-substituted aryl aldehydes, the desired acyloin products (**14k**−**14q**) were obtained in good yields. Even highly hindered aldehydes such as *ortho*-bromo substituted aromatic aldehydes underwent smooth conversion to the corresponding products in good yields (**14r** and **14s**). This methodology also worked very well for heteroaromatic aldehydes as well (e.g., **14u**−**14x**). In the case of aliphatic aldehydes such as hydrocinnamaldehyde and phenylacetaldehyde, complex mixtures were obtained. But, cinnamaldehyde was efficiently converted to the acyloin **14t** in 66% yield. We also tried to elaborate this methodology to other cyclic hemiacetals (such as lactols and carbohydrate derivatives) as well as acyclic acetals.[21] Unfortunately, none of them reacted with **1** under standard reaction conditions to give the crossed acyloin products. In all those cases, only benzoin **4** was observed.

It is obvious from the outcome of the reaction that the Breslow intermediate reacts with $CF_3CH(OH)OEt$ chemoselectively to deliver the crossed acyloin product. To understand the reaction in detail, a few experiments were performed. In a typical crossover experiment (Scheme 4), benzoin **15a** was treated with an excess of **2** under the standard reaction conditions and the reaction was monitored by ^1H NMR spectroscopy, but the crossed acyloin product **14a** was not detected even after 2 days. This experiment clearly indicates that benzoin **15a** did not undergo a retro-benzoin reaction under the reaction conditions. This result also suggests that the formation of **15a** is irreversible. In another experiment, the standard reaction (Table 1, entry 5) was monitored by ^1H NMR spectroscopy. In this case, the formation of product **3** was observed prior (within 5 min) to the formation of **4**. The above experiments clearly show that the chemoselectivity outcome of the reaction is controlled by kinetic factors.

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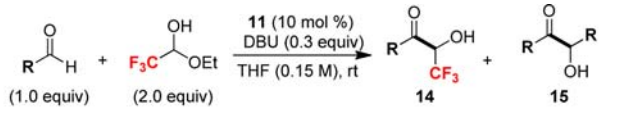
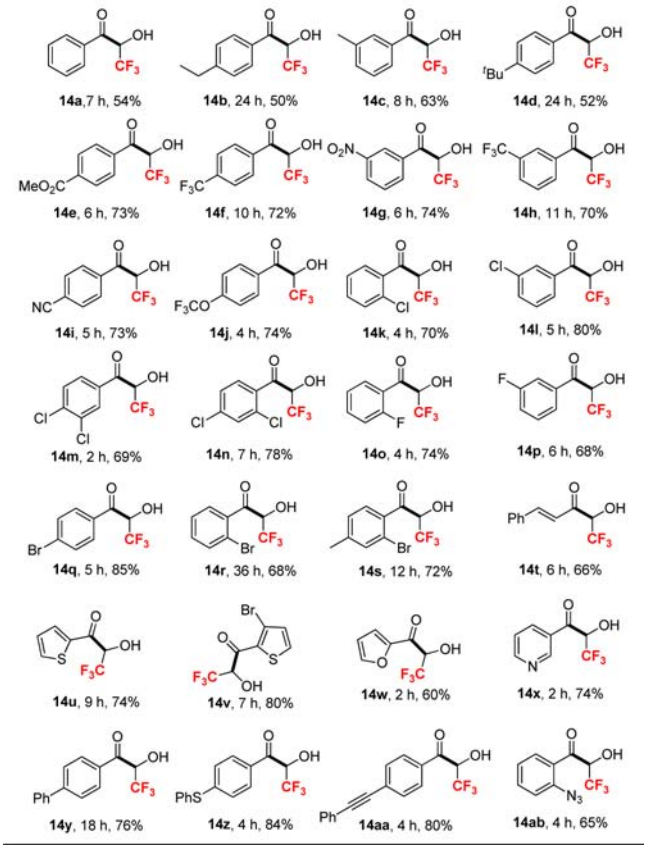
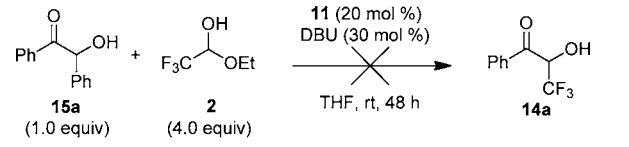
Scheme 3. Substrate Scope[a]





[a]Yields reported are isolated yields. [b] Ratio determined by ^{1}H NMR analysis of the crude mixture after workup. rt = 23−26 °C.

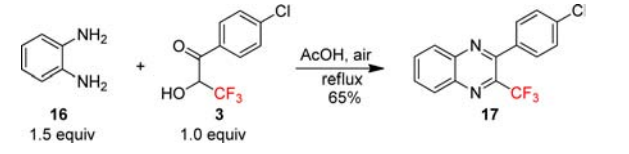
Scheme 4. Crossover Experiment Using Benzoin



To demonstrate the synthetic utility of the products, one of the trifluoromethyl containing crossed acyloin products (**3**) was refluxed with a small amount of excess of *o*-phenylenediamine (**16**) in acetic acid and the CF_3-containing quinoxoline **17** was obtained in 65% yield (Scheme 5).[22]

In summary, we developed a highly chemoselective crossed acyloin reaction of aromatic aldehydes with $CF_3CH(OH)OEt$ using NHC as a catalyst. Further elaboration to an enantioselective version will be the focus in the near future. Also, detailed investigation to understand the mechanism is currently underway.

Scheme 5. Synthetic Utility of Crossed Acyloin Product



■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rvijayan@iisermohali.ac.in.

Notes

The authors declare no competing financial interest.

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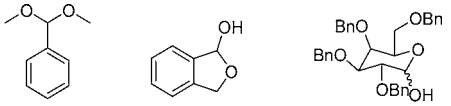
(20) Another conceivable explanation for the outcome of the reaction is that even if trifluoroacetaldehyde is present in the solution, the Breslow intermediate derived from it is expected to have a poor nucleophilicity; therefore, it may not react with another molecule of trifluoroacetaldehyde to give **5**.

(21) The cross acyloin reaction of *p*-chlorobenzaldehyde (**1**) with the following hemiacetals/acetals (**A**–**C**) was tried under standard conditions.



A B C

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