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Chemoselective N-Heterocyclic Carbene-Catalyzed Cross-Benzoin Reactions: Importance of the Fused Ring in Triazolium Salts

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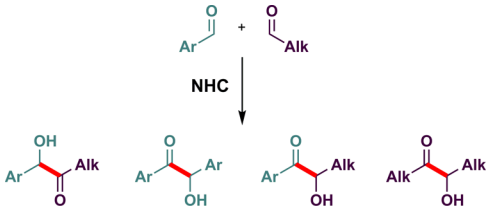
Supporting Information

ABSTRACT: Morpholinone- and piperidinone-derived triazolium salts are shown to catalyze highly chemoselective cross-benzoin reactions between aliphatic and aromatic aldehydes. The reaction scope includes *ortho*-, *meta*-, and *para*-substituted benzaldehyde derivatives with a range of electron-donating and -withdrawing groups as well as branched and unbranched aliphatic aldehydes. Catalytic loadings as low as 5 mol % give excellent yields in these reactions (up to 99%).

From its humble beginnings in 1943,[1] the *N*-heterocyclic carbene (NHC)-catalyzed benzoin reaction has seen a variety of approaches to expand its applications.[2] Initial successes focused on the homocoupling of aldehydes and impressive enantioselective approaches are well-known.[3] The addition of a second aldehyde increases the number of possible products to four (Scheme 1), and formation of one to the exclusion of others

Scheme 1. General Cross-Benzoin Reaction



becomes the main concern. Even with this challenge intramolecular couplings have been achieved with excellent chemo- and enantioselectivity,[4] notably in Mennen and Miller's macrocyclization of *o*-substituted dialdehydes.[5] Despite these advances a general approach to chemoselective intermolecular cross-benzoin reactions remains elusive. Many methods expand on the original work of Stetter[6] which demonstrates that use of α-branched aldehydes and/or *o*-substituted aromatic aldehydes leads to selectivity.[7] Particularly promising work by Connon and Zeitler shows that *o*-bromobenzaldehyde can be coupled with a slight excess of aliphatic aldehyde in up to 90% yield.[7c] Yang *et al.* have shown that an excess of aliphatic aldehyde (10−15 equiv) can be used to improve yield, though this may not always be practical in synthetic applications.[8] In parallel with these developments, Kuhl and Glorius reported the hydroxymethylation of aldehydes, which achieves good levels of chemoselectivity when electron-poor benzaldehyde derivatives are reacted with paraformaldehyde.[9] The Scheidt group has developed an ingenious approach toward aliphatic−aliphatic cross-couplings through *O*-silyl thiazolium carbinols, though a stoichiometric amount of the preformed acyl anion equivalent is required.[10] Others have effected cross-benzoin reactions using ketones[11] or α-keto esters[12] as acceptors, thereby largely avoiding the chemoselectivity issues. Analogous ThDP-dependent benzaldehyde lyase work has yielded highly chemoselective cross-couplings between *o*-substituted and non-*o*-substituted electron-deficient benzaldehyde derivatives[13] and moderate success between α-branched aliphatic aldehydes and benzaldehyde.[14] Thus, there currently exists no general method to perform chemoselective cross-benzoin reactions between aldehydes despite extensive efforts over the last seven decades. Here we report the first highly chemoselective cross-benzoin reactions between aromatic and aliphatic aldehydes, utilizing catalyst rather than substrate control.

The primary issue with chemoselectivity in cross-benzoin reactions is one of reactivity.[15] Namely, in a typical reaction the acyl anion equivalent (Breslow intermediate)[16] is formed faster with the most electrophilic aldehyde. Other factors remaining constant, it should thus prefer to attack another equivalent of the same aldehyde, leading to homobenzoin products. If the electrophilicity of the two aldehydes is similar there is little impetus for selectivity, and a statistical mixture is generally obtained. The issue of chemoselectivity is compounded by the commonly observed reversibility of the benzoin reaction. Achieving chemoselectivity via kinetic control therefore depends on the choice of substrates, catalyst, and reaction conditions.

While previous reports have suggested various structural features of NHCs which aid in achieving chemoselectivity,[17] many exciting results are still obtained by serendipity. During our recent investigations of cross-benzoin reactions using α-ketoesters, we observed that the use of triazolium catalysts incorporating a fused morpholine ring resulted in fast reactions when aliphatic aldehydes are used as substrates.[12b] In contrast, aromatic aldehydes were found to be unreactive under the same conditions. It was surmised that the fused morpholine ring was perhaps leading to a more facile formation of a Breslow intermediate with aliphatic aldehydes than with aromatic aldehydes. With these considerations in mind, we compared the outcome of benzoin reactions between benzaldehyde and hydrocinnamaldehyde using a range of representative catalysts. Table 1 shows the variation in yield and selectivity between several azolium salts. Thiazolium catalyst **1** displays limited selectivity, with **7** being a minor product. While catalyst **2** is more reactive, morpholinone-derived salt **3** proves far superior in

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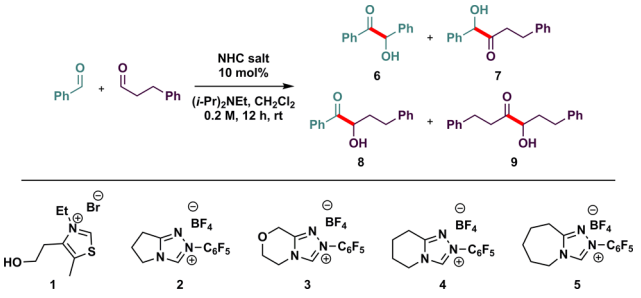
Table 1. Comparison of Catalysts in Cross-Benzoin Reactions



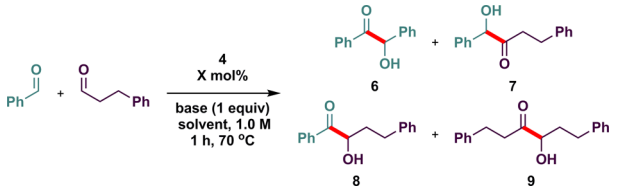
entry	precatalyst	product ratio (6:7:8:9)	yield[a]
1[b]	1	6:12:21:61	2
2	2	2:59:25:14	43
3	3	2:93:0:5	19
4	4	2:94:0:4	16
5	5	21:68:9:2	26

[a]Yield of compound 7 determined by ^{1}H NMR analysis using dimethyl terephthalate as an internal standard. [b]Performed using 1,8-diazabicyclo[5.4.0]undec-7-ene (10 mol %) instead of $(i\text{-Pr})_2$NEt.

terms of chemoselectivity (entries 2−3). To explore whether the oxygen atom plays a role in the observed selectivity, triazolium salt **4** bearing a fused piperidine ring was also prepared and screened. As this catalyst displays similar reactivity and chemoselectivity to **3**, it was concluded that selectivity is the result of the ring size and not the presence of the oxygen atom. Salt **5** was screened to see if this trend continued with increasing ring size. A loss of chemoselectivity (entry 5) suggests that the six-membered ring is optimal. With catalyst **4** readily available on a gram scale (see Supporting Information (SI)), it was selected for further study.

An optimization of the reaction was then performed (Table 2). Elevated temperatures improved the rate of reaction without affecting chemoselectivity; refluxing conditions were used to minimize reaction times. Selectivity and yield proved invariant to

Table 2. Reaction Optimization



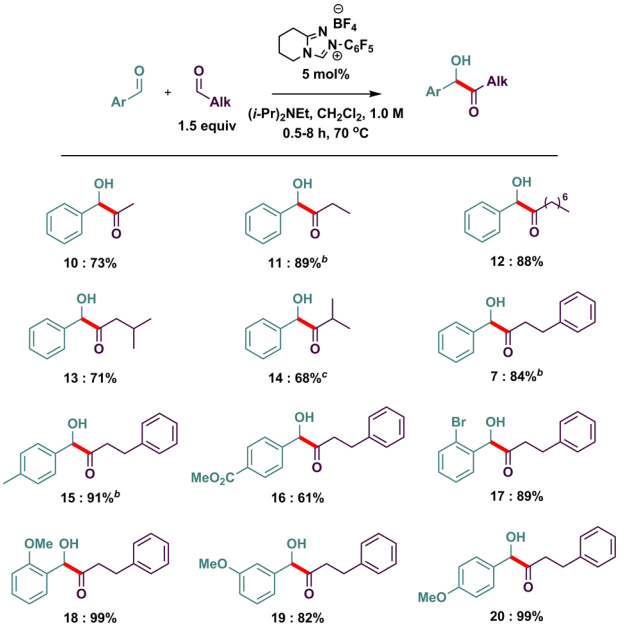
	solvent	×	base	product ratio 6	7	8	9	yield[a] (%)
1	CH_2Cl_2	10	$(i\text{-Pr})_2$NEt	6	82	8	4	66
2	THF	10	$(i\text{-Pr})_2$NEt	6	88	3	3	69
3	toluene	10	$(i\text{-Pr})_2$NEt	7	89	0	4	63
4	THF	10	DBU[b]	3	86	8	3	63
5	THF	10	NaOAc	5	88	2	5	66
6	THF	5	$(i\text{-Pr})_2$NEt	4	88	2	6	69
7[c]	THF	5	$(i\text{-Pr})_2$NEt	3	89	2	6	68
8[c,d]	THF	5	$(i\text{-Pr})_2$NEt	1	86	2	11	75
9[c,d]	CH_2Cl_2	5	$(i\text{-Pr})_2$NEt	1	84	5	10	82

[a]Yield of compound 7 determined by ^{1}H NMR analysis using dimethyl terephthalate as an internal standard. [b]Performed using 0.05 equiv DBU. [c]Reaction time decreased to 30 min. [d]Performed using 1.5 equiv of hydrocinnamaldehyde. THF = tetrahydrofuran; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

either base or solvent choice (entries 1−5). While surprising, this also means that the reaction is amenable to a variety of solvents and bases. Equally as exciting were the observations that both catalytic loading and reaction time could be halved while maintaining the yield and selectivity (entries 6−7). A slight excess of aliphatic aldehyde increased the yield, with the effect being more pronounced in CH_2Cl_2 (entries 8−9). Several other parameters were varied to further enhance the yield with no effect.[18]

The reaction scope was explored using the optimized conditions (Table 3). Both short and long chain aliphatic

Table 3. Scope of the Reaction[a]



[a]Isolated yields after chromatography. [b]Corrected yield accounting for small amounts of other benzoin products. [c]5 equiv of isobutyraldehyde used.

aldehydes afford good to excellent yields (**10**, **11**, and **12**). β-branched aliphatic aldehydes resulted in comparable yields (**13**), albeit with extended reaction times. α-branched isobutyraldehyde showed decreased reactivity, and both a larger excess and prolonged reaction time were needed to obtain good yields (**14**). The aromatic ring was shown to be tolerant to both electron-withdrawing and -donating groups at the *para* position (**15** and **16**, respectively), as well as functionalization at both *meta* (**19**) and *ortho* (**17** and **18**) positions to furnish the products in good to excellent yields. Notably, heteroaromatic aldehydes were found to show varied selectivity for cross-benzoin products, but competing reactions and issues with purification lead to their exclusion as efficient substrates (details in SI). Compounds **6**, **10**, and **14** also displayed unusual susceptibility to decomposition and/or isomerization on silica gel; characterization was performed on a mixture containing small amounts of other benzoin products.

Chiral morpholinone-based triazolium precatalysts are well-known and easily accessible from amino acids. Valine-derived triazolium salt **21** was used in an enantioselective synthesis of **7** (Scheme 2). Chemoselectivity remained consistent with that of **4** (**6**:**7**:**8**:**9** = 2:77:0:21 ; excess aliphatic aldehyde leads to an increase in **9** after benzaldehyde has been consumed), though high enantioselectivity was not achieved. Work with this family of

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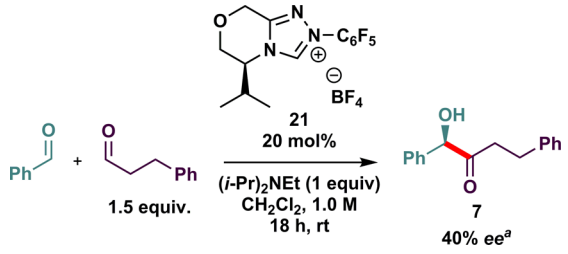
Scheme 2. Enantioselective Cross-Benzoin Reaction

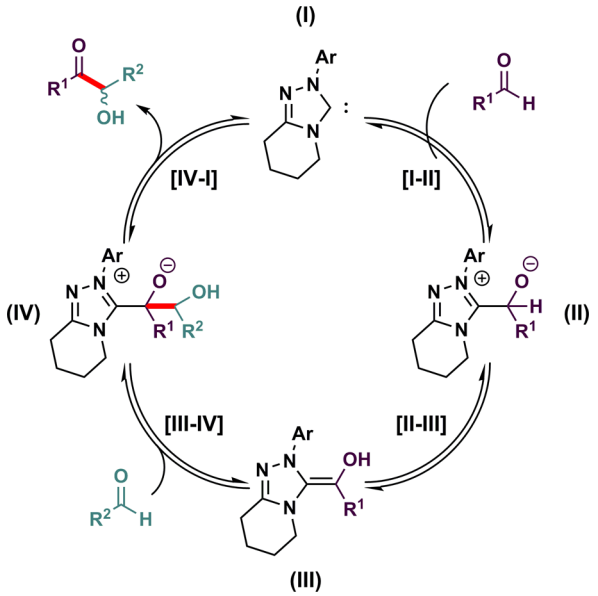


[a]Determined by HPLC; assignment of absolute configuration based on order of elution.[19]

NHCs toward an enantio- and chemo-selective cross-benzoin reaction is an ongoing area of investigation in our laboratories.

Although the specific origin of chemoselectivity remains uncertain, it is clear the size of the fused ring plays a critical role. Scheme 3 below highlights the generally accepted mechanism of

Scheme 3. Mechanism of the Cross-Benzoin Reaction



the benzoin reaction. First, attack of the carbene on an aldehyde [**I**–**II**] results in the formation of a tetrahedral intermediate. A proton transfer [**II**–**III**] yields the Breslow intermediate, which acts as an acyl anion equivalent and attacks another aldehyde [**III**–**IV**]. A proton-transfer step at this stage may be concerted or stepwise. Collapse of the intermediate releases the benzoin product and turns-over the catalyst [**IV**–**I**]. A pair of crossover experiments were performed to determine the reversibility of the formation of the homobenzoin products. Subjection of compound **6** and hydrocinnamaldehyde, or **9** and benzaldehyde, to reaction conditions results only in formation of **9** or **6**, respectively (see SI).[20] These results suggest that both homobenzoin products are formed irreversibly under reaction conditions. This further implies that, under reaction conditions, the observed chemoselectivity results from kinetic control.

Following the rates of consumption of benzaldehyde and hydrocinnamaldehyde in their respective homobenzoin reactions show that these reactions are higher than first order with respect to the aldehyde.[21] Additionally, the cross-benzoin reaction shows at least first order dependence in each aldehyde (details in SI) and is at least second order overall. Given that the reaction is under kinetic control, chemoselectivity is determined by the relative energies of the rate-determining step in each of the possible pathways. With each pathway's rate-limiting step being approximately second-order overall, we conclude that selectivity is determined at or after the C–C bond formation step ([**III**–**IV**] or [**IV**–**I**]).[22]

In summary, a general protocol for the catalyst-controlled chemoselective coupling of aromatic and aliphatic aldehydes was developed. Catalysts displaying a fused morpholine (**3**) or piperidine (**4**) ring show dramatically improved chemoselectivity over commonly employed catalyst **2**, displaying a fused pyrrolidine ring. The reaction is tolerant to a range of solvents and bases without detrimental effects to either yield or chemoselectivity. Relatively low catalytic loadings are needed, and only a slight excess of the aliphatic aldehyde increases the yield. Most importantly, the reaction features a wide substrate scope in both the aliphatic and aromatic aldehyde. Based on crossover experiments and determination of the order of the reaction, the reaction and product distribution are under kinetic control. More precise details on the origins of this kinetic bias are the object of current investigations, as are enantioselective variants of this cross-benzoin reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. 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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