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Highly Chemo- and Enantioselective Cross-Benzoin Reaction of Aliphatic Aldehydes and α-Ketoesters

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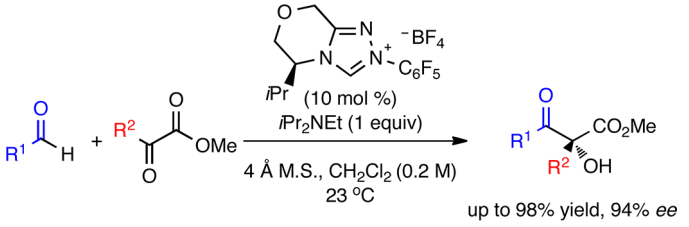
ABSTRACT



An electron-deficient, valine-derived triazolium salt is shown to catalyze a highly chemo- and enantioselective cross-benzoin reaction between aliphatic aldehydes and α-ketoesters. This methodology represents the first high yielding and highly enantioselective intermolecular cross-benzoin reaction using an organocatalyst (up to 94% *ee*). Further diastereoselective reduction of the products gives access to densely oxygenated compounds with high chemo- and diastereoselectivity.

N-Heterocyclic carbene (NHC) catalysis with its attractive ability to invert the reactivity of aldehydes (*umpolung*) has led to intensive research in the area.[1] Although the NHC-catalyzed benzoin reaction dates back to 1943,[2] the chemo- and enantioselective coupling of two different aldehydes still remains elusive. Despite the recent advances in the field in which highly enantioselective intermolecular homocoupling of aldehydes has been achieved,[3] the study of the chemo- and enantioselective coupling of acyl anion equivalents with different carbonyl partners remains in its infancy.[4,5] Indeed, such transformations have only recently been achieved with varying levels of success. Pioneering work on the *intramolecular* cross coupling of

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(2) Ukai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 269.

(3) For recent examples on the enantioselective homocoupling of aldehydes, see: (a) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (b) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645. (c) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367. (d) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (e) Soeta, T.; Tabatake, Y.; Inomata, K.; Ukaji, Y. *Tetrahedron* **2012**, *68*, 894.

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(5) Enantio- and chemoselective cross-benzoin reactions: (a) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282. (b) O'Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2011**, *76*, 347. (c) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett.* **2011**, *13*, 880. (d) Rose, C. A.; Gundala, S.; Fagan, C. -L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012**, *3*, 735. Enzymatic coupling employing α-diketones: (e) Giovannini, P. P.; Fantin, G.; Massi, A.; Venturi, V.; Pedrini, P. *Org. Biomol. Chem.* **2011**, *9*, 8038.

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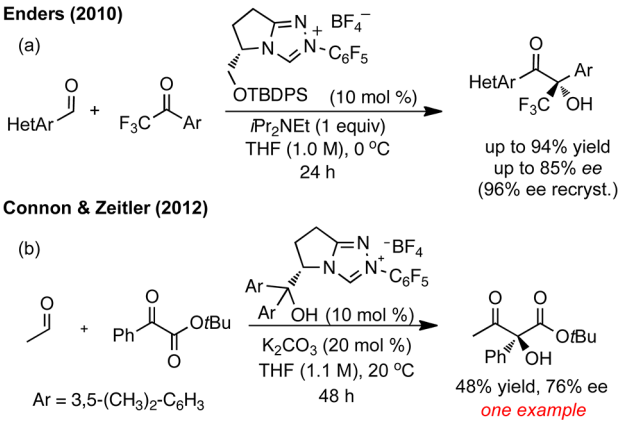
aldehydes with ketones was reported by the groups of Enders and Suzuki, in which high yields as well as high diastereo- and enantioselectivities were achieved.[6] In contrast, chemo- and enantioselective *intermolecular* cross-benzoin reactions using a small molecule organocatalyst have proven difficult, and only a few reports have been published (Scheme 1).[5] In related work, Müller and co-workers reported the use of ThDP-dependent enzymes to achieve the decarboxylative coupling of α-ketoacids and carbonyl compounds, as well as the chemo- and enantioselective coupling between aromatic aldehydes.[7] Very recently, Domínguez de María and co-workers disclosed an enzyme-catalyzed diastereoselective coupling between aromatic and aliphatic aldehydes.[8]

Despite these advances, the intermolecular cross-benzoin reaction is still limited by a narrow reaction scope, moderate enantioselectivities, or both. Importantly, only enzyme-catalyzed intermolecular cross-benzoin reactions have achieved high enantioselectivities (> 90% ee) to date. Aliphatic aldehydes in particular are challenging coupling partners in NHC-catalysis because of their low reactivity and the presence of enolizable protons under basic conditions.[9] On the basis of our previous success utilizing α-ketoesters as useful Stetter acceptors,[10] we hypothesized that the combination of these highly reactive substrates[11] and aliphatic aldehydes as coupling partners could be used in cross-benzoin reactions. As our studies were in progress, the groups of Connon and Zeitler jointly disclosed their results in the cross-benzoin reaction using α-ketoesters and an achiral catalyst. Although this detailed report firmly established the use of a variety of functionalized aldehydes as coupling partners, a general and highly enantioselective version of the reaction remained elusive. In one example, moderate yield and moderate enantioselectivity was achieved at ambient temperature (Scheme 1b).[5d] In view of the current absence of highly enantioselective intermolecular cross-benzoin reactions utilizing organocatalysts, we pursued our studies with the aim of uncovering such a reaction.

Scheme 1. Cross-Benzoin Reaction between Aldehydes and Ketones



A brief catalyst screen was performed with various chiral electron-deficient triazolium derived carbenes **8a**–**e** (Table 1, entries 1–5). Triazolium precatalyst **8a**[12] furnished the desired cross-benzoin product in good yield and good enantioselectivity (entry 1). In contrast to the long reaction times required under the conditions reported by Connon, Zeitler, and co-workers,[5d] good conversion was observed after a few hours (4 h). The use of Rovis' aminoindanol-derived precatalyst **8b**[13] led to a decrease in both the yield and enantioselectivity of the reaction (entry 2). However, the use of a closely related triazolium salt **8c**[10] furnished the cross-benzoin product in moderate yield and improved enantioselectivity (entry 3). In an effort to increase the steric bulk near the reactive center, dimethyl-substituted triazolium salt **8d**[10] was used. However, this modification resulted in complete suppression of reactivity since neither desired cross-benzoin nor homobenzoin products were observed (entry 4). Use of valine-derived triazolium salt **8e**[14] resulted in increased enantioselectivity, albeit at the expense of yield (entry 5). Addition of molecular sieves had a beneficial effect on the yield and was accompanied by a slight reduction in the observed enantioselectivity (entry 6). Further efforts showed a strong influence of the ester moiety on the outcome of the reaction (entries 7–8). Aiming to improve the enantioselectivity of the reaction with NHC precatalyst **8e**, substrate **3** bearing a bulky *tert*-butyl ester moiety was synthesized. Surprisingly, the reaction suffered from a decrease in both the reactivity and enantioselectivity (entry 7) compared to that using ethyl α-ketoester **2**. In light of this result, the use of a substituent smaller than the

(6) For examples on the intramolecular cross-benzoin reaction between aldehydes and ketones, see: (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (b) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111. (c) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431. (d) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (e) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (f) Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713. (g) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263. (h) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866. (i) Takada, A.; Hashimoto, Y.; Takikawa, H.; Hikita, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2297.

(7) (a) Pohl, M.; Lingen, B.; Müller, M. *Chem.—Eur. J.* **2002**, *8*, 5288. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084. (c) Lehwald, P.; Richter, M.; Röhr, C.; Hung-wen, L.; Müller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2389. Beigi, M.; Waltzer, S.; Fries, A.; Eggeling, L.; Sprenger, G. A.; Müller, M. *Org. Lett.* **2013**, *15*, 452.

(8) Müller, C.; Pérez-Sánchez, M.; Domínguez de María, P. *Org. Biomol. Chem.* **2013**, *11*, 2000.

(9) Rovis and co-workers have shown efficient, enantioselective transformations with aliphatic aldehydes for the NHC-catalyzed Stetter and aza-benzoin reactions. (a) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2391. (b) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904.

(10) Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942.

(11) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1678.

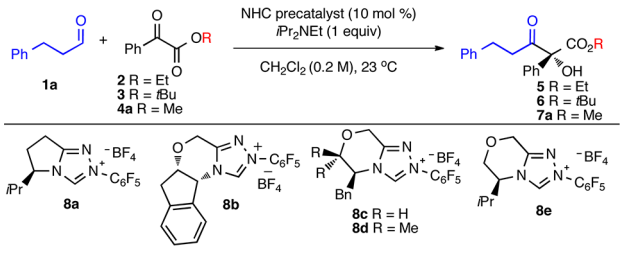
(12) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *31*, 10872.

(13) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5726.

(14) An analogous *N*-Ph salt has been reported: Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

ethyl group present in **2** was then considered. Gratifyingly, the methyl ester substrate underwent the reaction with an improvement in both the yield and enantioselectivity (entry 6 vs entry 8). The use of a lower catalyst loading led to decreased yields.

Table 1. Reaction Optimization[a]



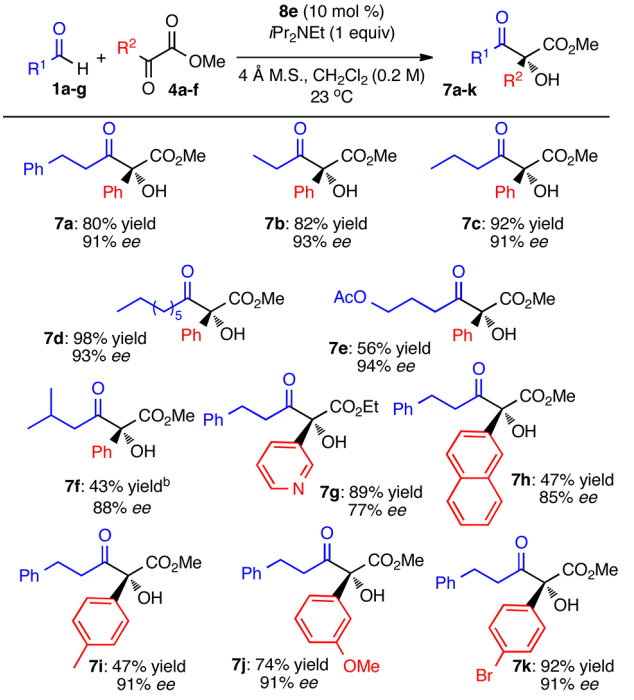
entry	substrate	NHC precat	additive	yield (%)[b]	ee (%)[c]
1	**2**	**8a**	none	77	80
2	**2**	**8b**	none	22	74
3	**2**	**8c**	none	55	89
4	**2**	**8d**	none	0	–
5	**2**	**8e**	none	27	91
6	**2**	**8e**	4 Å M.S.	61	89
7	**3**	**8e**	4 Å M.S.	22	74
8	**4a**	**8e**	4 Å M.S.	80	91

[a] Unless otherwise noted, all reactions were performed by the addition of iPr$_2$NEt (1 equiv) to a solution of aldehyde **1a** (1.5 equiv), α-ketoester (1 equiv), and precatalyst (0.1 equiv) in dry CH_2Cl_2 under inert atmosphere at 23 °C. [b] Yield of isolated product. [c] Enantiomeric excess determined by HPLC analysis on chiral stationary phase. M.S. = molecular sieves.

Having established optimal conditions, the scope of the cross-benzoin reaction was then investigated. Aliphatic aldehydes of varying chain length were explored (Scheme 2).

The use of hydrocinnamaldehyde **1a** furnished the desired cross-benzoin product **7a** in good yield and good enantioselectivity (80% yield, 91% *ee*). Short linear aldehydes such as propanal **1b** and butanal **1c** led to the corresponding cross-benzoin products **7b** and **7c**, respectively, in good yields and good enantiomeric excess. With longer linear carbon chain aldehydes, such as octanal **1d**, the high enantioselectivity was preserved to furnish **7d** in excellent yield (98% yield, 93% *ee*). The presence of esters was also found to be compatible under the optimized conditions, furnishing the desired cross-benzoin product **7e** in moderate yield and excellent enantioselectivity (56% yield, 94% *ee*). The introduction of a substituent at the b position of the aldehyde provided **7f** with good enantioselectivity, albeit at the expense of reactivity (43% yield, 88% *ee*). On the other hand, α-branched aliphatic aldehydes and aromatic aldehydes did not undergo any reaction under these conditions, presumably as a result of steric hindrance.[15] Some modifications on the acceptor are also

Scheme 2. Scope of the Cross-Benzoin Reaction[a]



[a] All reactions were performed by the addition of iPr$_2$NEt (1 equiv) to a solution of aldehyde **1** (1.5 equiv), α-ketoester **4** (1 equiv), powdered 4 Å M.S. (1:1 w/w with respect to **4**) and precatalyst **8e** (0.1 equiv) in dry CH_2Cl_2 (0.2 M) under inert atmosphere at 23 °C. [b] Performed with 30 mol % catalytic loading.

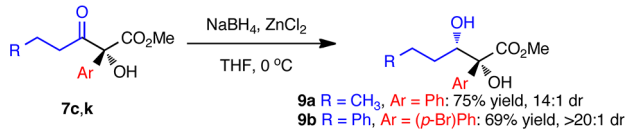
possible. As can be seen in Scheme 2, various aryl-substituted α-ketoester acceptors furnished the desired cross-benzoin products with moderate to good yields and enantioselectivities (products **7g**[16]–**7k**). Excellent reactivity was observed with the 3-pyridyl α-ketoester acceptor, which was however accompanied by a small decrease in the enantioselectivity (**7g**). The use of a large naphthalene substituent led to a significant decrease in the yield and a slight decrease in the enantiomeric excess of the cross-benzoin product (**7h**). In contrast, the use of a *p*-tolyl-α-ketoester acceptor led to the corresponding cross-benzoin product **7i** in excellent enantioselectivity, albeit in moderate yield. Reactions performed with electron-poor aryl substituents also afforded the products with very good enantioselectivity (**7j** and **7k**). Alkyl-substituted α-ketoester acceptors did not participate in the reaction under these conditions. Nevertheless, the excellent reactivity observed between various aliphatic aldehydes and aryl-substituted α-ketoester acceptors is noteworthy, as all reactions were completed within 3–24 h.

Cross-benzoin products **7** could be reduced with very high chemo- and diastereoselectivity, as shown in Scheme 3. Reduction using 1 equiv of sodium borohydride in the presence of zinc chloride cleanly afforded the corresponding *syn* diols. This simple cross-benzoin/reduction sequence

(15) Similar limitations in the aldehyde partner were found using an amino indanol-derived triazolium salt for aza-benzoin reactions; see ref 9b.

(16) Because of the ease of preparation of **4b**, the ethyl ester substrate was used instead of the methyl ester counterpart.

Scheme 3. Diastereoselective Reduction of Cross-Benzoin Products to Access *syn* Diols



thus affords densely oxygenated products with high chemo-, diastereo-, and enantioselectivity. The minor *anti* diastereomer obtained from the reduction of **7c** was used to determine its absolute configuration. The absolute configuration of all other cross-benzoin products (**7a**–**k**) was assigned by analogy (see Supporting Information for details).

The stereochemical outcome of the cross-benzoin reaction can be rationalized by a five-membered transition state featuring a hydrogen bonding interaction (Figure 1).[17] The favored transition state (TS-1) has the large aryl substituent oriented away from the carbene catalyst. The transition state that leads to the formation of the minor enantiomer (TS-2) orients the large aryl substituent beneath the catalyst framework, causing steric repulsion. In both cases, the acceptor approaches from the face opposite the isopropyl substituent.

An enantioselective cross-benzoin reaction has been realized through the development of a new valine-derived triazolium catalyst. Excellent enantioselectivity is observed with aliphatic aldehydes and various aryl α-ketoester acceptors. This transformation provides access to enantiomerically enriched tertiary alcohols in two steps from readily accessible starting materials. Furthermore, the cross-benzoin products were conveniently reduced to *syn* diols with excellent diastereoselectivity. Further work on cross-benzoin and other NHC-catalyzed reactions is ongoing in our laboratories.

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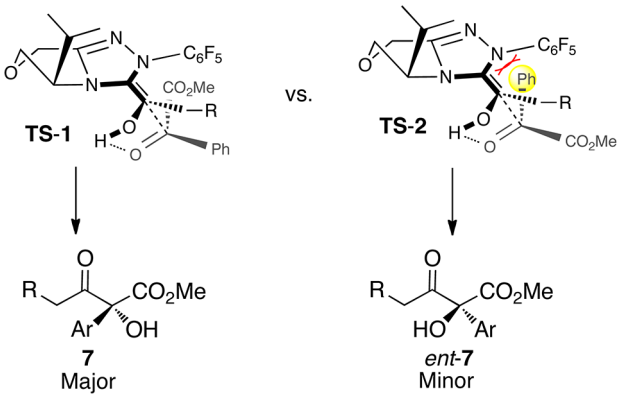

Figure 1. Proposed rationale for the stereochemical outcome.

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Supporting Information Available. Experimental procedures, characterization data and NMR spectra for all new compounds; HPLC chromatograms for cross-benzoin products **7** and diols **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.