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Highly Enantioselective Benzoin Condensation Reactions Involving a Bifunctional Protic Pentafluorophenyl-Substituted Triazolium Precatalyst

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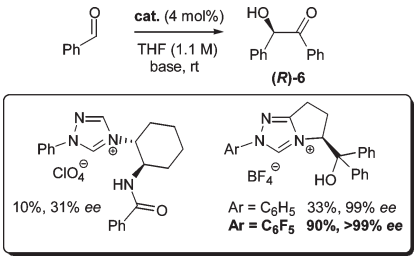
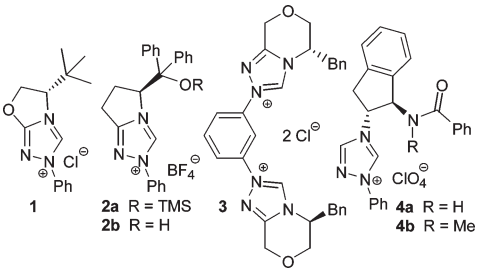


Improved catalyst design by incorporating a hydrogen bond donating substituent to improve enantiocontrol together with an acidifying pentafluorophenyl substituent to enhance catalyst efficiency results in a triazolium ion precatalyst that promotes the asymmetric archetypal benzoin condensation with excellent efficiency and unprecedented enantioselectivity.

First discovered in 1832,[1] the benzoin condensation (BC)[2] is a catalytic carbon−carbon bond forming process of considerable synthetic utility that allows the construction of a α-hydroxy ketone motif from two aldehyde molecules with the formation of a new stereocenter. Initial attempts to develop an asymmetric variant of the reaction with use of chiral thiazolium ion precatalysts in the presence of a base resulted in low-moderate product enantiomeric excess;[3] however, seminal work by Enders[4] and then by Leeper[5] later demonstrated the clear superiority of chiral triazolium ion precatalysts—which culminated in 2002 with the isolation of benzoin from the condensation of benzaldehyde in greater than 90% ee (83% yield) catalyzed by the carbene derived from the chiral bicyclic triazolium ion **1** (Scheme 1).[6] As had been observed in previous systems, both catalyst efficacy and selectivity were highly dependent on the steric and electronic characteristics of the aromatic aldehyde used: activated aldehydes gave lower product ee, while electron-rich analogues afforded benzoins with higher levels of enantiopurity at the expense of product yield.

SCHEME 1. Chiral Triazolium Catalysts for the Benzoin Condensation



Very recently three reports have emerged which have prompted us to report our results in this field: Enders disclosed that the pyroglutamic acid-derived precatalyst **2a** could promote the BC of benzaldehyde in an outstanding 95% ee (66% yield) in toluene using KHMDS as the base; however, as has traditionally been the case, substrates either more or less electron rich than benzaldehyde proved problematic.[7] You and co-workers[8] demonstrated that the bis-triazolium precatalyst **3** could promote BC reactions with high-excellent enantioselectivity (84−95% ee) and moderate-excellent product yields (41−95%) while also very recently Ye et al. reported the use of **2a** and its desilylated derivative **2b** (along with related analogues) for the promotion of highly enantioselective ketene dimerizations,[9] Staudinger cycloadditions,[10] and aza-Baylis−Hillman reactions.[11]

Recently Connon et al.[12] reported the first example of the use of hydrogen bond donation as a control element in an

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(2) Recent reviews: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5506. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (d) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (e) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (f) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (g) Zeitler, K. *Ernst Schering Found. Symp. Proc.* **2007**, *2*, 183.
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(10) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.
(11) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715.
(12) O'Toole, S. E.; Connon, S. J. *Org. Biomol. Chem.* **2009**, *7*, 3584.

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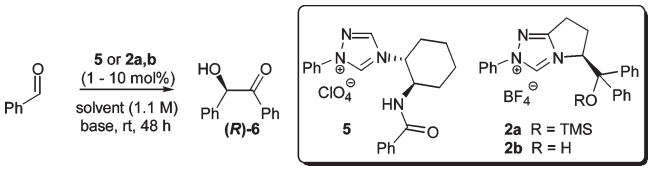
TABLE 1. The Asymmetric Benzoin Reaction: Initial Studies



entry	cat.	catalyst loading (mol %)	base	base loading (mol %)	yield (%)[a]	ee (%)[b]
1	**5**	4	K_2CO_3/KOH	2.88/0.64	0	
2	**5**	4	K_2CO_3	3.2	10	31[c]
3	**2a**	4	K_2CO_3/KOH	2.88/0.64	18	53
4	**2b**	4	K_2CO_3/KOH	2.88/0.64	33	99
5	**2b**	2	K_2CO_3/KOH	1.44/0.32	14	96
6	**2b**	10	K_2CO_3/KOH	7.19/1.62	25	96
7	**2b**	4	NEt_3	6.4	22	93
8	**2b**	4	DBU	6.4	0	0
9	**2b**	4	Cs_2CO_3	3.2	32	98
10	**2b**	4	Rb_2CO_3	3.2	29	>99
11	**2b**	1	KO^{t}Bu	6.4	0	0
12[d]	**2b**	10	KHMDS	9.81	14	96

[a]Determined by ^{1}H NMR spectroscopy, using (*E*)-stilbene as an internal standard. [b]Determined by CSP-HPLC. [c](*S*)-**6** obtained. [d]In toluene (1.0 M).

asymmetric BC reaction:[13] precatalyst **4a** incorporating a secondary amide substituent could promote the BC of benzaldehyde with a maximum enantiomeric excess of 62%, while its *N*-methylated analogue **4b** furnished the same product in 13% ee. While this study established proof of concept, neither product yield nor enantioselectivity reached synthetically useful levels. We therefore considered exploring the potential of these systems further through the synthesis of the rigid, bicyclic alcohol **2b**[14] and the 1,2-diaminocyclohexane-derived triazolium salt **5**—where the relative positioning of the nucleophile-generating and electrophile-activating components would differ subtly from those associated with catalyst **4a**.

In preliminary experiments these were evaluated as precatalysts for the BC reaction in the presence of a variety of bases known to be suitable (from our previous study) for use in the BC (Table 1). While **5** did not represent an improvement over **4a**, the silylated precatalyst **2a** (4 mol %) furnished (*R*)-**6** with moderate enantioselectivity and low yield (entries 1−3). The protic precatalyst **2b** (which had not previously been evaluated as a BC precatalyst) furnished the product in almost enantiopure form under identical conditions, albeit in disappointing yield (entry 4). Attempts to optimize the reaction conditions (base, solvent, catalyst/base loading) to improve catalyst efficiency met with failure (entries 4−12), although it is notable that **2b** possessed a reproducibly higher selectivity profile when used in conjunction with Rb_2CO_3 than with other bases (entry 10).

It was clear at this stage that while **2b** represents a solution to the enantioselectivity issue that often bedevils the BC, product yields with this system (ca. 30%) were unacceptable—therefore modification of the catalyst structure to improve catalyst efficacy was necessary. Speculating that the low yield may be related in part to the ability of benzoin to reprotonate the carbene, we were intrigued to read a report from Suzuki's group[15] where the judicious modification of triazolium ion substituents[16] to render them more electron withdrawing in nature led to higher product yields in intramolecular BC reactions involving enolizable substrates prone to aldol side reactions. To test this hypothesis, the achiral salt **7a** and its pentafluorophenyl analogue **7b** were prepared[17] and evaluated as precatalysts for the BC reaction under conditions compatible with **2b**.[18]

The results of these experiments are outlined in Table 2. Under conditions in which the phenyl-substituted model catalyst **7a** either fails completely (entries 1, 5, and 8) or produces trace amounts of **6**, the pentafluoro analogue **7b** promotes highly efficient BC reactions with product yields as high as 98% (entries 2−4, 6−7, and 9) at low catalyst loadings. Precatalyst **7b** was also of sufficient acidity to form the carbene in the presence of mild amine bases (entry 9).

We were therefore prompted to prepare the triazolium salt **8**—a structure that aspires toward a marriage of the highly enantioselective catalysis associated with the core structure **2b** with the catalytic efficiency of **7b**. Gratifyingly, on evaluation of **8** as a promoter of the BC reaction (Table 3) this proved to be the case: uniformly high-excellent product

(13) Miller had previously designed chiral H-bond donating thiazolium ion precatalysts for the promotion of intramolecular Stetter reactions and intermolecular aldehyde−imine couplings, see: (a) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654.

(14) We were prompted by success we have had in using similar hydrogen bond-donating motifs to control stereochemistry in the design of catalysts for enantioselective acylation chemistry previously (see following references); however, it should be acknowledged that Ye disclosed the design of **2b** (refs 9−11) while this project was in progress: (a) O'Dálaigh, C.; Hynes, S. J.; Maher, D. J.; Connon, S. J. *Org. Biomol. Chem.* **2005**, *3*, 981. (b) O'Dálaigh, C.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watson, G. W.; Connon, S. J. *Org. Biomol. Chem.* **2006**, *4*, 2785. (c) O'Dálaigh, C.; Connon, S. J. *J. Org. Chem.* **2007**, *72*, 7066. (d) Gleeson, O.; Tekoriute, R.; Gun'ko, Y. K.; Connon, S. J. *Chem.—Eur. J.* **2009**, *15*, 5669.

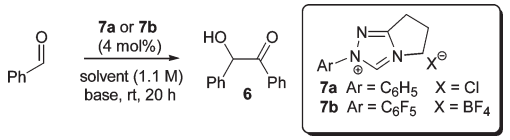
(15) Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713.

(16) For an account detailing the importance of the *N*-aryl substituents see: Rovis, T. *Chem. Lett.* **2008**, *37*, 1.

(17) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725.

(18) Recently the pK_a of catalyst **7a** (H_2O) has been determined to be 17.7: Campbell, C. D.; Duguet, N.; Gallagher, K. A.; Thomson, J. E.; Lindsay, A. G.; O'Donoghue, A. C.; Smith, A. D. *Chem. Commun.* **2008**, 3528.

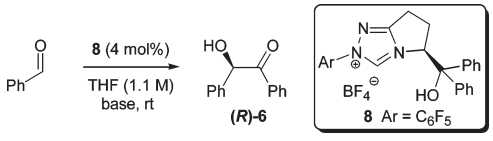
TABLE 2. Evaluating the Influence of Catalyst Electronics on Yield



entry	cat.	solvent	base	base loading (mol %)	yield (%)[a]
1	**7a**	THF	K_2CO_3	3.2	0
2	**7b**	THF	K_2CO_3	3.2	98
3	**7b**	THF	Cs_2CO_3	3.2	87
4	**7b**	THF	Rb_2CO_3	3.2	75
5	**7a**	THF	Cs_2CO_3	3.2	0
6	**7b**	PhMe	K_2CO_3	3.2	39
7	**7b**	CCl_4	K_2CO_3	3.2	11
8	**7a**	THF	$^iPr_2NEt$	4.0	4
9	**7b**	THF	$^iPr_2NEt$	4.0	84

[a]Determined by ^1H NMR spectroscopy, using an internal standard.

TABLE 3. The Asymmetric Benzoin Reaction with Catalyst 8



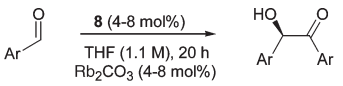
entry	base	base loading (mol %)	time (h)	yield (%)[a]	ee (%)[b]
1	K_2CO_3/KOH	2.88/0.64	21	85	98
2	K_2CO_3	3.20	20	84	96
3	Cs_2CO_3	3.20	20	81	98
4	Rb_2CO_3	3.20	20	87	98
5[c]	Rb_2CO_3	2.00	20	84	96
6	Rb_2CO_3	4.00	20	90	97
7	Rb_2CO_3	6.00	20	87	96
8	Rb_2CO_3	3.20	20	86	99
9	Rb_2CO_3	4.00	20	89	99
10	Rb_2CO_3	4.00	24	90	>99
11	K_2CO_3/KOH	2.88/0.64	21	85	98
12	NEt_3	6.40	21	76	92

[a]Determined by ^1H NMR spectroscopy, using (*E*)-stilbene as an internal standard. [b]Determined by CSP-HPLC. [c]2 mol % of both catalyst and base used.

yields and enantioselectivities were obtained under a variety of conditions, the optimization of which (entry 10) allowed the use of 4 mol % of precatalyst **8** at ambient temperature to generate (*R*)-**6** in 90% yield and >99% ee—the highest level of enantiopurity achieved to date with an artificial catalyst system to the best of our knowledge. The precatalyst could also mediate highly enantioselective BC reactions at lower loadings of 2 mol % (entry 5) and was also compatible with triethylamine, a convenient and inexpensive base (entry 11).

With a highly active and selective precatalyst in hand we next turned to the question of substrate scope (Table 4), an issue that has severely limited the utility of the BC reaction in the past. We evaluated the performance of **8** in BC reactions involving a range of aromatic aldehydes (including the little-tested 2-substituted analogues) and were pleased to find the catalyst of relatively broad scope. 2-Naphthylaldehyde (**9**) proved an excellent substrate (entry 1), while as expected 2-chlorobenzaldehyde (**10**) proved difficult to convert with high selectivity (entry 2). Chlorobenzaldehydes **11** and **12**

TABLE 4. Evaluation of Catalyst Scope



9 Ar = 2-naphthyl
10 Ar = 2-Cl-C_6H_4
11 Ar = 3-Cl-C_6H_4
12 Ar = 4-Cl-C_6H_4
13 Ar = 2-furyl
14 Ar = 2-CH_3-C_6H_4
15 Ar = 4-CH_3-C_6H_4
16 Ar = 2-MeO-C_6H_4
17 Ar = 4-MeO-C_6H_4

(*R*)-**18** Ar = 2-naphthyl
(*R*)-**19** Ar = 2-Cl-C_6H_4
(*R*)-**20** Ar = 3-Cl-C_6H_4
(*R*)-**21** Ar = 4-Cl-C_6H_4
(*R*)-**22** Ar = 2-furyl
(*R*)-**23** Ar = 2-CH_3-C_6H_4
(*R*)-**24** Ar = 4-CH_3-C_6H_4
(*R*)-**25** Ar = 2-MeO-C_6H_4
(*R*)-**26** Ar = 4-MeO-C_6H_4

entry	substrate	temp (°C)	cat. loading (mol %)	yield (%)	ee (%)[a]
1	**9**	18	4	86	94
2	**10**	18	4	17	43
3	**11**	18	4	64	67
4	**11**	0	4	83	83
5	**11**	−20	8	86	83
6	**12**	18	4	75	89
7	**12**	0	4	91	92
8	**13**	18	4	100	40
9	**13**	0	4	100	47
10	**13**	−60	4	92	90
11	**14**	18	4	0	0
12	**15**	18	4	87	95
13	**16**	18	4	11	64
14	**16**	0	8	21	82
15	**17**	18	4	13	93
16	**17**	18	8	26	97

[a]Determined by CSP-HPLC.

could be transformed into (*R*)-**20** and (*R*)-**21** with high yield and enantioselectivity at either ambient temperature or at 0 °C (entries 3−7), while the excellent activity of **8** is illustrated by its ability to promote the conversion of the challenging (from an enantioselectivity standpoint) substrate furfural (**13**) to (*R*)-**22** at −60 °C with 90% ee and 92% yield (entry 10). In line with the findings of our previous study[12] the little utilized *o*-tolualdehyde (**14**) proved resistant to the BC; however, the corresponding para-isomer **15** underwent reaction at ambient temperature without difficulty and with excellent enantioselectivity (entries 11 and 12). The traditionally problematic deactivated anisaldehyde substrates underwent slow reactions and furnished products in lower yields but with high-excellent enantioselectivity (entries 13−16).

In summary, we have developed the concept of utilizing hydrogen bonding to control the stereochemical outcome of the BC reaction further through the introduction of the triazolium salt **8**, a rigid bicyclic precatalyst incorporating not only a chiral protic substituent that improves product enantioselectivity, but also a pentafluorophenyl moiety that dramatically enhances catalyst efficacy. Salt **8** is readily accessible from pyroglutamic acid and is active at low loadings of 2−4 mol %. At room temperature it promotes the BC of benzaldehyde with the highest levels of enantiocontrol reported for this reaction with use of an artificial catalyst and it can convert a wide spectrum of aromatic aldehydes to the corresponding benzoins—in several cases also with unprecedented enantioselectivity.

Experimental Section

Optimized Conditions for the Benzoin Condensation. To a 5 mL round-bottomed flask, equipped with a magnetic stirring

bar, was added Rb_2CO_3 (99.995%, anhydrous, 0.044 mmol, 10.16 mg) that had been finely ground with a mortar and pestle. The reaction vessel was put under vacuum and heated with a heat gun for 1 min over 2-min intervals for a total of 4 min. Upon cooling, the appropriate catalyst (0.044 mmol) and (*E*)-stilbene (0.138 mmol, 24.78 mg) were added and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was distilled under vacuum and used directly. THF (1.0 mL) and the aldehyde (1.100 mmol) were added via syringe and the reaction was stirred at room temperature for 20 h, after which time CH_2Cl_2 (3.0 mL) and deionized H_2O (3.0 mL) were added. The organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4×3.0 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified with column chromatography. With the above procedure (*R*)-**6** (105 mg, 90%) could be prepared as a white solid, mp 131−132 °C, 99.8% ee. $[\alpha]^{20}_D$ −35.1 (*c* 1.0 in CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 5.98 (s, 1H), 7.29−7.40 (m, 5H (overlapping with $CHCl_3$ resonance)), 7.43 (app. t, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H). HPLC conditions and retention times: Chiralpak AD (4.6 mm × 25 cm), hexane/IPA 9/1, 1.0 mL min^{-1}, rt, UV detection at 220 nm, retention times 20.4 min (major enantiomer) and 26.9 (minor enantiomer).

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Supporting Information Available: Synthesis of all catalysts, general procedures, NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.