N-heterocyclic carbene catalysed asymmetric cross-benzoin reactions of heteroaromatic aldehydes with trifluoromethyl ketones†

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A new triazolium salt derived N-heterocyclic carbene catalyses an asymmetric cross-benzoin-type reaction of heteroaromatic aldehydes and various trifluoromethyl ketones in good to excellent yields (69–96%) and moderate to good enantioselectivities (ee = 39–85%). Up to 99% ee can be achieved by recrystallisation.

Since the first report of Liebig and Wöhler[1] about the self-condensation of benzaldehyde to benzoin in the presence of cyanide there has been a lot of effort devoted towards the development of an asymmetric version of this reaction.[2] The introduction of N-heterocyclic salts as catalyst precursors led to a breakthrough in this area.[3] Nowadays there are several successful catalysts in the case of the reaction of two identical aldehydes, yet the cross-benzoin condensation is still a challenge.[4]

Initial studies on the cross-benzoin reaction were published by Stetter and Dämbkes in 1977.[5] These showed that in a mixture of different aldehydes using a thiazolium salt-derived catalyst the thermodynamic product was formed reversibly. For certain combinations of aldehydes a very high chemoselectivity was achieved. A decade later López-Calahorra *et al.* added reactive iminium salts as acceptor molecules to the aldehydes to selectively form α-aminoketones,[6] with cross-aza-benzoin type reaction under kinetic control. Murry *et al.* and Scheidt *et al.* continued this method using acyl- and phosphinoylimines to obtain the corresponding products in high yields.[7] Their work led Miller *et al.* to develop an asymmetric version of the reaction using a thiazolium derived catalyst with a synthetic tripeptide backbone.[8]

At the same time there were several developments in the cross coupling of two different aldehydes or aldehydes with ketones. Both Suzuki *et al.* and our group discovered independently the asymmetric intramolecular benzoin condensation between aldehydes and ketones by employing different tetracyclic triazolium salts as catalyst precursors to promote this reaction in a highly enantioselective manner.[9] Meanwhile, a breakthrough in the intermolecular reaction came with the introduction of the cyanide catalysed reaction of acylsilanes with aldehydes by Johnson *et al.*[10] Later they showed that the replacement of the cyanide catalyst by a chiral phosphate led to high ee values.[10b] Furthermore, Tarr and Johnson[10d] and Demir *et al.*[10e] demonstrated independently that acylsilanes and acylphosphonates are suitable substrates for the aldehyde ketone cross-coupling. Unfortunately, so far chiral phosphates have proved to be inactive in the reaction of such acylsilanes with ketones. To the best of our knowledge the only example of an asymmetric intermolecular cross coupling of aldehydes and ketones has been carried out enzymatically by Müller *et al.*[11] Since the corresponding α-hydroxy ketones bearing a quaternary centre are important motifs in natural products,[12] the development of the asymmetric version of this reaction would be an important tool in synthetic organic chemistry.

Very recently, we have published the direct NHC-catalysed reaction of aromatic aldehydes with an excess of trifluoroacetophenone derivatives affording the corresponding products in good to excellent yields.[13] Unfortunately, as we attempted to apply enantiopure catalysts the yield dropped dramatically with selectivities close to zero. Now we present triazolium derived catalysts successfully promoting this reaction in good to excellent yields and moderate to good enantioselectivities.

We reexamined the reaction of furfural and trifluoroacetophenone using the salts **4–9** as catalyst precursors (Scheme 1). They were chosen as they have successfully been employed in the benzoin condensation (**6**[4b], **9**[3]) or in the Stetter reaction (**4**[14a], **8**[14b]). In addition, we prepared new derivatives of these triazolium salts to tune the electronic and steric properties. The best results were observed with triazolium salt **5** yielding α-hydroxy ketone **3a** in 84% yield and 77% ee. Significantly, no excess of ketone was necessary when an equivalent of Hünig's base was used instead of DBU.[13a]

Then we turned our attention to the optimisation of the reaction conditions (Table 1). Hence trifluoroacetophenone and the ketone with the thienyl moiety were reacted with furfural. The results indicated a strong temperature dependence with regard to yield but only gave a slight increase in selectivity with decreased temperature. Both the higher catalyst loading and an excess of ketone accelerated the reaction at the cost of selectivity. Therefore, we combined low temperature, 10% catalyst loading and an excess of ketone to achieve optimal results in terms of both yield and enantioselectivity. Interestingly, the process of changing the conditions as outlined above affected the less reactive thienyl ketone strongly.

The absolute configuration of the α-hydroxy ketones **3** given as (*S*) could not be unambiguously determined by X-ray analysis (Fig. 1) because of a large standard deviation of the Flack parameter[16] and is based on CD-measurements and theoretical calculations.[17] We propose the transition state given in Fig. 2. Using DFT methods Hawkes and Yates[18] calculated that the configuration of the enolamine should be *E* due to steric and stereoelectronic interactions. Dudding and Houk[19] predicted that the aromatic moieties of the aldehyde

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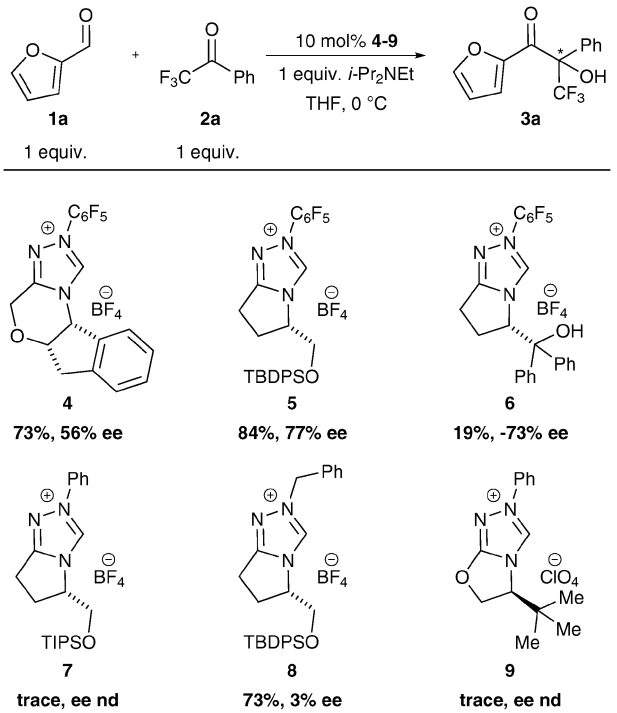
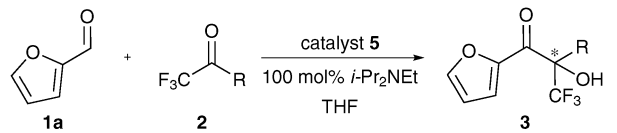


Scheme 1 Catalyst screening result of the reaction between furfural (**1a**) and trifluoroacetophenone (**2a**).

Table 1 Optimisation studies of the reaction conditions[a]



3	R	Substrate ratio	Catalyst loading (%)	Temperature/ °C	Yield[b] (%)	ee[c] (%)
a	Ph	1 : 1	10	0	61	78
a	Ph	1 : 1	20	22	83	70
a	Ph	1 : 1	10	22	84	77
a	Ph	1 : 2	10	0	86	78
b	2-Thienyl	1 : 1	10	22	47	51
b	2-Thienyl	1 : 2	10	22	62	49
b	2-Thienyl	1 : 2	10	0	71	61

[a] All reactions were performed on a 1 mmol scale in 1 mL THF for 24 h. [b] Yield of isolated **3**. [c] Determined by HPLC analysis on a chiral stationary phase.

and the triazole must turn out of plane to avoid the disfavoured steric interactions. In our case the backside was blocked by the sterically demanding silyl protecting group attached to the triazole catalyst. Thus, the ketone should approach from the opposite side. In their theoretical study Houk *et al.* also discussed attractive interactions with the aromatic moiety of the approaching molecule and the developing iminium charge during C–C bond formation. Further possible stabilising effects are π-stacking between the aromatic residues in the Breslow intermediate and the hydrogen bond between the reacting substrates.[20]

Finally, we tested various substrates to determine the scope of the reaction (Table 2). Good to excellent yields (69–96%) as well as moderate to good enantioselectivities were achieved, with electron-poor ketones performing better than their electron-rich or heteroaromatic counterparts. By prolonging the reaction time however, this disadvantage could be somewhat diminished.

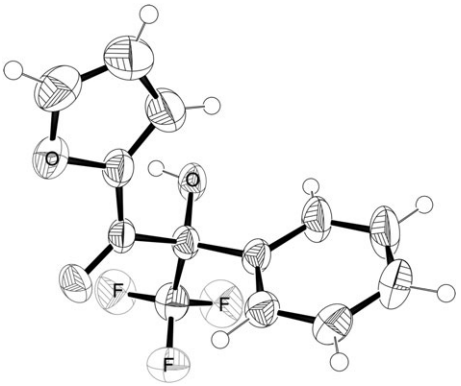


Fig. 1 ORTEP plot of **3a** determined by X-ray analysis.[15]

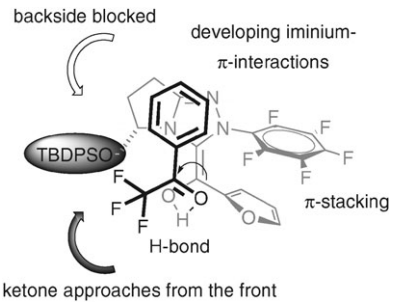
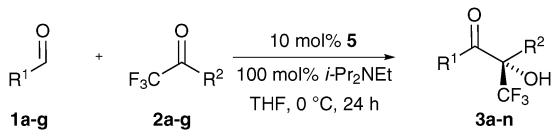


Fig. 2 Proposed transition state.

Table 2 Examination of the substrate scope under optimised conditions[a]



3	R^1	R^2	Yield[b] (%)	ee[c] (%)
a	2-Furyl	Ph	86 (43)	78 (99)
b	2-Furyl	2-Thienyl	71	61
c[d]	2-Furyl	4-$MeOC_6H_4$	69	82
d	2-Furyl	4-BrC_6H_4	89 (49)	73 (99)
e	2-Furyl	4-ClC_6H_4	90 (46)	73 (81)
f	2-Furyl	4-$CF_3C_6H_4$	96 (41)	52 (96)
g[d]	2-Furyl	2-Furyl	86	39
h[d]	2-Thienyl	4-BrC_6H_4	93	65
i	2-(5-Me-Furyl)	Ph	94 (62)	84 (99)
j[d]	2-(4,5-Di-Me-Furyl)	Ph	90	85
k[d]	2-(5-(4-ClC_6H_4)-Furyl)	Ph	75 (50)	62 (94)
l	2-Pyridyl	Ph	73	62
m[d]	2-Benzofuryl	Ph	85	67
n[d]	2-Pyrryl	Ph	85 (41)	45 (93)

[a] All reactions were performed on a 1 mmol scale in 1 mL THF under optimised conditions. [b] Yield of isolated **3**; values in parentheses indicate yield after crystallisation. [c] Determined by HPLC analysis on a chiral stationary phase; values in parentheses indicate ee after crystallisation. [d] Reaction time was prolonged to 48 h.

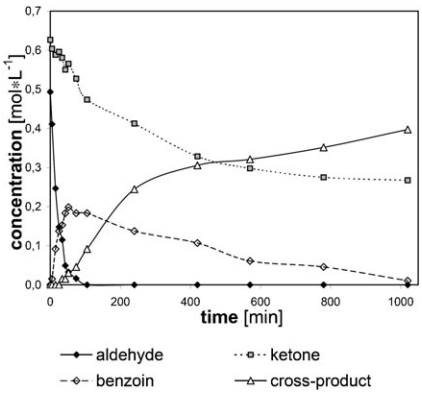


Fig. 3 Direct observation of the reaction progress *via* ^{1}H-NMR-spectroscopy. The reaction was performed using 0.5 mmol aldehyde, 0.65 mmol ketone, 0.5 mmol *i*-Pr_2NEt and 0.01 mmol catalyst **5** in 1 mL THF-d_8 at room temperature.

The enantioselectivities ranged between 39 and 85%. There appeared to be no obvious correlation between the substituents and the enantioselectivity, perhaps indicating a more complicated relationship dictated by a number of steric or stereoelectronic effects. Serendipitously, a number of products crystallised as either enantiopure compounds (Table 1, **3a**, **3d**, **3e**, **3f**, **3i**) or as racemates (**3k**, **3n**). Thus, by crystallisation some of the compounds could be isolated as a single enantiomer.

In our previous report we postulated a mechanism for the cross-benzoin reaction,[13a] which now we were able to observe directly using ^{1}H-NMR. Therefore, the reaction was carried out in an NMR tube using 2 mol% catalyst **5** without stirring to decrease the reaction rate. At the beginning of the reaction furoin was observed far before the first cross product was detected (Fig. 3). After approximately one hour the formation of the intermediate was complete and the benzoin began to react slowly with the ketone producing the cross product. This corroborated previous observations that the formation of the benzoin is thermodynamically controlled under the reported conditions. Then we turned our attention to the second step of this reaction. Several racemisation experiments were performed to determine the character of the cross-benzoin formation. We exposed enantiomerically pure **3a** to a racemic catalyst under the optimized reaction conditions for several days. If the second step of this reaction had been reversible and under thermodynamic control we would have achieved racemisation of **3a**. In fact the ee stayed at the initial value. Therefore, we state that the product is irreversibly formed under kinetic control.

In summary, we have synthesised a novel chiral triazolium salt which is a potent catalyst precursor for the asymmetric cross-benzoin reaction of aldehydes with ketones. Several hetero-aromatic aldehydes successfully reacted with various aromatic trifluoroketones in good to excellent yields and moderate to good enantioselectivities which could be improved by crystallisation. Direct observation of the reaction by NMR along with racemisation experiments showed that the product is formed under kinetic control.

Notes and references

1 J. Liebig and F. Wöhler, *Ann. Pharm.*, 1832, **3**, 249.
2 For recent reviews on NHC catalysis, see: (*a*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*b*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534; (*c*) N. Marion, S. Díes-González and S. P. Nolan, *Angew. Chem.*, 2007, **119**, 3046 (*Angew. Chem., Int. Ed.*, 2007, **46**, 2988); (*d*) P. Hoyos, J. Sinisterra, F. Molinari, A. R. Alcántara and P. D. María, *Acc. Chem. Res.*, 2010, **43**, 288.
3 D. Enders and U. Kallfass, *Angew. Chem.*, 2002, **114**, 1822 (*Angew. Chem., Int. Ed.*, 2002, **41**, 1743).
4 (*a*) Y. Ma, S. Wei, J. Wu, F. Yang, B. Liu, J. Lan, S. Yang and J. You, *Adv. Synth. Catal.*, 2008, **350**, 2645; (*b*) L. Baragwanath, C. A. Rose, K. Zeitler and S. J. Connon, *J. Org. Chem.*, 2009, **74**, 9214.
5 H. Stetter and G. Dämbkes, *Synthesis*, 1977, 403.
6 J. Castells, F. López-Calahorra, M. Bassedas and P. Urrios, *Synthesis*, 1988, 314.
7 (*a*) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696; (*b*) A. E. Mattson and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 4363.
8 S. M. Mennen, J. D. Gipson, Y. R. Kim and S. J. Miller, *J. Am. Chem. Soc.*, 2005, **127**, 1654.
9 (*a*) Y. Hachisu, J. W. Bode and K. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 8432; (*b*) Y. Hachisu, J. W. Bode and K. Suzuki, *Adv. Synth. Catal.*, 2004, **346**, 1097; (*c*) D. Enders and O. Niemeier, *Synlett*, 2004, 2111; (*d*) D. Enders, O. Niemeier and T. Balensiefer, *Angew. Chem.*, 2006, **118**, 1491 (*Angew. Chem., Int. Ed.*, 2006, **45**, 1463); (*e*) H. Takikawa, Y. Hachisu, J. W. Bode and K. Suzuki, *Angew. Chem.*, 2006, **118**, 3572 (*Angew. Chem., Int. Ed.*, 2006, **45**, 3492).
10 (*a*) X. Linghu and J. S. Johnson, *Angew. Chem.*, 2003, **115**, 2638 (*Angew. Chem., Int. Ed.*, 2003, **42**, 2534); (*b*) X. Linghu, J. R. Potnick and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 3070; (*c*) C. C. Bausch and J. S. Johnson, *Adv. Synth. Catal.*, 2005, **347**, 1207; (*d*) J. C. Tarr and J. S. Johnson, *Org. Lett.*, 2009, **11**, 3870; (*e*) A. S. Demir, Ö. Reis, A. Ç. İğdir, İ. Esiringü and S. Eymur, *J. Org. Chem.*, 2005, **70**, 10584.
11 For enzymatically promoted benzoin condensations, see: (*a*) H. Iding, T. Dünnwald, L. Greiner, A. Liese, M. Müller, P. Siegert, J. Grötzinger, A. S. Demir and M. Pohl, *Chem.–Eur. J.*, 2000, **6**, 1483; (*b*) A. S. Demir, M. Pohl, E. Janzen and M. Müller, *J. Chem. Soc., Perkin Trans. 1*, 2001, 633; (*c*) P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl and M. Müller, *J. Am. Chem. Soc.*, 2002, **124**, 12084; (*d*) P. Lehwald, M. Richter, C. Röhr, H. Liu and M. Müller, *Angew. Chem.*, 2010, **122**, 2439 (*Angew. Chem., Int. Ed.*, 2010, **49**, 2389).
12 R. Kourist, P. D. María and U. T. Bornscheuer, *ChemBioChem*, 2008, **9**, 491.
13 (*a*) D. Enders and A. Henseler, *Adv. Synth. Catal.*, 2009, **351**, 1749; (*b*) D. Enders, A. Henseler and S. Lowins, *Synthesis*, 2009, 4125.
14 (*a*) J. R. Alaniz, M. S. Kerr, J. L. Moore and T. Rovis, *J. Org. Chem.*, 2008, **73**, 2033; (*b*) D. Enders, J. Han and A. Henseler, *Chem. Commun.*, 2008, 3989.
15 CCDC 781144 contains the supplementary crystallographic data for the compound **3a** reported in this paper.
16 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876.
17 G. Raabe and S. Wehrse, RWTH Aachen University, unpublished results.
18 K. J. Hawkes and B. F. Yates, *Eur. J. Org. Chem.*, 2008, 5563.
19 T. Dudding and K. N. Houk, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5770.
20 For a recent review on interactions between aromatic compounds, see: E. A. Meyer, R. K. Castellano and F. Diederich, *Angew. Chem.*, 2003, **115**, 1244 (*Angew. Chem., Int. Ed.*, 2003, **42**, 1210).

