Synthetic Methods

DOI: 10.1002/anie.201202442

Catalytic Asymmetric Cross-Aza-Benzoin Reactions of Aliphatic Aldehydes with N-Boc-Protected Imines**

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The benzoin reaction has been studied for more than a century, since the initial report by Wöhler and Liebig in 1832.[1,2] Nature has long utilized the concept of "umpolung" (reversal of polarity) in the form of thiamine-dependent enzymes, which are required for life.[3] However, a general method for the asymmetric cross-benzoin reaction has not yet been discovered.[4] The inherent problem with this transformation lies in the lack of chemoselectivity between aldehyde partners. A few elegant methodologies have addressed this problem, thus making the synthesis of enantioenriched hetero-benzoin products possible.[5,6]

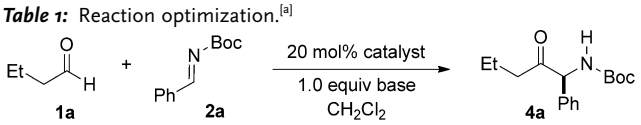
Related to the cross-benzoin reaction of aldehydes is the cross-aza-benzoin reaction of aldehydes and imines.[7] This concept has a variety of advantages. The difference in reactivity between an aldehyde and an imine is inherently greater but can also be tuned because of the trivalency of nitrogen. Furthermore, α-amido ketones represent an important class of medicinal agents and are a synthon for the ubiquitous 1,2-amino-alcohol motif.[8,9]

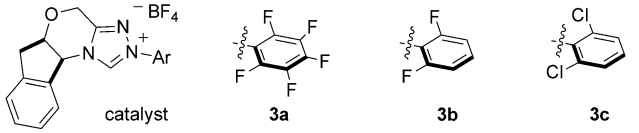
Murry, Frantz, and co-workers reported the first example of an aldehyde–imine cross-benzoin reaction catalyzed by thiazolylidene carbenes, using arylsulfonylamides as imine precursors.[10,11] Later, Miller and co-workers disclosed an asymmetric variant of this work by implementing their peptide-derived thiazolium salt as a precatalyst to deliver aryl aldehyde derived α-amido ketones.[12] They further noted some epimerization of the newly formed stereocenter when they used more activated coupling partners.

The speculation about the reversibility of active catalyst addition to an imine has led to the dogma that slow in situ generation of the imine or attenuation of its electrophilicity would be necessary for catalyst turnover.[13] We have recently disclosed a study of aza-Breslow intermediates derived from the interaction of one of our chiral triazolylidene carbenes with iminium salts.[14] This study showed that addition of these carbene species to an iminium salt is facile and leads to a stable intermediate; however, in the presence of a weak acid this process is highly reversible. We wondered if we could take advantage of this reversibility when electrophilic acyl imines are used as substrates, negating the requirement for a slow addition protocol.

With the assumption that a less activated system would lead to increased stability of the newly formed stereocenter as well as a more synthetically valuable product, we began to evaluate the addition of butanal **1a** to N-Boc-protected imine **2a**. In our study of aza-Breslow intermediates we found acetic acid to be a competent catalyst for the regeneration of the active carbene. Acetate salts have been used as bases in a variety of processes catalyzed by N-heterocyclic carbene (NHC), and their implementation in this system would generate catalytic amounts of the required acid in situ.[15] We were pleased to find that catalyst **3c** in combination with cesium acetate provides the desired α-amido ketone **4a** in good yield (89%) and excellent enantioselectivity (96%; Table 1). Amine bases, such as diisopropylethylamine, are not effective, except when catalytic amounts of acid are added to the reaction.[16] Addition of 4 Å molecular sieves is necessary to suppress imine hydrolysis, likely because of the hygroscopic nature of cesium acetate, while lowering the temperature led to a significant reduction in post reaction epimerization.

Table 1: Reaction optimization.[a]





Entry	Cat.	*T* [°C]	Base	Additive	Yield [%][b]	*ee* [%][c]
1	**3c**	0	iPr_2NEt	none	<5%	n.a.
2	**3c**	0	iPr_2NEt	AcOH	91	90
3	**3c**	0	NaOAc	none	33	99
4	**3c**	−10	CsOAc	4 Å M.S.	83	90
5	**3c**	**−20**	**CsOAc**	**4 Å M.S.**	**89**	**96**
6	**3c**	−25	CsOAc	4 Å M.S.	68	97
7	**3c**	−30	CsOAc	4 Å M.S.	61	98
8	**3a**	−20	CsOAc	4 Å M.S.	38	25
9	**3b**	−20	CsOAc	4 Å M.S.	51	87

[a] Reactions conducted with **1a** (1.5 equiv) and **2a** (1.0 equiv). [b] Yield of isolated product after purification by column chromatography. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. Optimized reaction conditions in bold. Boc = *tert*-butoxycarbonyl, M.S. = molecular sieves, n.a. = not available.

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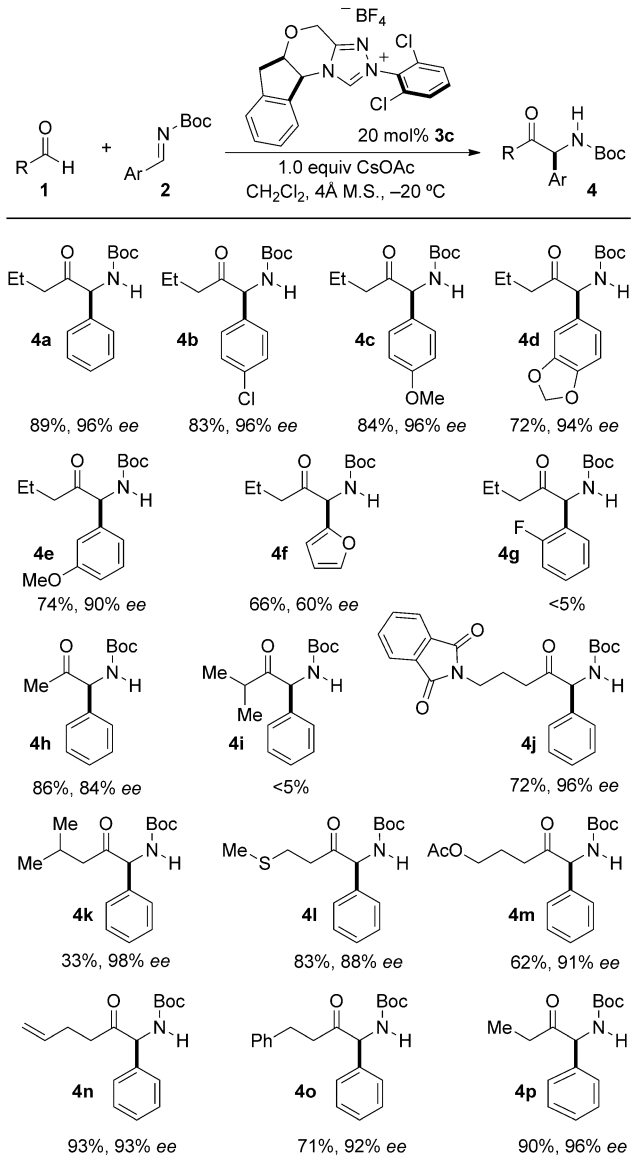
[**] We thank the NGIMS for generous support of this research (GM 72586), and Donald Gauthier (Merck) for a gift of aminoindanol. T.R. thanks Amgen and Roche for support. Boc = *tert*-butoxycarbonyl.

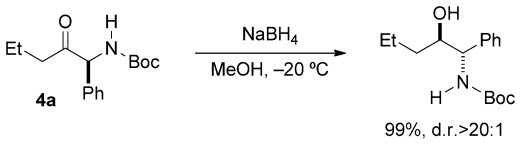
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202442.

With an efficient catalyst system in hand, we evaluated the scope of this transformation (Scheme 1). A variety of aliphatic aldehydes, which contained a diverse range of functionality, were examined. Straight-chain aldehydes produced the desired products in high yield (71–93%) and excellent enantioselectivity (84–93% *ee*), while β-branched aldehydes gave the desired products with excellent enantioselectivity (98% *ee*), but in lower yields (33%).[17] Heteroatoms could be incorporated into the tether without deleterious impact on yield or enantioselectivity, thus allowing the incorporation of functionality, such as thioethers, imides, and esters. Currently, α-branched aldehydes do not participate in the reaction. The scope of the imine partner was assessed by using N-Boc-protected imines of varying electronic nature. Electron-rich and electron-poor aryl derivatives gave the products in comparable yields (72–74%), despite some small variation in enantioselectivity (90–94% *ee*). The common methylenedioxyphenyl motif could be incorporated with high selectivity (94% *ee*); heterocycles, such as furan, could also be incorporated, but with lower selectivity (60% *ee*). *Ortho*-substituted aryl derivatives led to an unexpected loss of reactivity.



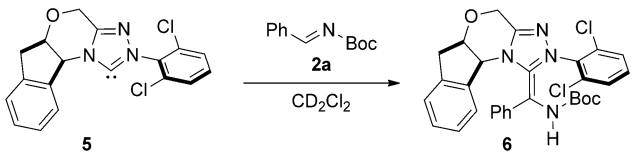
Scheme 1. Reaction scope. Reactions conducted with 1.5 equiv **1** and 1.0 equiv **2**. Yields of isolated products after column chromatography. Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase. Absolute stereochemistry of products assigned by analogy; see the Supporting Information.

The α-amido ketone products are useful intermediates in the synthesis of 1,2-aminoalcohols. Reduction of **3a** provided the anti-1,2-aminoalcohol as the sole diastereomer in quantitative yield (Scheme 2).[18]



Scheme 2. Diastereoselective reduction of amidoketones.

Upon devoloping an efficient catalyst system, we were interestested in probing the interaction between N-Boc-protected imines and our active carbene to gain further evidence for the reversible formation of an aza-Breslow intermediate in the catalytic cycle. Subjection of precatalyst **3c** to an excess of KO*t*Bu shows clean formation of carbene **5** by ^{1}H NMR spectroscopy. Addition of 1.0 equivalent of N-Boc-protected imine **2a** immediately produces a bright yellow solution and shows the formation of a new species, which was assigned as aza-Breslow intermediate **6** by ^{1}H NMR spectroscopy and HRMS (Scheme 3).[19] To test the reversibility of this process under the reaction conditions, **6** was treated with an excess of AcOH, leading to the regeneration of a colorless solution. ^{1}H NMR analysis confirmed the disappearance of intermediate **6** but neither carbene **5** nor imine **2a** could be identified, thus suggesting that the carbene may not be the resting state under these conditions.[20]



Scheme 3. NMR Studies of catalyst–substrate interaction.

In conclusion, we have developed a highly enantioselective cross-aza-benzoin reaction of aliphatic aldehydes and N-Boc-protected imines. This transformation provides access to useful 1,2-amino alcohol synthons in a single step. Crucial insight pertaining to the reversible formation of aza-Breslow intermediates in the catalytic cycle has enabled the direct implementation of highly reactive imines as substrates, thus negating the requirement for a slow-addition protocol.

Experimental Section

Triazolium salt precatalyst **3c** (26 mg, 0.058 mmol, 0.2 equiv), cesium acetate (55 mg, 0.29 mmol, 1.0 equiv), activated molecular sieves (4 Å, 8–12 mesh, 5–10 beads) and dichloromethane (1.5 mL) were added to a dry 4 mL vial equipped with a magnetic stirrer bar. Under constant stirring, the vial was placed in a cooling bath (−20 °C) and purged with argon. After 5 min, the aldehyde (0.43 mmol, 1.5 equiv) was added through a syringe, followed by a solution of the imine (0.28 mmol, 1.0 equiv) in dichloromethane (0.5 mL). The reaction was stirred at −20 °C for 24 h, then acetic acid (50 μL) was added, and the mixture was directly purified by column chromatography on silica gel with a mixture of hexanes:EtOAc (typically 20:1). The desired amido-ketone was obtained as a white amorphous solid.

Received: March 29, 2012
Published online: ■■ ■■, ■■■■

Keywords: benzoin reaction · carbenes · imines · organocatalysis · umpolung

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Communications

Synthetic Methods

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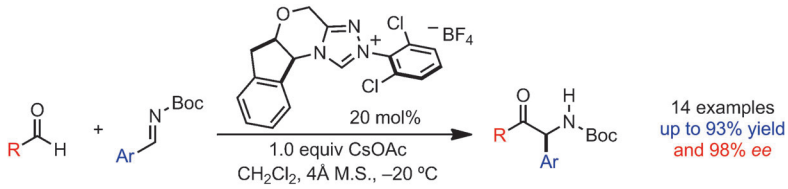

Crossed: A catalyst system has been developed that allows the direct asymmetric coupling of aliphatic aldehydes and N-Boc-protected imines in a cross-aza-benzoin reaction (see scheme; Boc = *tert*-butoxycarbonyl). The active catalyst is shown to react rapidly with the imine, however, the presence of an acid as co-catalyst renders this process reversible and allows the regeneration of the catalyst.

