Aminocatalysis Hot Paper

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The Catalytic Asymmetric α-Benzylation of Aldehydes**

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Dedicated to Professor Johann Mulzer

Abstract: *The first aminocatalyzed α-alkylation of α-branched aldehydes with benzyl bromides as alkylating agents has been developed. Using a sterically demanding proline derived catalyst, racemic α-branched aldehydes are reacted with alkylating agents in a DYKAT process to give the corresponding α-alkylated aldehydes with quaternary stereogenic centers in good yields and high enantioselectivities.*

Asymmetric S_N2 α-alkylations of carbonyl compounds with alkyl halides are powerful transformations that commonly involve chiral auxiliaries and phase-transfer catalysts.[1] Recently, however, organocatalysis has significantly advanced this area by providing new strategies for the direct catalytic asymmetric α-alkylation of aldehydes.[2] For example, our group has described an intramolecular α-alkylation reaction of haloaldehydes using proline-based enamine catalysis.[3] Subsequently, other groups have contributed additional aminocatalytic methods for the asymmetric α-alkylation of aldehydes, including strategies that combine enamine catalysis with radical or cationic (S_N1) reaction pathways.[4–13] Despite these unquestionable advancements though, the asymmetric intermolecular S_N2 α-alkylation of aldehydes with simple alkyl halides has remained a long-standing challenge for enamine catalysis (Scheme 1).[2]

Here we report progress with the first catalytic enantioselective α-benzylation of α-branched aldehydes. We have developed a new bicyclic proline analogue that catalyzes this reaction, delivering aldehydes with a quaternary center in α-position in high enantioselectivity.

Scheme 1. The catalytic asymmetric α-alkylation of aldehydes: A challenge for enamine catalysis.

A main difficulty in the aminocatalytic intermolecular α-alkylations of aldehydes with S_N2-type alkylating agents is the tendency of inherently Lewis basic amine catalysts to undergo N-alkylation. This process is normally irreversible and results in the complete deactivation of the aminocatalyst, at least unless S_N1-reactive benzhydryl-type alkylating reagents are utilized. The unproductive catalyst-alkylation reaction is further enhanced by the stoichiometric base, which is added to neutralize the strong acid formed in the α-alkylation, and which in principle can also be alkylated itself. The tendencies of aldehydes to undergo self-aldolization and racemization provide for additional complications.

After exploring several different and yet more or less unsuccessful strategies over the years, we hypothesized that a direct asymmetric aldehyde alkylation may be realizable, if α-branched aldehydes are utilized, as the corresponding products are stable and do not undergo racemization and, if an organic mixed acid/base "buffer" system is used instead of a base alone. Such a reaction medium was expected 1) to accelerate enamine formation through mild acid catalysis, 2) to "neutralize" the acid by-product, and 3) to suppress the alkylation of base and/or catalyst. It has been shown previously that mixtures of acids and bases can be beneficial in related S_N1 alkylations.[12]

Indeed, when we reacted hydratropaldehyde (**1a**) with benzyl bromide (**2a**) in the presence of (*S*)-proline (**3a**, 50 mol %) and a combination of both *p*-anisidic acid and Hünig's base (diisopropylethylamine, $i\mathrm{Pr}_2\mathrm{NEt}$), the desired product **4a** could be detected for the first time (Table 1, entry 1). Essentially no product was obtained in the absence of buffer and with acid or base alone. While both yield (12 %) and enantioselectivity (51:49 e.r.) were poor and a significant amount of N-benzylated (*S*)-proline was still formed as a side product, we were encouraged by this result. A broader screen of aminocatalysts towards improving the enantioselectivity and yield was therefore initiated. We investigated various types of organocatalysts, of which selected examples are summarized in Table 1. In contrast to what we found previously in our intramolecular variant, the use of (*S*)-α-methylproline **3b** as catalyst did not result in improved yield or enantioselectivity (Table 1, entry 2). Imidazolidinone catalysts such as **3c**[14] and prolinol ether catalyst **3d**[15] proved to be ineffective in catalyzing this reaction (Table 1, entries 3 and 4). (*S*)-Proline derivative **3e** and primary amino acids

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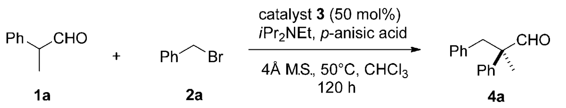
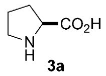
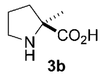
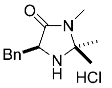
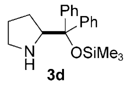
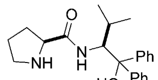
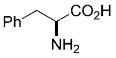
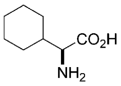
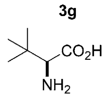
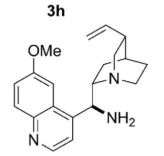
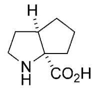
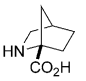
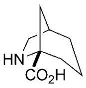
Table 1: Catalyst evaluation.[a]



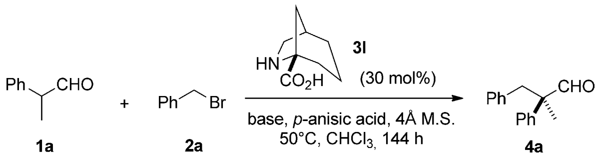
Entry	Catalyst	Yield [%][b]	e.r.[c]
1	 **3a**	12	51:49
2	 **3b**	10	51:49
3	 **3c**	n.r.	–
4	 **3d**	n.r.	–
5	 **3e**	65	80:20
6	 **3f**	52	60:40
7	 **3g**	46	79.5:20.5
8	 **3h**	55	86.5:13.5
9	 **3i**	n.r.	–
10	 **3j**	20	62.5:37.5
11	 **3k**	22	90.5:9.5
12	 **3l**	25	93.5:6.5

[a] Unless otherwise noted, reactions were conducted with aldehyde **1a** (0.1 mmol) and benzyl bromide **2a** (0.3 mmol), catalyst **3** (0.05 mmol), *i*Pr₂NEt (0.3 mmol), *p*-anisic acid (0.3 mmol), 4 Å M.S. (80 mg) in chloroform (0.5 mL) at 50 °C for 120 h. [b] Determined by GC-MS using *n*-dodecane as an internal standard. [c] Determined by GC analysis on a chiral stationary phase. n.r.: no reaction.

3f–h gave moderate yields but promising enantioselectivities (Table 1, entries 5–8). A cinchona-derived primary amine catalyst (**3i**) was found to be inactive in the reaction (Table 1, entry 9). This catalyst rapidly reacts with benzyl bromide and N-benzylated amines were detected by GC-MS analysis. In a theoretical study, azabicyclic proline analogues were predicted to give higher selectivities than simple proline in aldol reactions, due to better preorganization of the transition state and we reasoned that this might also be of help for our α-alkylation reaction.[16] Indeed, very interesting results were obtained when we tested the sterically more demanding secondary amino acid catalysts **3j–l** (Table 1, entries 10–12). High enantioselectivity (93.5:6.5 e.r.) was observed in the presence of catalyst **3l** even though the product was obtained in modest yield (Table 1, entry 12). Amino acid **3l** was developed by the group of Komarov in 2006,[17] but had not previously been investigated in asymmetric catalysis.

With these intriguing results in hand, we were curious whether real turnover could be accomplished by optimizing the reaction conditions. In earlier studies, we found that the added base has a pronounced effect on both the reactivity and stereoselectivity in the α-alkylation of aldehydes. Therefore, different bases were investigated and selected examples are summarized in Table 2.

Table 2: Influence of the base.[a]



Entry	Base	Yield [%][b]	e.r.[c]
1	DMAP	30	65:35
2	imidazole	33	61:39
3	DBU	20	79:21
4	1,3-diphenylguanidine	60	88:12
5	1,3-di-(*o*-tolyl)guanidine	63	90:10
6	*1,1,3,3-tetramethylguanidine*	*80*	*95.5:4.5*
7	2′,2′-(naphthalene-1,8-diyl)-bis(1,1,3,3-tetramethylguanidine)	80	53:47

[a] Reaction conditions: aldehyde **1a** (0.1 mmol) and benzyl bromide **2a** (0.5 mmol), catalyst **3l** (0.03 mmol), *p*-anisic acid (0.5 mmol), base (0.5 mmol), 4 Å M.S. (80 mg) in chloroform (0.5 mL) at 50 °C for 144 h. [b] Determined by GC-MS using *n*-dodecane as an internal standard. [c] Determined by GC analysis on a chiral stationary phase. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine.

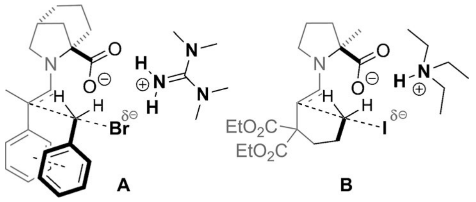
Gratifyingly, after an extensive screening of various bases (see the Supporting Information for more details), we found the addition of guanidines to be beneficial (Table 2, entries 4–7). In particular, 1,1,3,3-tetramethylguanidine not only gave some turnover but also did so with an even improved e.r. > 95:5 (Table 2, entry 6).

We also explored various acids as additives and found that *p*-anisic acid consistently gave the best results (see the Supporting Information). It is noteworthy that a significant improvement in yield and enantioselectivity was achieved when we used an excess of tetramethylguanidine, *p*-anisic acid, and benzyl bromide (5 equivalents each) under the optimized reaction conditions.[18]

After identifying a suitable catalyst and establishing optimized reaction conditions, we next investigated the scope of our catalytic asymmetric α-alkylation of α-branched aldehydes (Table 3). The reaction turned out to be tolerant of both electron-deficient and electron-rich aromatic substrates. The desired products were obtained in moderate to good yields (55–82 %) and high enantioselectivities (e.r. up to 98.5:1.5). α-Branched aldehydes that possess *meta* or *para* substituents on the aromatic structure furnish the corresponding alkylated products in good yields and enantioselectivities (Table 3, entries 2–11 and 17). In general, the reaction takes place slowly at 50 °C. However, with aldehyde **1d** and electrophile **2j**, the reaction could be carried out at lower temperature (Table 3, entries 5–7 and 14–16). Excellent enantioselectivities were observed in both cases (up to 98.5:1.5 e.r. with **1d** and 97.5:2.5 e.r. with **2j**). Unfortunately, aliphatic aldehydes did not lead to product formation under our reaction conditions. We also attempted using linear aldehydes as substrates. However, in this case no desired product could be isolated. A GC-MS analysis of the crude reaction mixture revealed the predominant formation of products resulting from double alkylation and self-aldolization.

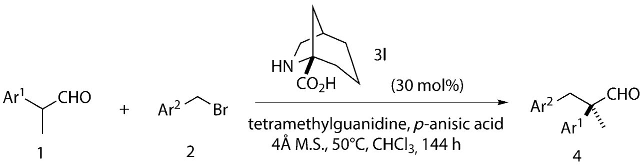
The absolute configuration of product **4a** was determined to be *R* by comparison of the optical rotation with the literature value.[19] The absolute configuration is consistent with the proposed transition state **A** (Scheme 2). In previous DFT-based calculation studies on the asymmetric intramolecular α-alkylation of aldehydes,[20] we showed that the base-assisted reaction is more facile and exhibits a different stereoselectivity. In the corresponding transition state **B**, the added base is present as a trialkylammonium carboxylate, which activates the leaving group in the S_N2-type nucleophilic substitution, by providing an electrostatic stabilization of the developing negative charge at the halide. Based on this study, we propose the analogous transition state **A** for the intermolecular α-alkylation of α-branched aldehydes, which may be further stabilized by π–π interactions.[21]

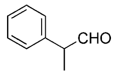
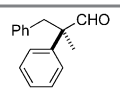
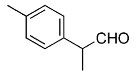
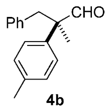
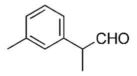
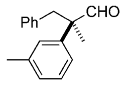
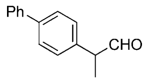
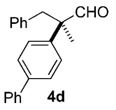
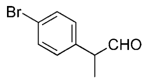
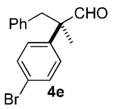
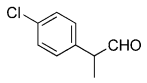
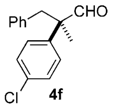
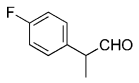
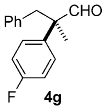
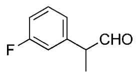
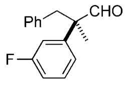
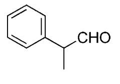
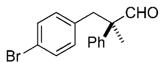
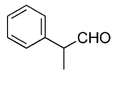
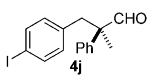
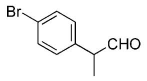
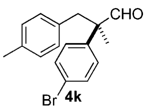
In conclusion, we have developed the first catalytic asymmetric α-alkylation of α-branched aldehydes using simple alkylating agents via enamine catalysis. Racemic α-branched aldehydes can be converted into the corresponding enantiomerically enriched products with e.r. values of up to 98.5:1.5 in a dynamic kinetic asymmetric transformation (DYKAT). Our reaction also features a new sterically demanding proline-derived catalyst, which can be easily synthesized in both enantiomeric forms and which may be of use in other challenging asymmetric reactions.



Scheme 2. Proposed transition state **A** of the intermolecular α-alkylation. Calculated transition state **B** of the intramolecular α-alkylation.

Table 3: Substrate scope.[a]



Entry	Substrate **1**	Product **4**	Yield [%]	e.r.[b]
1	 **1a**	 **4a**	80	95.5:4.5
2	 **1b**	 **4b**	82	95:5
3	 **1c**	 **4c**	77	95:5
4	 **1d**	 **4d**	70	92:8
5[c]			65	95:5
6[d]			60	97.5:2.5
7[e]			60	98.5:1.5
8	 **1e**	 **4e**	72	90:10
9	 **1f**	 **4f**	71	91:9
10	 **1g**	 **4g**	70	86:14
11	 **1h**	 **4h**	68	84:16
12	 **1a**	 **4i**	80	94:6
13	 **1a**	 **4j**	80	91.5:8.5
14[c]			75	93.5:6.5
15[f]			65	95:5
16[d]			55	97.5:2.5
17	 **1e**	 **4k**	65	88:12

[a] Reaction conditions: Aldehyde **1** (0.5 mmol), benzyl bromide **2** (2.5 mmol), catalyst **3l** (0.15 mmol), *p*-anisic acid (2.5 mmol), base (2.5 mmol), 4 Å M.S. (400 mg) in chloroform (2.5 mL) at 50 °C for 144 h. [b] Determined by GC or HPLC analysis on a chiral stationary phase. [c] At RT. [d] At 0 °C for 168 h. [e] At −15 °C for 168 h. [f] At 20 °C for 168 h.

Experimental Section

General procedure for the catalytic asymmetric α-alkylation of α-branched aldehydes: The catalyst **31** (0.15 mmol, 0.3 equiv) and *p*-anisic acid (2.5 mmol, 5 equiv) were dissolved in $CHCl_3$ (0.2 M) and 4 Å molecular sieves (400 mg) were added. The starting aldehyde (0.5 mmol, 1 equiv) was added to the solution followed by the alkylating agent (2.5 mmol, 5 equiv). Tetramethylguanidine (2.5 mmol, 5 equiv) was added at the end. The mixture was stirred at the optimized temperature. After stirring for 144 h, the reaction mixture was left at or allowed to come to RT and poured into water and the aqueous phase was extracted with EtOAc. The organic fractions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-pentane/*t*BuOMe, 95:5 to 85:15) afforded compounds **4a**–**4k**.

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Keywords: α-alkylation · α-branched aldehydes · DYKATt · enamine catalysis · organocatalysis

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