Aminocatalysis

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The Catalytic Asymmetric Knoevenagel Condensation**

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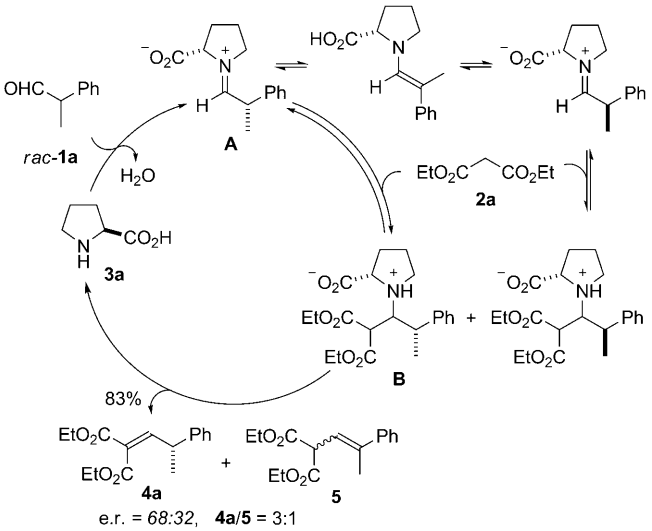
The Knoevenagel condensation[1] is a powerful, general, and frequently used reaction for the formation of carbon–carbon bonds, but is also the archetype of modern organocatalysis.[2] Surprisingly, however, despite its long history and numerous industrial applications, there has not been a single example of an asymmetric variant, neither by using chiral auxiliaries nor catalysts. Here we report an asymmetric Knoevenagel condensation that proceeds through dynamic kinetic resolution of α-branched aldehydes and is catalyzed by a newly designed and readily available cinchona-derived primary amine catalyst.

Recent progress in asymmetric aminocatalysis has led to several highly useful transformations, including aldol, Mannich, and Michael reactions, α-alkylations, α- and β-functionalizations, Diels–Alder reactions, transfer hydrogenations, epoxidation reactions, and many more.[3] Remarkably though, while the Knoevenagel reaction, as the historic basis of all these processes, has been incorporated into asymmetric organocascades and domino reactions,[4] and even malonates derived from chiral auxiliaries have been studied,[5] a variation in which the Knoevenagel reaction itself is utilized to establish asymmetry has remained elusive.

The lack of previous catalytic and stoichiometric asymmetric Knoevenagel condensations may be partly due to the absence of apparent stereogenic elements created in the process. An asymmetric version should nonetheless be realizable. Recently, we designed several catalytic enantioselective reactions that are based on nucleophilic additions to chiral, α-branched aldehydes through dynamic kinetic resolution (DKR).[6] Encouraged by these studies, we envisioned an extension of our DKR strategy to the Knoevenagel reaction.[7]

At the onset we hypothesized that Knoevenagel conditions could be established under which α-branched aldehydes such as hydratropaldehyde (**1a**) would readily undergo racemization in the presence of an aminocatalyst such as proline,[8] via an equilibrium between an iminium ion and an enamine. An enantioselective reaction with DKR could then be realized if the intermediary diastereomeric iminium ions **A** or Mannich products **B** (if generated reversibly) reacted with different rates to give the Knoevenagel product (Scheme 1).



Scheme 1. A proline-catalyzed asymmetric Knoevenagel reaction.

In the event we found that proline (**3a**) indeed catalyzes the reaction of hydratropaldehyde (**1a**) with diethylmalonate (**2a**) to furnish the corresponding Knoevenagel product **4a** in good yield and moderate enantioselectivity (68:32), which in principle confirms our kinetic resolution hypothesis. However, in addition to the moderate enantioselectivity, the previously observed formation of significant amounts of the isomeric olefin by-product **5** complicated the situation even further. A broader screen of aminocatalysts to improve the enantioselectivity and product **4a**/**5** ratio was, therefore, initiated.

We investigated various types of aminocatalysts, of which selected examples are summarized in Table 1. In contrast to proline (entry 1), imidazolidinone catalysts such as **3b**[3d] and prolinol catalyst **3c** proved to be essentially ineffective in catalyzing this reaction (entries 2 and 3).[9] Pyrrolidine-derived catalyst **3d** was found to be active, but the enantioselectivity was only slightly improved compared to proline and the olefin/isomer ratio was still only 62:38 (entry 4). We next focused on primary amine catalysts. Diamine **3e** was tested, but unfortunately by-product **5** was now obtained as the major product (entry 5). Since amine **3e** turned out to be quite active, we also screened different primary amine catalysts derived from cinchona alkaloids (entries 6–13).[10] Although quinidine derivative **3f** gave the desired product **4a** in reasonable yield and significantly improved **4a**/**5** ratio, the enantioselectivity was still only moderate (entry 6). An improvement in the enantioselectivity was observed with quinine derivative **3j** (entry 10), which provided product **4a**

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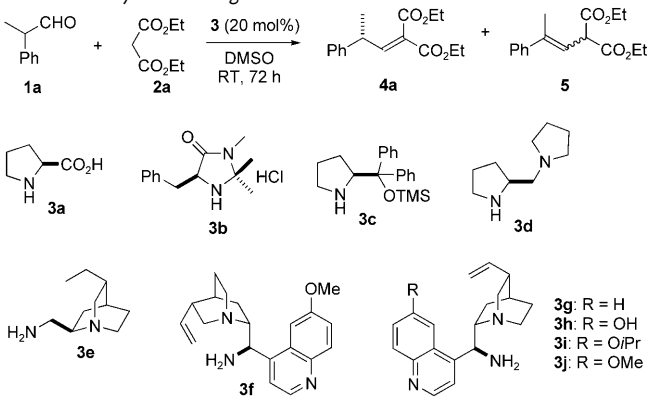
Table 1: Catalyst screening.[a]



Entry	Catalyst	Yield [%][b]	**4a**/**5**[b]	e.r.[c]
1	**3a**	83	73:27	68.0:32.0
2	**3b**	–	–	–
3	**3c**	8	n.d.	n.d.
4[d,e]	**3d**	91	62:38	72.0:28.0
5	**3e**	97	4:96	n.d.
6	**3f**	34	93:7	23.0:77.0
7	**3g**	51	77:23	78.0:22.0
8	**3h**	63	57:43	82.0:18.0
9	**3i**	60	60:40	82.0:18.0
10	**3j**	61	52:48	84.0:16.0
11[f]	**3j**	54	52:48	92.5:7.5
12[f,g]	**3j**	80	95:5	92.0:8.0
13[h]	**3j**	90	98:2	94.0:6.0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst **3** (0.02 mmol), DMSO (1.0 mL), RT, 72 h. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 10 mol% catalyst was used. [e] Reaction was carried out for 20 h. [f] 60 mol% benzene-1,3,5-tricarboxylic acid was added. [g] 30 equivalents of **2a** were used. [h] Reaction conditions: **1a** (0.1 mmol), **2a** (5.0 mmol), catalyst **3j** (0.01 mmol), benzene-1,3,5-tricarboxylic acid (0.06 mmol), DMSO (1.0 mL), 20°C, 168 h.

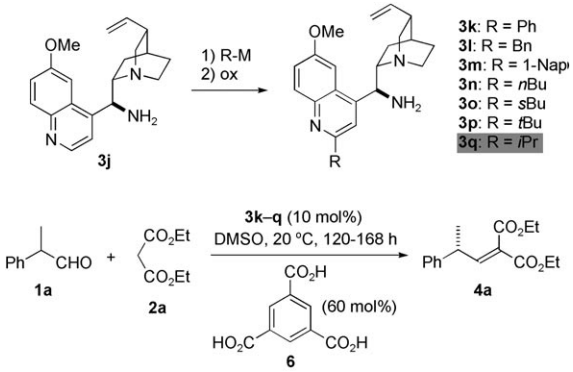
with an enantiomeric ratio of 84:16; this catalyst was, therefore, selected for further optimization.

During these studies (see the Supporting Information for details) we found the addition of 60 mol% benzene-1,3,5-tricarboxylic acid to be beneficial, with the enantiomeric ratio improving to 92.5:7.5 (entry 11). However, the yield was only moderate (54%) and the ratio of the desired product **4a** to by-product **5** was still disappointing (52:48). A significant improvement in yield and selectivity was realized when we used an excess of diethylmalonate **2a** (30 eqiuv). The desired product **4a** was obtained in 80% yield with an excellent **4a**/**5** selectivity (95:5) and good enantioselectivity (e.r. = 92:8) at room temperature (entry 12). Optimized conditions were then established by using 50 equivalents of diethylmalonate, which improved the yield and selectivity even further (entry 13).

However, despite these enhancements in enantiomeric ratio, and especially the isomeric ratio of the olefins, we were still curious if the reaction could be further improved through systematic modification of the catalyst. Such modifications of cinchona-based catalysts have mostly been limited to N-alkylyation of quinuclidine, O-alkylation of alcohols, and demethylation of quinoline.[11] Recently, Hintermann et al. described an interesting new modification of the cinchona skeleton, in which the 2′-position of the quinoline ring can be alkylated upon the addition of organometallic reagents, followed by an in situ oxidation.[12]

We were pleased to find that this method can easily be extended with similar efficiency to the corresponding amino-cinchona catalysts, specifically to compound **3j**. Accordingly, simply treating quinoline **3j** with different organolithium and Grignard reagents, followed by an in situ reoxidation, provided analogues **3k–q** in moderate to good yields. Remarkably, even sterically demanding reagents such as *tert*-butyllithium could be added without difficulty (Table 2, see also the Supporting Information for details).

Table 2: Knoevenagel reaction using novel catalysts.[a]



Entry	Catalyst	Yield [%][b]	e.r.[c]
1	**3k**	87	95.5:4.5
2	**3l**	89	91.0:9.0
3	**3m**	85	95.0:5.0
4	**3n**	92	95.0:5.0
5	**3o**	91	95.0:5.0
6	**3p**	86	94.5:5.5
7	**3q**	91	95.5:4.5

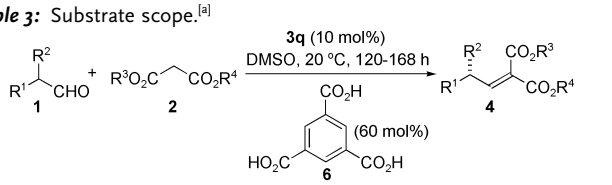
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (5.0 mmol), catalyst **3** (0.01 mmol), benzene-1,3,5-tricarboxylic acid (0.06 mmol), DMSO (1.0 mL), 20°C, 120–168 h. In all cases, only traces of by-product **5** were detected by GC-MS. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

Upon testing the newly synthesized catalysts in our model reaction we were delighted to obtain product **4a** in generally high enantioselectivity (e.r. up to 95.5:4.5) and very good yield (85–92%, Table 2). Among the investigated catalysts, amine **3q** proved to be the most promising one, also with different substrates, and was therefore chosen for our further studies.

The screening experiments of different substrates in the presence of the novel catalyst **3q** under our optimized conditions are summarized in Table 3. Diverse substituted α-branched aromatic and aliphatic aldehydes were applied to the reaction with diethylmalonate under these conditions (Table 3, entries 1–11).

The reaction turned out to be tolerant of both electron-deficient and electron-rich aromatic substrates, and the products were obtained in good yields (81–92%) and enantioselectivities (e.r. up to 95.5:4.5). 2-Phenylbutanal can

Table 3: Substrate scope.[a]



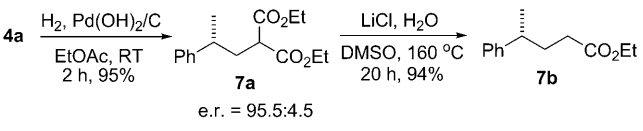
Entry	R^1	R^2	R^3	R^4	Product	Yield [%][b]	e.r.[c]
1	Ph	Me	Et	Et	**4a**	91	95.5:4.5
2	4-OMeC_6H_4	Me	Et	Et	**4b**	81	87.0:13.0
3	4-MeC_6H_4	Me	Et	Et	**4c**	87	93.5:6.5
4	4-ClC_6H_4	Me	Et	Et	**4d**	86	93.5:6.5
5	2-FC_6H_4	Me	Et	Et	**4e**	90	89.5:10.5
6	3-FC_6H_4	Me	Et	Et	**4f**	91	93.5:6.5
7	4-FC_6H_4	Me	Et	Et	**4g**	92	94.5:5.5
8	3-MeC_6H_4	Me	Et	Et	**4h**	90	95.0:5.0
9	Ph	Et	Et	Et	**4i**	91	91.5:8.5
10	*c*-C_6H_{11}	Me	Et	Et	**4j**	92	60.0:40.0
11	4-*i*Pr$C_6H_4CH_2$	Me	Et	Et	**4k**	90	52.5:47.5
12	Ph	Me	Me	Me	**4l**	97	94.5:5.5
13	Ph	Me	*n*Pr	*n*Pr	**4m**	96	95.0:5.0
14	Ph	Me	*n*Bu	*n*Bu	**4n**	96	94.5:5.5
15[d]	Ph	Me	Bn	Et	**4o**	94	93.5:6.5 92.5:7.5
16	Ph	Me	Bn	Bn	**4p**	84	90.5:9.5

[a] Reaction conditions: **1** (0.2 mmol), **2** (10.0 mmol), catalyst **3q** (0.02 mmol), additive **6** (0.12 mmol), DMSO (2.0 mL), 20°C, 120–168 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Product **4o** (*E*/*Z* = 1:1), measured by HPLC analysis.

also be used, and leads to the formation of α-ethyl-branched alkylidene malonate **4i** in good yield and enantiomeric ratio (Table 3, entry 9). Aliphatic aldehydes are also suitable substrates in the dynamic kinetic resolution, although the enantiomeric ratios are significantly lower (Table 3, entries 10 and 11).

We also explored a variety of different malonates in the reaction with 2-phenylpropanal (Table 3, entries 12–16). In all cases, good to excellent yields (84–97%) were observed and the products were obtained with high enantioselectivities. Benzylethylmalonate gave *E* and *Z* products as a 1:1 mixture, both in high enantioselectivity (entry 15).

To illustrate the utility of our reaction products compound **4a** was converted into (*R*)-ethyl-4-phenylpentanoate (**7b**) by a hydrogenation and a Krapcho reaction sequence (Scheme 2). The absolute configuration of product **4a** was determined to be *R* after transformation to 2-phenyl-1-propanol by ozonolysis followed by reductive work up and comparison of its GC retention time on a chiral stationary phase (see the Supporting Information).



Scheme 2. Synthetic utility of product **4a**.

In conclusion, we have developed the first catalytic asymmetric Knoevenagel condensation. Racemic α-branched aldehydes can be converted in a dynamic kinetic resolution into the corresponding enantiomerically enriched products with enantiomeric ratios of up to >95:5 . Our reaction also features a new cinchona amine catalyst, which can be easily synthesized and which may be of use for other catalysts and reactions.

Experimental Section

General procedure for the catalytic asymmetric Knoevenagel condensation reaction: The catalyst **3q** (0.02 mmol, 0.1 equiv) and additive **6** (0.12 mmol, 0.6 equiv) were dissolved in DMSO (2.0 mL). The solution was cooled to 20°C and **1a** (0.2 mmol, 1 equivalent) was added. The reaction mixture was stirred for 10 min and then **2a** (10.0 mmol, 50 equiv) was added at the same temperature. After stirring the reaction mixture for 120–168 h it was poured into water (3 mL) and extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on silica gel (*n*-pentane/diethyl ether, 90:10) afforded **4a** as a colorless oil (91% yield).

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