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Asymmetric aldol addition of α-azido ketones to ethyl pyruvate mediated by a cinchona-based bifunctional urea catalyst

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Dedicated to the memory of Prof. Dr. Ayhan S. Demir

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ABSTRACT

The first asymmetric synthesis of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates via a cinchona organocatalyst induced aldol addition of α-azido ketones to ethyl pyruvate has been developed. The coupling reaction under optimized conditions was carried out to furnish tetrafunctionalized synthons with enantioselectivities of up to 91:9 and enriched diastereoselectivities of up to 95:5 (*syn*:*anti*).

Undoubtedly, the aldol reaction is a powerful tool for the construction of complex molecules with new stereogenic centers.[1] In asymmetric organocatalytic aldol reactions, stereoselective C–C bond formation is enhanced by using a catalytic amount of a chiral promoter in an atom economical fashion.[2] Enantiomerically pure or diastereomerically enriched chiral aldol products are important not only for modern synthetic chemistry, but are also very important in nature.[1]

α-Azido ketones have highly acidic α-protons due to the anion-stabilizing effect of the azide functionality. Their base-promoted deprotonation leads to formation of a carbanion intermediate, which readily reacts with an electrophilic carbonyl moiety.[3]

Aldol addition of α-azido ketones to ethyl pyruvate allows the synthesis of ethyl 2-azido-3-hydroxy-1,4-diones, which are valuable tetrafunctionalized synthons.[4] The different functionalities present in such compounds make them potential precursors for the synthesis of α-amino ketones,[5] azido alcohols,[6] 1,2-amino alcohols,[7] and 1,2,3-triazoles.[8] Besides allowing many transformations, such compounds are also important due to their having a tertiary alcohol moiety. Chiral tertiary alcohols and α-hydroxyesters comprise essential components and building blocks for many bioactive natural products.[9,10]

Patonay and co-worker have demonstrated trapping of the corresponding carbanion intermediate from α-azido ketones with various carbon electrophiles such as aldehydes, ketones, α-oxo aldehydes, and α-keto esters in the presence of DBU as a base.[4] Recently, the highly enantioselective aldol reaction between azidoacetone and aromatic or heteroaromatic aldehydes catalyzed by a cooperative proline-guanidinium salt catalyst system was reported.[11] Additionally, Barbas and co-workers have obtained a high enantiocontrol in the direct asymmetric Mannich reaction of α-azido ketones in the presence of an L-proline-derived tetrazole catalyst.[12] Among these, the reaction of phenacyl azides with ethyl pyruvate resulted in tetrafunctionalized ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates, but only the 4-(4-methoxyphenyl) derivative could be isolated. The failure to isolate other derivatives was attributed to a rapid retro-aldol reaction due to the hindrance around the stereogenic methine carbon. Also, the diastereoselectivity of the isolated derivative was low with a diastereomeric ratio of 67:33 (*syn*:*anti*).[4,13]

In this contribution, our challenge was to overcome isolation issues, together with enhancement of the diastereoselectivity and enantioselectivity. For this purpose, we explored the efficiency of cinchona alkaloids in asymmetric aldol reactions (Scheme 1).

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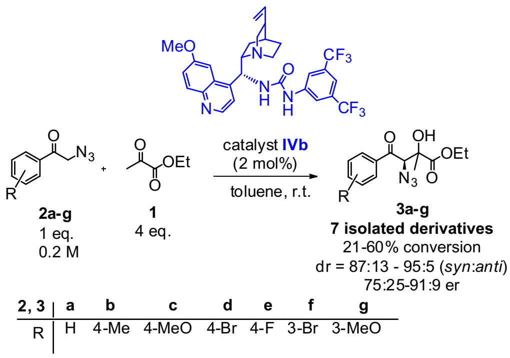


Scheme 1. Current work.

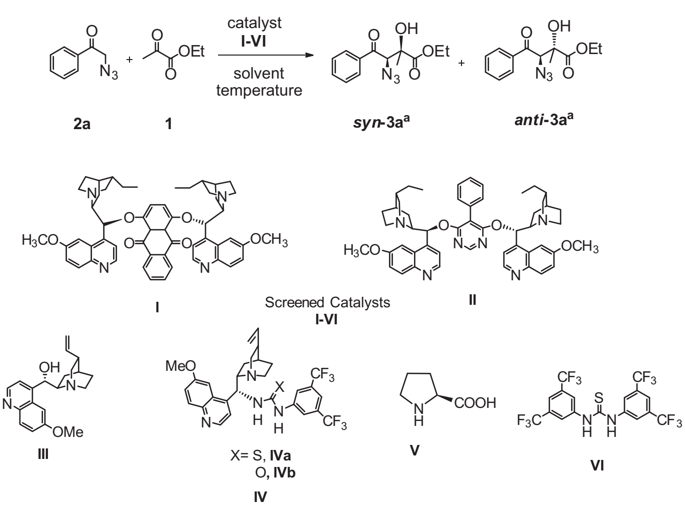
Cinchona alkaloids are well-known naturally occurring catalysts with a Brønsted basic quinuclidine nitrogen and having a wide range of applications in many relevant transformations.[14] Inspired by the competitive use of cinchona alkaloids in various aldol reactions,[15] and the study of Barbas,[12] we surveyed catalysts **I**–**VI** in the reaction of phenacyl azide and ethyl pyruvate (Table 1, entries 1–8).

Although enantiomeric excess was observed in the presence of C_2 symmetric catalysts **I** and **II**, it was relatively low compared to bifunctional catalysts **IVa**, **b**.[16] The reaction yielded aldol adduct **3a** in poor conversion, but with somewhat better stereoselectivity in the presence of bifunctional cinchona-(thio)urea catalysts **IVa**, **b** (entries 4 and 5). The poor enantioselectivity obtained in the presence of **III** supports the enhancement of selective substrate binding via the hydrogen bond donor (thio)urea moiety. Considering the study of Barbas,[12] L-proline and its combination with **IVb** and achiral thiourea **VI** were also tested, however, these trials gave inferior results in terms of conversion and enantioselectivity besides leading to faster retro-aldol reactions as well (entries 7–9). Choosing **IVb** as the best catalyst, parameters such as the solvent, molarity, catalyst loading, and temperature were investigated to find the optimum conditions (entries 9–16).

Though polar aprotic solvents such as dichloromethane and chloroform resulted in higher conversions, the enantioselectivity was lower than that obtained in toluene. Toluene also led to both higher conversions and enantiomeric ratios than when using acetonitrile. Of the solvents screened, toluene proved to be the best in terms of selectivity (entries 9–11).[17]

At this stage, we established that the prolonged reaction times might have caused a decrease in the diastereomeric ratio due to epimerization of product **3a** and/or a possible retro-aldol reaction.

Table 1
Screening of the catalyst and reaction conditions for the aldol reaction



Entry[a]	Catalyst	Eq. of **1**	Molarity of **2a**	Solvent	Cat. loading (mol %)	Time (h)	Conversion (%)[c]	dr[c] *syn:anti*	er[d] *syn*
1	**I**	4	0.55 M	CH_3CN	10	48	92	76:24	35:65
2	**II**	4	0.55 M	CH_3CN	10	48	93	75:25	36:64
3	**III**	4	0.55 M	CH_3CN	10	48	87	84:16	41:59
4	**IVa**	4	0.55 M	CH_3CN	10	48	60	80:20	77:23
5	**IVb**	4	0.55 M	CH_3CN	10	48	64	82:18	78:22
6	**V**	0.83	0.24 M	Toluene	5	27	4	50:50	50:50
7	**V+IVa**	0.83	0.24 M	Toluene	5+5	1	27	83:17	80:20
8	**V+VI**	0.83	0.24 M	Toluene	5+5	6	7	75:25	50:50
9	**IVb**	4	0.55 M	Toluene	10	96	77	81:19	81:19
10	**IVb**	4	0.55 M	CH_2Cl_2	10	96	86	80:20	79:21
11	**IVb**	4	0.55 M	$CHCl_3$	10	96	84	81:19	77:23
12	**IVb**	4	1.0 M	Toluene	10	24	68	87:13	83:17
13	**IVb**	4	0.6 M	Toluene	10	12	68	89:11	84:16
14	**IVb**	4	0.2 M	Toluene	10	12	56	92:8	86:14
15	**IVb**	4	0.2 M	Toluene	2	12	47	93:7	87:13
16[b]	**IVb**	4	0.2 M	Toluene	2	24	45	90:10	83:17

[a] Relative configuration is depicted for **3a**.
[b] Reaction performed at 0 °C.
[c] Determined from the crude ^1H NMR spectrum.
[d] Determined by chiral HPLC.