Tetrahedron Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Seda Okumuş, Cihangir Tanyeli *, Ayhan S. Demir ✠

Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey

ARTICLE INFO

Article history:
Received 24 January 2014
Revised 26 May 2014
Accepted 5 June 2014
Available online xxxx

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

Keywords:
Aldol reaction
α-Azido ketone
Bifunctional urea
C–C coupling
Cinchona alkaloids

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]

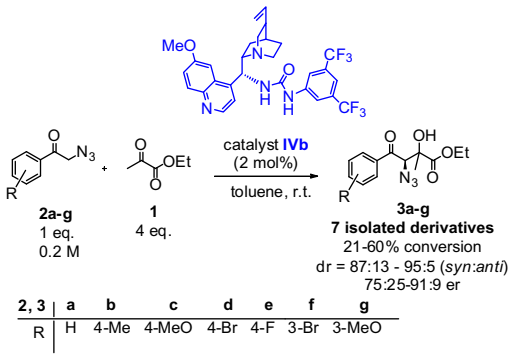
Aldol addition of α-azido ketones to ethyl pyruvate allows the synthesis of ethyl 2-azido-3-hydroxy-1,4-diones, which are valuable tetrafunctionalized synthons.[4] The different functionalities present in such compounds make them potential precursors for the synthesis of α-amino ketones,[5] azido alcohols,[6] 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).

* Corresponding author. Tel.: +90 312 2103222; fax: +90 312 2103200.
E-mail address: tanyeli@metu.edu.tr (C. Tanyeli).
✠ Deceased on June 24, 2012.

http://dx.doi.org/10.1016/j.tetlet.2014.06.018
0040-4039/



Scheme 1. Current work.

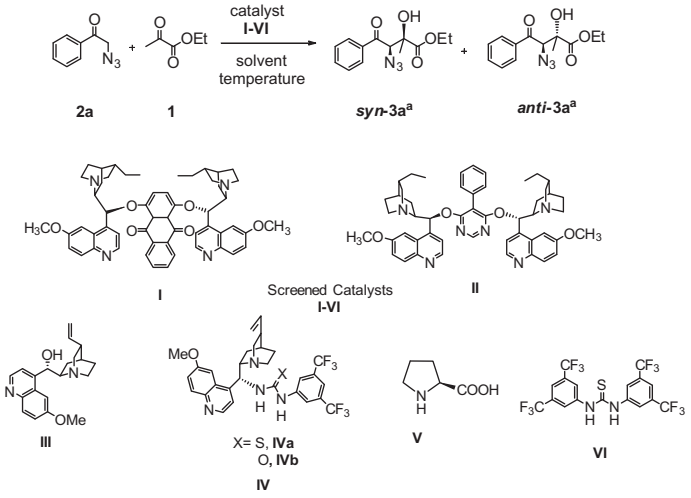
Cinchona alkaloids are well-known naturally occurring catalysts with a Brønsted basic quinuclidine nitrogen and having a wide range of applications in many relevant transformations.[14] Inspired by the competitive use of cinchona alkaloids in various aldol reactions,[15] and the study of Barbas,[12] 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 ^{1}H NMR spectrum.
[d] Determined by chiral HPLC.

In this regard, the decrease in the diastereomeric ratio was confirmed by checking the change in the ratio and conversion of the products at the end of specific time intervals (by ^{1}H NMR analysis of the crude product) in subsequent screening studies.

Considering entries 12–14, as the concentration of **2a** decreases, an increase in enantioselectivity was detected. Accordingly, a concentration of 0.2 M gave the highest er (86:14) and diastereoselectivity, dr = 92:8 (*syn*:*anti*), obtained so far (entry 14).[17] Among the trials with higher and lower catalyst loadings, 2 mol % of the catalyst afforded an 87:13 er, and a better diastereomeric ratio (93:7) (entry 15). Our effort to decrease the catalyst loading to 1 mol % for atom economy brought about a very low conversion without any increase in the selectivity.[17] Consequently, the optimum catalyst loading was 2 mol %. A lower temperature was also examined using the previously optimized conditions, but it did not enhance the stereoselectivity (entry 16). Elevated temperatures were not tried due to the thermally labile nature of azides.[18]

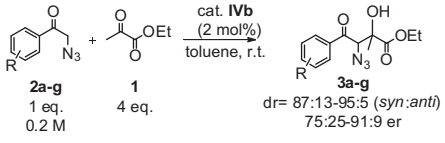
Despite the fact that model compound **3a** could not be isolated under the racemic conditions of Patonay's study,[4] at the end of our optimization trials, it was found that the isolation of **3a** was possible by suppressing the aforementioned retro-aldol process via the assistance of asymmetric organocatalysts. Having established the optimum reaction conditions, a variety of α-azido ketones **2a**–**g**[19] as aldol donors were probed and the stereocontrol on derivatives was explored to some extent with reasonable conversions (Table 2). *p*-Methoxy derivative **3c** yielded the best enantioselectivity, but the lowest conversion (entry 3). This situation can be attributed to a decrease in the acidity of the methylene protons. On the other hand, when the methoxy group was at the *meta*-position, (**3g**), although the conversion was relatively high (41%), the enantioselectivity was quite low (entry 7). In the case of 4-Br substituted derivative **3d**, the obtained enantiomeric ratio was 75:25. In spite of providing almost the same conversion, 3-Br substituted adduct **3f** led to an 80:20 er (entries 4 and 6, respectively). Besides its electronic effect, bromide may have a steric effect on the transition state.

Substrate scope studies also revealed that the enantiomeric ratio of each derivative decreases after reaching a maximum value due to epimerization of the major enantiomer and/or a possible retro-aldol reaction in the presence of **IVb** (see Supplementary data, Graph S1).[17]

Among the derivatives, the major diastereomer of **3c** was isolated whereas other derivatives were isolated as mixtures of *syn* and *anti* isomers. The ^{1}H and ^{13}C NMR spectra of isolated **3c** were in accord with the results reported for the *syn*-adduct by Patonay and co-workers.[13] The *syn*-preference over the *anti*-isomer in the coupling reactions of α-azido ketones with carbon electrophiles, reported in the work of Patonay,[4] Padwa[20] and Barbas,[12] allowed us to assign the diastereomers in the whole series on the basis of the characteristic differences in their ^{1}H NMR spectra. The stereogenic methine proton of the 4-MeO substituted *syn*-adduct, which is in accordance with the literature,[13] resonates at higher field (δ = 4.55) than its *anti* counterpart (δ = 4.67). Likewise, the stereogenic methine carbon atom of the *syn*-isomer was observed at a higher field ($\Delta\delta$ = 1.7) than its *anti* counterpart in the ^{13}C NMR spectrum. Similarly, in the ^{1}H NMR spectra of all the derivatives, the stereogenic methine proton of the major diastereomers appeared at a higher field ($\Delta\delta$ = 0.11–0.13) than the methine proton of the minor diastereomer.[17]

In summary, for the first time, we have demonstrated direct asymmetric aldol reactions of α-azido ketones and ethyl pyruvate to afford ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates by controlling the rate of the retro-aldol reaction, even under asymmetric conditions. Diastereo- and enantiocontrol was achieved by using bifunctional cinchona-based urea catalyst **IVb** as a chiral auxiliary. A significant induction of diastereoselectivity [up to 95:5 (*syn*:*anti*) diastereomeric ratio] and enantioselectivity of up to 91:9 were obtained using a very low (2 mol %) catalyst loading. Further studies on increasing the stereoselectivity and conversions are in progress.

Table 2
Scope of the α-azido ketones **2a-g**[a]



Entry	R	Time (h)	Conversion[b] (%)	dr[c] *syn*:*anti*	er[d] *syn*
1	H (**3a**)	12	47 (40)	93:7	87:13
2	4-Me (**3b**)	18	27 (23)	95:5	89:11
3	4-MeO (**3c**)	18	21 (18)	92:8	91:9
4	4-Br (**3d**)	16	60 (55)	91:9	75:25
5	4-F (**3e**)	24	44 (39)	92:8	88:12
6	3-Br (**3f**)	18	(55)	87:13	80:20
7	3-MeO (**3g**)	24	41 (39)	92:8	84:16

[a] The reaction was performed with **1** (4 equiv), α-azido ketone (**2a-g**), (1 equiv, 0.2 M) and the catalyst **IVb** (2 mol %) in toluene. **syn-3c** was separated by column chromatography.
[b] Isolated yields are in parentheses.
[c] Determined from the crude ^{1}H NMR spectrum.
[d] Determined by chiral HPLC.

Acknowledgments

We are indebted to the Department of Chemistry (Middle East Technical University) for financial support.

Supplementary data

Supplementary data (experimental details, chiral HPLC traces, and copies of ^{1}H and ^{13}C NMR spectra for all compounds generated in this work) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.018. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004.
2. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
3. Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1995**, *60*, 2368–2377.
4. Juhász-Tóth, È.; Patonay, T. *Eur. J. Org. Chem.* **2002**, 3055–3064.
5. (a) Nakajima, M.; Loeschorn, C. A.; Cimbrelo, W. E.; Anselme, J. P. *Org. Prep. Proced. Int.* **1980**, *12*, 265–268; (b) Patonay, T.; Rákosi, M.; Litkei, G.; Bognár, R. *Liebigs Ann. Chem.* **1979**, 161–173; (c) Patonay, T.; Patonay-Pèli, E.; Litkei, G.; Szilágyi, L.; Batta, G.; Dinya, Z. *J. Heterocycl. Chem.* **1988**, *25*, 343–347; (d) Winternitz, F.; Engel, C. R. *Steroids* **1965**, *6*, 805–840.
6. (a) Moody, C. J.; Ward, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2903–2909; (b) Benaissa, T.; Hamman, S.; Beguin, C. G. *J. Fluorine Chem.* **1988**, *3*, 163–173; (c) Bateson, J. H.; Fell, S. C. M.; Southgate, R.; Eggleston, D. S.; Baures, P. W. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1305–1312.
7. (a) Brenelli, E. C. S.; Fernandes, J. L. N. *Tetrahedron: Asymmetry* **2003**, *14*, 1255–1259; (b) Wallner, S. R.; Lavandera, I.; Mayer, S. F.; Öhrlein, R.; Hafner, A.; Edegger, K.; Faber, K.; Kroutil, W. *J. Mol. Catal. B: Enzym.* **2008**, *55*, 126–129.
8. Kumar, D.; Reddy, V. B.; Varma, R. S. *Tetrahedron Lett.* **2009**, *50*, 2065–2068.
9. Garcia, C.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849–1889.
10. (a) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, 1997; (b) Marques, C. S.; Moura, N.; Burke, A. J. *Tetrahedron Lett.* **2006**, *47*, 6049–6052.
11. Martínez-Castañeda, Á.; Kędziora, K.; Lavandera, I.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Chem. Commun.* **2014**, 2598–2600.
12. Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2006**, *8*, 2839–2842.
13. Patonay, T.; Jekö, J.; Juhász-Tóth, È. *Eur. J. Org. Chem.* **2008**, 1441–1448.
14. Marcelli, T. In *Organocatalysis: Cinchona Catalysts*; John Wiley & Sons, 2011; Vol. 1,; pp 142–152
15. Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229–1279.

16. Catalysts **IVa** and **IVb** were synthesized according to the literature: Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969.
17. See Supplementary data for details and further discussions.
18. Patonay, T.; Konya, K.; Juhász-Tóth, È. *Chem. Soc. Rev.* **2011**, *40*, 2797–2847.
19. For the synthesis and characterization data of **2a**,**e**, see: (a) Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1994**, *59*, 2902–2905; for **2b**, see: (b) Reddy, M. S.; Narender, M.; Rao, K. R. *Tetrahedron* **2007**, *63*, 331–336; for **2c**, see: (c) Juhász-Tóth, È.; Patonay, T. *Eur. J. Org. Chem.* **2002**, *2*, 285–295; for **2d**, see: (d) Lourenço, N. M. T.; Afonso, C. A. M. *Tetrahedron* **2003**, *59*, 789–794; (e) see the Supplementary data for the synthesis and characterization data of **2f**, **g**.
20. Padwa, A.; Sá, M. M.; Weingarten, M. D. *Tetrahedron* **1997**, *53*, 2371–2386.

Please cite this article in press as: Okumuş, S.; et al. *Tetrahedron Lett.* (2014), http://dx.doi.org/10.1016/j.tetlet.2014.06.018