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Highly enantioselective synthesis of α-azidoβ-hydroxy methyl ketones catalyzed by a cooperative proline-guanidinium salt system†

Ángel Martínez-Castañeda, Kinga Kędziora, Iván Lavandera, Humberto Rodríguez-Solla, Carmen Concellón* and Vicente del Amo*

The combined activity of (S)-proline and an achiral tetraphenylborate TBD-derived guanidinium salt permits the aldol reaction between azidoacetone and aromatic, or heteroaromatic aldehydes. The α -azido- β -hydroxy methyl ketones obtained as products can be isolated in good yield, with high diastereo- and enantioselectivity.

Organic azides represent an important class of compounds, being used as masks of amino functions, source of nitrenes, valuable dipoles in [3+2]-dipolar cycloaddition reactions, and substrates in the synthesis of iminophosphoranes for the aza-Wittig reaction.¹ In this family, the densely functionalized α -azido- β -hydroxy ketones **1** possess a considerable synthetic value, showing up a particularly interesting chemical behaviour in comparison with simple alkyl or aryl azides.² Compounds **1** are typically accessed by a base-promoted aldol reaction of an α -azidoketone **2** and a non-enolizable aldehyde **3**³ (Scheme 1).

Although these protocols render the aldol adducts **1** with optimum chemical yield, undesired mixtures of *anti* and *syn* isomers are always present. In fact, to our knowledge, there are no methodologies described in the literature that allow gaining access to α -azido- β -hydroxy ketones **1** in a controlled diastereoand enantioselective manner. Following on with our studies on organocatalysis,⁴ herein we report the first organocatalyzed synthesis of enantioenriched *anti*- α -azido- β -hydroxy ketones **1**,⁵ employing the cooperative participation of (*S*)-proline and a TBD (triazabicyclo[4.4.0]dec-5-ene)-derived guanidinium salt.



Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, C/Julián Clavería 8, 33006, Oviedo, Spain. E-mail: ccf@uniovi.es, vdelamo@uniovi.es † Electronic supplementary information (ESI) available. See DOI: 10.1039/ c3cc49371g

Proline is the most popular organocatalyst. This naturally occurring amino acid is cheap, readily available in both enantiomeric forms, and can be used for a wide range of synthetic transformations.⁶ With the aim of avoiding the use of other synthetically elaborated organocatalysts, our group⁴ and others⁷ have demonstrated how the addition of additives can enhance the reactivity and selectivity of this off-the-bench catalyst in classical transformations such as the aldol reaction. Moreover, the addition of additives can also expand the boundaries of proline as a catalyst. In this sense, we have reported the first proline-catalyzed asymmetric synthesis of chlorohydrins through the intermolecular aldol reaction between chloroacetone and aromatic aldehydes, made feasible by the participation of a guanidinium salt as an additive.^{4c}

Motivated by our previous results, we decided to explore the behaviour of our catalytic guanidinium salt-proline system towards a reaction like that illustrated in Scheme 1. 4-Nitrobenzaldehyde, 4a, was adopted as the model substrate for preliminary reactions. Azidoacetone (5, 1-azidopropan-2-one) was prepared on a multigram scale, in 96% yield, from chloroacetone and sodium azide. In correspondence with our previous work, we decided to evade the use of any organic solvent, apart from ketone 5, which acts as both reagent and reaction medium.8 A careful optimization of the stoichiometries involved in the reaction, time, temperature, as well as the judicious choice of the anion accompanying the guanidinium salt, revealed ideal conditions (see ESI⁺ for details, Tables S1-S5). So when a suspension of (S)-proline (10 mol%), guanidinium salt 6 (15 mol%) and 4-nitrobenzaldehyde 4a, in a moderate excess of azidoacetone 5 (10 eq. respect to the aldehyde), was stirred for 120 hours at -10 °C, the α -azido- β -hydroxy ketone 7a was produced in quantitative conversion, with good diastereo- (anti-7a/syn-7a, d.r. 90:10) and enantioselectivity (97% ee for anti-7a, Table 1, entry 1).

Although neither α -azido- β -hydroxy methyl ketone 7 has been previously prepared, the relative spatial configuration of product 7**a** could be unambiguously assigned considering the value of its ${}^{3}J_{\text{H-H}}$ coupling constants, measured for the protons borne on carbons C4 (CH-OH) and C3 (CH-N₃), on the ¹H NMR spectra of the crude reaction mixture (${}^{3}J_{anti} = 6.9 \text{ Hz}$; ${}^{3}J_{syn} = 3.3 \text{ Hz}$). These figures are in agreement with other ${}^{3}J_{\text{H-H}}$ coupling constants measured on

Table 1 (S)-Proline/guanidinium salt **6** co-catalyzed synthesis of α -azido- β -hydroxy ketones **7a**-i^a

Me	0 N ₃ H Ar (S)-p 5 4a-l	6 (15 mol%) roline (10 mol%) AT, -10 °C, 120 h Ta-I	H O `Ar _→ N ₃	OH Ar
Entry	ArCHO	Conversion ^{b} (%)	d.r. ^c	ee^{d} (%)
1	4a 4-NO ₂ -C ₆ H ₄	>99 (90)	90:10	94
2	4b $3 - NO_2 - C_6 H_4$	>99 (91)	90:10	95
3	$4c 2-NO_2-C_6H_4$	99 (88)	90:10	97^e
4	$4d C_6H_5$	>99 (84)	90:10	95
5	4e 4-Cl-C ₆ H ₄	98 (85)	90:10	94
6	4f 4-Br-C ₆ H ₄	98 (84)	89:11	95
7	4g 4-CO ₂ Me-C ₆ H ₄	99 (83)	88:12	95
8	4h 2-furyl	>99 (78)	85:15	93
9	4i 2-pyridyl	>99 (80)	87:13	88
10^{f}	4a 4-NO ₂ -C ₆ H ₄	12	82:18	n.d.

^{*a*} Reaction conditions: azidoacetone 5 (2.0 mmol), ArCHO (0.2 mmol), (*S*)-proline (10 mol%), 6 (15 mol%), no solvent. The reaction mixture was stirred for 120 h at -10 °C. ^{*b*} Determined by ¹H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehydes 4 (limiting reagent) into α -azido- β -hydroxy ketones 7. The chemical yield of isolated compounds *anti*-7 is given in brackets. ^{*c*} Diastereoisomeric ratio of *anti*- to *syn*-7 determined by ¹H NMR spectroscopy of the crude reaction mixtures. ^{*d*} Enantiomeric excess of analytically pure α -azido- β -hydroxy ketones 7 and the rude reaction α -azido- β -hydroxy ketones α determined by HPLC analysis in chiral stationary phases. ^{*c*} Ketone 7c was isolated as an inseparable mixture of *anti*- and *syn*-isomers. ^{*f*} Reaction carried out without the addition of guanidinium salt 6. The enantiomeric excess of the product was not determined as a consequence of the low conversion.



Fig. 1 Reported ${}^{3}J_{H-H}$ values for different α -substituted- β -hydroxy methyl ketones **9** and **10**. Measured ${}^{3}J_{H-H}$ constants for compound **7a** are presented for comparison.

analogous *anti-* and *syn-* α -chloro- β -hydroxy methyl ketones **9**,^{4c,9} and *anti-* and *syn-* α -methoxy- β -hydroxy methyl ketones **10**,¹⁰ which are well characterized in the literature (Fig. 1).

Subsequently, a set of aldehydes **4b–g**, decorated with different functional groups and substitution patterns, were reacted with azidoacetone **5** under our finest reaction conditions (Table 1, entries 2–7). All of these reactions proceeded smoothly, with good conversion and high *anti*-diastereoselectivity and enantioselectivity (around 97% ee in all cases), independently of the nature of the aldehyde employed. Also, heteroaromatic aldehydes such as 2-furylcarboxaldehyde, **4h**, and 2-pyridylcarboxaldehyde, **4i**, proved

to be appropriate substrates for this reaction, the corresponding products 7h and 7i displaying good selectivity figures (Table 1, entries 8 and 9). The tolerance of the reaction for heteroaromatic aldehydes, challenging substrates in aldol-type C-C bond forming reactions, confirms the reproducibility and robustness of this transformation. Moreover, adducts anti-7a-i could be easily isolated by flash chromatography on silica gel, affording analytically pure products in high vield and with high ee. Also, it is important to remark that the presence of the corresponding regioisomers 8a-i was not observed in either of these transformations. A blank experiment performed without additive 6 (Table 1, entry 10) presented a significantly low conversion, as well as a poorer diastereomeric ratio for the reaction product.¹¹ It demonstrates the positive effect of the guanidinium salt on the reaction course, which facilitates a reaction that is not favorable with the single use of proline. Alternatively, the sole presence of guanidinium salt 6 was insufficient for catalysing to any extent the aldol reaction between aldehydes 4 and azidoacetone 5. Although the role played by the additive is not fully disclosed yet, we postulate that the guanidinium core of salt 6 could form doubly H-bonded motifs with the carboxylate function of proline, as well as with the carbonyl moieties of ketone 5 and aldehydes 4, thus enhancing their electrophilicity (reactivity).4a,b

In order to determine the absolute stereochemical configuration of the α -azido- β -hydroxy ketones 7, we contemplated the possibility of crystallizing either of the compounds *anti*-7**a**-**i** for X-ray diffraction experiments. Unfortunately, ketones 7**a**-**i** were all isolated as oils or amorphous waxy solids. Also, attempts by us to derivatize compounds *anti*-7 into other structures, whose spatial configuration would be well determined in the literature, resulted to be problematic.

As a plausible alternative, we considered the bioreduction of the ketone moiety of diastereopure α -azido- β -hydroxy methyl ketone anti-7d, used as a representative model, employing stereocomplementary alcohol dehydrogenases (ADHs) with 2-propanol as the hydrogen source.¹² In this sense, two ADHs, one from Rhodococcus ruber (ADH-A)¹³ and another from Lactobacillus brevis (LBADH)14 have shown excellent stereoselectivities towards the reduction of, e.g. α -azido ketones¹⁵ and α -alkyl- β -keto esters,¹⁶ and more importantly, with opposite stereopreference. Thus, ADH-A affords selectively the corresponding (S)-alcohols while LBADH the (R)-configured antipodes.¹⁷ This methodology opened up the possibility of carrying out an orthogonal reduction of ketone anti-7d giving access to the corresponding azido diols 11d and 12d in a diastereomerically enriched form (Scheme 2). Densely functionalized, chiral compounds such as 11d and 12d are not easily accessible by other synthetic methodologies available.

Remarkably, both diols, **11d** and **12d**, were achieved with the same diastereopurity (97%) coming from substrate *anti*-**7d**, demonstrating that during the bioreduction process the ADH showed perfect stereoselectivity. Since the absolute configuration of the new alcohol function formed was known, measuring the coupling constants between the protons at positions C2 (CH-N₃) and C3 (CH₃CH-OH) in diols **11d** (${}^{3}J_{syn}$ = 2.6 Hz) and **12d** (${}^{3}J_{anti}$ = 6.5 Hz), allowed the unambiguous assignation of the absolute stereo-chemical configuration of the α -azido- β -hydroxy methyl ketones *anti*-(3*S*,4*S*)-7 rendered from our organocatalyzed reaction.



Scheme 2 Stereodivergent bioreduction of *anti-7d* with ADH-A (S-selective enzyme) affording diol *anti,syn-11d* and LBADH (*R*-selective biocatalyst) giving access to diol *anti,anti-12d*. In the middle, a representation of the nicotinamide cofactor present in both ADHs is drawn.

To conclude, we have presented the first enantioselective synthesis of α -azido- β -hydroxy ketones, through the intermolecular direct aldol reaction of azidoacetone and several aromatic aldehydes. This methodology employs catalytic amounts of inexpensive (*S*)-proline, aided by the cooperative participation of a TBD-derived tetraphenylborate guanidinium salt. The products from this reaction were obtained with very high diastereo- and enantiomeric excess and they can be selectively bioreduced by stereocomplementary ADHs, affording densely functionalized 2-azido-1,3-diols with three chiral centers in an enantiopure manner. The development of other enantioselective reactions that employ readily available organocatalysts is ongoing in our laboratory and will be reported in due course.

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Notes and references

- For reviews, see: (a) E. V. F. Scriven and K. Turnbull, *Chem. Rev.*, 1988, 88, 297; (b) S. Bräse, C. Gil, K. Knepper and V. Zimmerman, *Angew. Chem., Int. Ed.*, 2005, 44, 5188; (c) S. Cenini, F. Ragaini, E. Gallo and A. Caselli, *Curr. Org. Chem.*, 2011, 15, 1578; (d) N. Jung and S. Bräse, *Angew. Chem., Int. Ed.*, 2012, 51, 12169; (e) C. Shunsuke, *Synlett*, 2012, 21.
- 2 T. Patonay, K. Kónya and E. Juhász-Tóth, *Chem. Soc. Rev.*, 2011, **40**, 2797.
- 3 (a) T. Patonay and R. V. Hoffman, J. Org. Chem., 1995, 60, 2368;
 (b) T. Patonay, E. Juhász-Tóth and A. Bényei, Eur. J. Org. Chem., 2002, 285;
 (c) E. Juhász-Tóth and T. Patonay, Eur. J. Org. Chem., 2002, 3055;
 (d) T. Patonay, J. Jeko and E. Juhász-Tóth, Eur. J. Org. Chem., 2008, 1441.
- 4 (a) A. Martínez-Castañeda, B. Poladura, H. Rodríguez-Solla, C. Concellón and V. del Amo, Org. Lett., 2011, 13, 3032; (b) A. Martínez-Castañeda, H. Rodríguez-Solla, C. Concellón and V. del Amo, J. Org. Chem., 2012, 77, 10375; (c) A. Martínez-Castañeda, B. Poladura, H. Rodríguez-Solla, C. Concellón and V. del Amo, Chem.-Eur. J., 2012, 18, 5188.
- 5 Related products *syn-α*-azido-β-amino ketones can be accessed by means of an organocatalyzed Mannich-type reaction between α-azido ketones, aldehydes and anilines: N. S. Chowdari, M. Ahmad, K. Albertshofer, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2006, **8**, 2839.
- 6 For general reviews, see: (a) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (b) S. K. Panday, *Tetrahedron: Asymmetry*, 2011, **22**, 1817.
- 7 (a) T. Darbre and M. Machuqueiro, *Chem. Commun.*, 2003, 1090;
 (b) J. Kofoed, M. Machuqueiro, J.-L. Reymond and T. Darbre, *Chem. Commun.*, 2004, 1540; (c) A. I. Nyberg, A. Usano and P. M. Pikho,

Synlett, 2004, 1891; (d) M. Amedjkouh, Tetrahedron: Asymmetry, 2005, 16, 1411; (e) R. Fernández-López, J. Kofoed, M. Machuqueiro and T. Darbre, Eur. J. Org. Chem., 2005, 5268; (f) J. Kofoed, J.-L. Reymond and T. Darbre, Org. Biomol. Chem., 2005, 3, 1850; (g) Y. Zhou and Z. Shan, J. Org. Chem., 2006, 71, 9510; (h) Y. Zhou and Z. Shan, Tetrahedron: Asymmetry, 2006, 17, 1671; (i) P. M. Pikho, K. M. Laurikainen, A. Usano, A. I. Nyberg and J. A. Kaavi, Tetrahedron, 2006, 62, 317; (j) J. Kofoed, T. Darbre and J.-L. Reymond, Chem. Commun., 2006, 1482; (k) N. Zotova, A. Franzke, A. Armstrong and D. G. Blackmond, J. Am. Chem. Soc., 2007, 129, 15100; (1) N. Zotova, A. Morán, A. Armstrong and D. G. Blackmond, Adv. Synth. Catal., 2009, 351, 2765; (m) Ö. Reis, S. Eymur, B. Reis and A. S. Demir, Chem. Commun., 2009, 1088; (n) S. L. Poe, A. R. Bogdan, B. P. Mason, J. L. Steinbacher, S. M. Opalka and D. T. McQuade, J. Org. Chem., 2009, 74, 1574; (o) X. Companyó, G. Valero, L. Crovetto, A. Moyano and R. Ríos, Chem.-Eur. J., 2009, 15, 6564; (p) D. G. Blackmond, A. Morán, M. Hughes and A. Armstrong, J. Am. Chem. Soc., 2010, 132, 7598; (q) A. S. Demir and S. Eymur, Tetrahedron: Asymmetry, 2010, 21, 405; (r) N. El-Hamdouni, X. Companyó, R. Ríos and A. Moyano, Chem.-Eur. J., 2010, 16, 1142; (s) W.-H. Wang, T. Abe, X.-B. Wang, K. Kodama, T. Hirose and G.-Y. Zhang, Tetrahedron: Asymmetry, 2010, 21, 2925; (t) S. M. Opalka, J. L. Steinbacher, B. A. Lambiris and D. T. McQuade, J. Org. Chem., 2011, 76, 6503; (u) A. S. Demir and S. Basceken, Tetrahedron: Asymmetry, 2013, 24, 515; (v) R. Porcar, N. Ríos-Lombardía, Busto, V. Gotor-Fernández, V. Gotor, E. García-Verdugo, E M. I. Burguete and S. V. Luis, Catal. Sci. Technol., 2013, 3, 2596.

- 8 For recent examples of organocatalyzed aldol reactions carried out under solvent-free conditions, see: (a) B. Rodríguez, T. Rantanen and C. Bolm, Angew. Chem., Int. Ed., 2006, 45, 6924; (b) B. Rodríguez, A. Bruckmann and C. Bolm, Chem.-Eur. J., 2007, 13, 4710; (c) G. Guillena, M. d. C. Hita, C. Nájera and S. F. Viózquez, Tetrahedron: Asymmetry, 2007, 18, 2300; (d) G. Guillena, C. Nájera and S. F. Viózquez, Synlett, 2008, 3031; (e) D. Almasi, D. A. Alonso and C. Nájera, Adv. Synth. Catal., 2009, 350, 2467; (f) C. Worch and C. Bolm, Synlett, 2009, 2425; (g) D. Almasi, D. A. Alonso, A. N. Balaguer and C. Nájera, Adv. Synth. Catal., 2009, 351, 1123; (h) A. Banon-Caballero, G. Guillena and C. Nájera, Green Chem., 2010, 12, 1599; (i) J. G. Hernández, V. García-López and E. Juriasti, Tetrahedron, 2012, 68, 92; (j) F. Zhang, C. Li and C. Qi, Tetrahedron: Asymmetry, 2013, 24, 380; (k) A. Banon-Caballero, G. Guillena, C. Nájera, E. Faggi, R. M. Sebastián and A. Vallribera, Tetrahedron, 2013, 69, 1307.
- 9 X.-Y. Xu, Y.-Z. Wang and L.-Z. Gong, Org. Lett., 2007, 9, 4247.
- 10 G. Guillena, M. d. C. Hita, C. Nájera and S. F. Viózquez, J. Org. Chem., 2008, 73, 5933.
- 11 Other reactions performed without additive 6 were messy, rendering complex mixtures of unidentifiable products, from which is difficult to infer conversion values to aldol adducts 7.
- 12 Recent bibliography: (a) F. Hollmann, K. Bühler and B. Bühler, in Enzyme Catalysis in Organic Synthesis, ed. K. Drauz, H. Gröger and O. May, Wiley-VCH, Weinheim, 2012, pp. 1325–1438; (b) E. García-Urdiales, I. Alfonso and V. Gotor, Chem. Rev., 2011, 111, 110; (c) M. M. Musa and R. S. Phillips, Catal. Sci. Technol., 2011, 1, 1311.
- 13 W. Stampfer, B. Kosjek, C. Moitzi, W. Kroutil and K. Faber, Angew. Chem., Int. Ed., 2002, 41, 1014.
- 14 M. Wolberg, W. Hummel, C. Wandrey and M. Müller, *Angew. Chem.*, *Int. Ed.*, 2000, **39**, 4306.
- 15 A. Cuetos, F. R. Bisogno, I. Lavandera and V. Gotor, *Chem. Commun.*, 2013, **49**, 2625.
- 16 A. Cuetos, A. Rioz-Martínez, F. R. Bisogno, B. Grischek, I. Lavandera, G. de Gonzalo, W. Kroutil and V. Gotor, *Adv. Synth. Catal.*, 2012, 354, 1743.
- 17 This is true when the Cahn–Ingold–Prelog (CIP) rules correlate with the steric demand of both substituents attached to the alcohol moiety.