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Highly Enantioselective Synthesis of α-Azido-β-Hydroxy Methyl Ketones Catalyzed by a Cooperative Proline/Guanidinium Salt System

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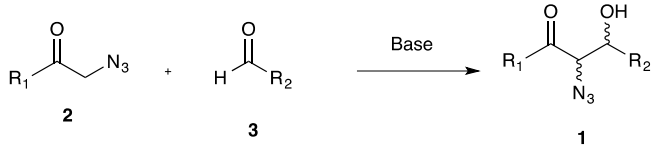
The combined activity of (*S*)-proline and an achiral tetraphenylborate TBD-derived guanidinium salt permits the aldol reaction between azidoacetone and aromatic, or heteroaromatic aldehydes. The α-azido-β-hydroxy methyl ketones obtained as products can be isolated in good yield, with high diastereo- 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] Among this family, the densely functionalized α-azido-β-hydroxy ketones **1** posses 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).



Scheme 1

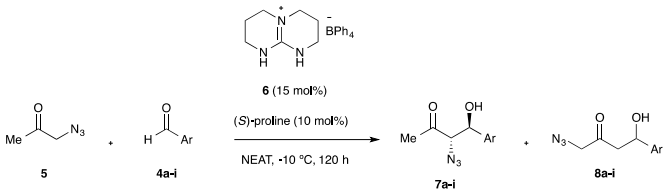
Although these protocols render the aldol aducts **1** with optimum chemical yield, undesired mixtures of *anti* and *syn* isomers are always present. In fact, to our knowledge, there are no methodologies described in the literature that allow gaining access to α-azido-β-hydroxy ketones **1** in a controlled diastereo- and enantioselective manner. Following on with our studies on organocatalysis,[4] herein we report the first organocatalyzed synthesis of enantio-enriched *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.

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] Aiming to avoid the use of other synthetically elaborated organocatalysts, our group,[4] and others,[7] 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 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 in multi-gram 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 media.[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 Supporting Information (SI) 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 ºC, 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).

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



Entry	ArCHO	Conversion (%)[b]	d.r.[c]	*ee* (%)[d]
1	**4a** 4-NO_2-C_6H_4	>99 (90)	90:10	94
2	**4b** 3-NO_2-C_6H_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_6H_4	98 (85)	90:10	94
6	**4f** 4-Br-C_6H_4	98 (84)	89:11	95
7	**4g** 4-CO_2Me-C_6H_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_6H_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 ºC. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. Conversion of aldehydes **4** (limiting reagent) into α-azido-β-hydroxy ketones **7**. Chemical yield of isolated compounds *anti*-**7** is given in brackets. [c] Diastereoisomeric ratio of *anti*- to *syn*-**7** determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [d] Enantiomeric excess of analytically pure α-azido-β-hydroxy ketones *anti*-**7** as determined by HPLC analysis on chiral stationary phases. [e] 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.

Although neither α-azido-β-hydroxy methyl ketone **7** has been previously prepared, the relative spatial configuration of product **7a** could be unambiguously assigned considering the value of its $^3J_{H\text{-}H}$ coupling constants, measured for the protons borne on carbons C4 (C*H*-OH) and C3 (C*H*-N_3), on the ^{1}H NMR spectra of the crude reaction mixture ($^3J_{anti}$ = 6.9 Hz; $^3J_{syn}$ = 3.3 Hz). These figures are in agreement with other $^3J_{H\text{-}H}$ coupling constants measured on 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 (Figure 1).

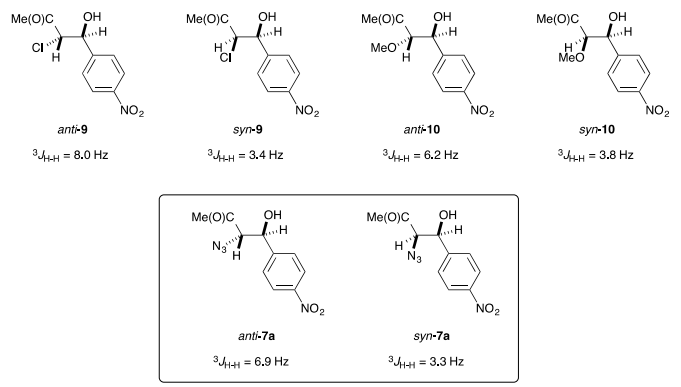


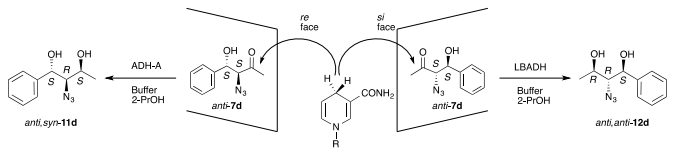
Figure 1

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, aducts *anti*-**7a-i** could be easily isolated by flash chromatography on silica gel, affording analytically pure products in high yield and 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 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 to catalyse 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*-**7a-i** for X-ray diffraction experiments. Unfortunately, ketones **7a-i** were all isolated as oils or amorphous waxy solids. Also, attempts to derivatize compounds *anti*-**7** into other structures, whose spatial

configuration would be well determined in the literature, resulted problematic in our hands.

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 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 ketones[15] 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.



Scheme 2

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 (C*H*-N_3) and C3 (CH_3C*H*-OH) in diols **11d** ($^3J_{syn}$ = 2.6 Hz) and **12d** ($^3J_{anti}$ = 6.5 Hz), allowed the unambiguous assignation of the absolute stereochemical configuration of the α-azido-β-hydroxy methyl ketones *anti*-(3*S*,4*S*)-**7** rendered from our organocatalyzed reaction.

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.

Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

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