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Asymmetric Synthesis of β-Amino-α-hydroxyaldehyde Derivatives Bearing a Quaternary Stereogenic Center

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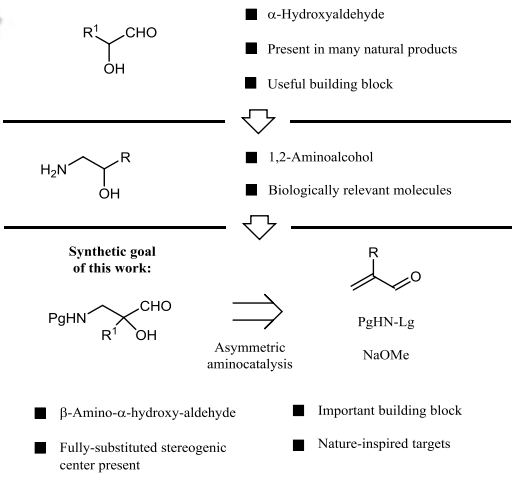
Abstract. An organocatalytic approach for the stereoselective synthesis of β-amino-α-hydroxyaldehydes bearing a fully substituted stereogenic center in the α-position with respect to the aldehyde moiety is presented. It utilizes a one-pot reaction cascade involving aziridination reaction followed by the sodium-methoxide-initiated rearrangement. In order to control the chemoselectivity of the rearrangement a new aziridinating reagent enabling the introduction of a nosyl protecting group at the nitrogen atom has been designed and introduced. Products of the reaction have thus been obtained as dimethyl acetal, exclusively. The possibility to deprotect the aldehyde moiety with the preservation of the introduced optical purity has also been demonstrated.

Keywords: organocatalysis; cascade reactions; β-amino-α-hydroxyaldehydes; 1,2-aminoalcohol; quaternary stereogenic center

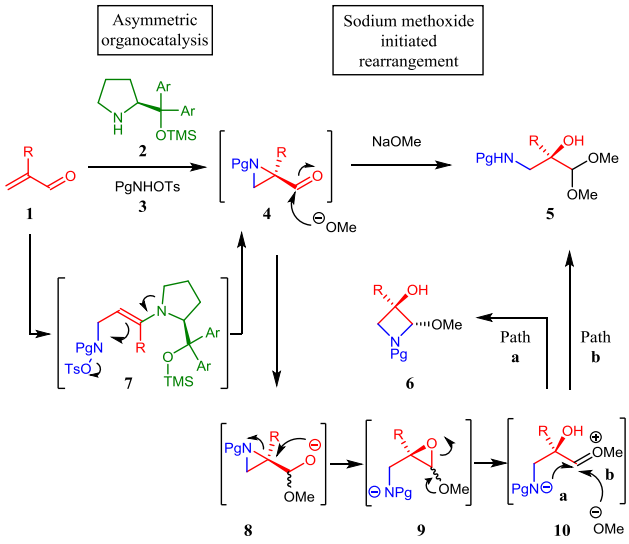
The α-hydroxyaldehyde structural motif is a key constituent of many natural products and bioactive molecules (Scheme 1, top).[1] It is also a useful building block widely employed in the synthesis of biologically relevant compounds.[2] Additionally, 1,2-aminoalcohols are common in nature and present in numerous compounds important for the life science such as e.g. amino- and iminosugars (Scheme 1, middle).[3] Synthetic methodologies for the direct and stereocontrolled introduction of 1,2-aminoalcohol moiety into a target molecule are limited and rely mainly on the Sharpless aminohydroxylation reaction.[4] Notably, the main drawbacks of that methodology are related to the cost and toxicity of osmium and problems with the control of regioselectivity of the process. Furthermore, the incorporation of a fully substituted carbon atom into a structure of either α-hydroxyaldehyde or 1,2-aminoalcohol in an enantioselective fashion is a highly challenging and important task in the contemporary organic and medicinal chemistry.[5] It is worth to stress out that the quaternary stereogenic centers are very often present in natural products and bioactive molecules.[6] Importantly, synthetic strategies leading to targets possessing such structural features remain limited.[7] In this context, asymmetric organocatalysis, where simple and chiral organic molecules are employed to promote stereocontrolled transformations, has recently introduced some novel and interesting solutions.[8]



Scheme 1. The relevance of α-hydroxyaldehyde and 1,2-aminoalcohol moieties and the synthetic objectives of this work.

Herein, we report our studies on the enantioselective synthesis of β-amino-α-hydroxyaldehydes bearing a quaternary stereogenic center (Scheme 1, bottom). Postulated mechanism of the devised cascade reactivity is outlined in the Scheme 2. It is initiated by the conjugate addition of the nitrogen nucleophile **3** to the iminium-ion derived from α-substituted acroleins **1**.[9] Subsequently, aziridine ring is formed

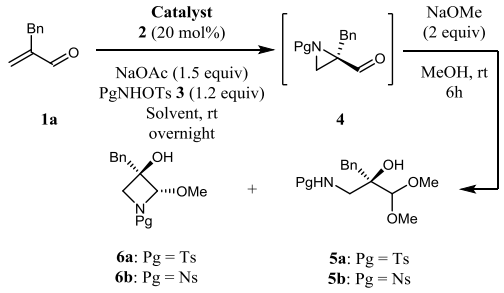
via an intramolecular nucleophilic substitution reaction. At this stage stereochemical information is transferred from the stereogenic center originating from the chiral aminocatalyst to the newly generated quaternary stereocenter. The reaction occurs from the side opposite to the bulky substituent present at C-2 of the pyrrolidine framework.[10] Hydrolytic cleavage of the catalyst **2** liberates the 2,3-aziridine aldehyde **4** that is subjected to the sodium methoxide initiated rearrangement in a one-pot fashion.[11] 1,2-Addition of methoxide anion to the aldehyde moiety in **4** initiates this stereospecific reaction. The alkoxide **8** thus obtained undergoes the aza-Payne-type reaction that leads to the formation of the epoxide **9**. Notably, at this stage a full inversion of the absolute configuration at the C-2 stereogenic center occurs. Epoxide-ring-opening takes place in the next step of the cascade to yield the corresponding oxocarbenium ion **10**. At this point, two different reaction pathways are possible. The intramolecular cyclization with the nitrogen atom serving as a nucleophilic species leads to the formation of the corresponding *N*,*O*-acetal **6** (Scheme 2, path a). The different reaction pathway relies on the 1,2-addition of a second methoxide anion to the oxocarbenium ion moiety in **10** to give the corresponding dimethyl acetal **5** as a final product (Scheme 2, path b).

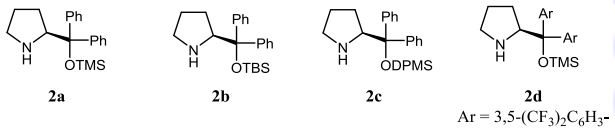


Scheme 2. Enantioselective synthesis of β-amino-α-hydroxyaldehyde dimethyl acetals **5** bearing a quaternary stereogenic center – mechanistic considerations.

Optimization studies were performed employing 2-benzylacroleine **1a** as a model α,β-unsaturated aldehyde, diphenylprolinol trimethylsilyl ether **2a** as the catalyst and **3a** as a model aziridinating reagent[12] (Table 1). To our delight, the one-pot reaction cascade consisting of initial aminocatalytic aziridination reaction and subsequent sodium methoxide initiated rearrangement proceeded efficiently (Table 1 entry 1). Interestingly, the desired α-hydroxy-β-aminoaldehyde derivative was formed as a mixture of the corresponding dimethyl acetal **5a** and the azetidine **6a** in which the acetal **5a** dominated. This observation is in marked contrast to the outcome of the reaction observed for linear α,β-unsaturated aldehydes.[11a] The solvent screening performed in the next stage of optimization studies (Table 1 entries 1-6) enabled to identify toluene as the most suitable choice for the one-pot cascade (Table 1 entry 6). Furthermore, it was found that lowering the reaction temperature to 0 °C was beneficial for its stereoselectivity (Table 1 entry 7). Subsequent catalyst screening (Table 1 entries 7-10) revealed that increasing the bulkiness of the silyl protecting group in **2** had no major influence on the reaction enantioselectivity (Table 1 entries 7-9). To our delight, the stereochemical reaction outcome could be improved by using **2d** as the catalyst[9a] (Table 1 entry 10). Disappointingly, the mixture of **5a** and **6a** was still formed in the course of the rearrangement reaction. However, it was postulated that a proper choice of an aziridinating reagent might enable the rearrangement to occur according to only one reaction pathway facilitating selective formation of one of the products. Therefore, further optimization studies were directed towards finding an aziridinating reagent that

Table 1. Enantioselective synthesis of β-amino-α-hydroxyaldehyde dimethyl acetals **5** bearing a quaternary stereogenic center – optimization studies.[a)]





	TsNHOTs **3a**	BocNHOTs **3b**	CbzNHOTs **3c**	NsNHOTs **3d**

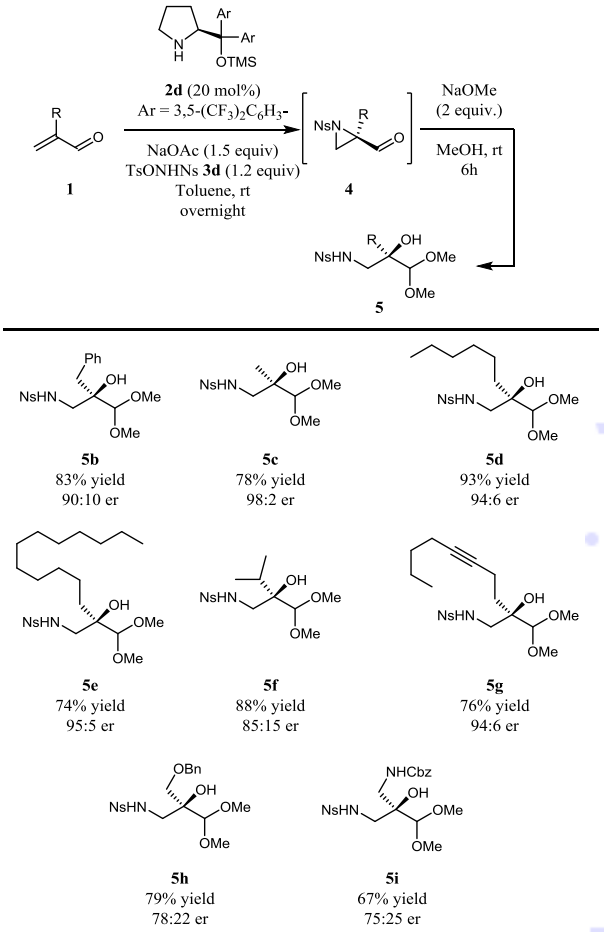
	Solvent	Cat./Azir. reagent	Yield. [%][b)]	**5**:**6** ratio[c)]	er[d)]
1	CCl_4	**2a**/**3a**	66	5:1	74:26
2	$CHCl_3$	**2a**/**3a**	65	5:1	77:33
3	CH_2Cl_2	**2a**/**3a**	63	4:1	65:35
4	Et_2O	**2a**/**3a**	37	4:1	77:23
5	Hexane	**2a**/**3a**	36	6:1	80:20
6	Toluene	**2a**/**3a**	64	3:1	77:23
7[e)]	Toluene[c]	**2a**/**3a**	68	4:1	80:20
8[e)]	Toluene[c]	**2b**/**3a**	51	4:1	80:20
9[e)]	Toluene[c]	**2c**/**3a**	60	3:1	79:21
10[e)]	Toluene[c]	**2d**/**3a**	75	4:1	90:10
11[e)]	Toluene[c]	**2d**/**3b**	<5	nd	nd

12[e)]	Toluene[c]	**2d**/**3c**	<5	nd	nd
13[e)]	Toluene[c]	**2d**/**3d**	80	>20:1	91:9

[a)] Reactions performed on 0.25 mmol scale using **1a** (1.0 equiv.) and **2a** (1.2 equiv) in 1.5 mL of the solvent (see Supporting Information for detailed reaction conditions). [b)] Isolated yield over two steps. [c)] Determined by ^{1}H NMR of a crude reaction mixture. [d)] Determined by a chiral stationary phase HPLC. [e)] Reaction performed at 0 °C.

would ensure the selective formation of **5** (Table 1 entries 10-13). Interestingly, it was found that when the carbamate protected aziridines **4** (Pg = Boc, Cbz) were employed in the rearrangement reaction no rearranged product formation was observed (Table 1 entries 11-12). Therefore, a novel aziridinating reagent **3d** bearing a *o*-nitrobenzenesulfonyl (Ns) group on the nitrogen atom was designed and synthesized. It was postulated that the presence of the highly-electron-withdrawing nosyl moiety will enable the rearrangement to occur with the exclusive formation of dimethyl acetal **5b** predominating for steric reasons. Furthermore, the presence of the nosyl group in the products **5** is beneficial as the it is easier to remove when compared with a tosyl moiety. To our delight, when **4d** was employed in the reaction sequence involving aziridination/NaOMe-initiated rearrangement, the reaction proceeded with the exclusive formation of **5b**. Furthermore, the reaction yield and enantioselectivity were high (Table 1 entry 13).

Successfully established the optimal conditions for the devised one-pot reaction cascade, the scope of the methodology was studied. Therefore, various α-substituted acroleins **1a-h** were tested in the

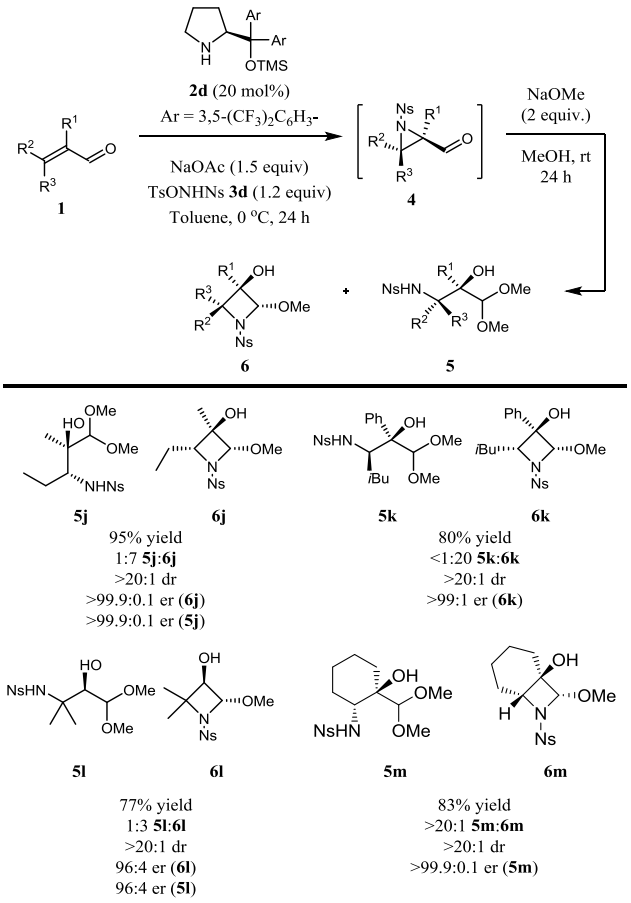


Scheme 3. Enantioselective synthesis of β-amino-α-hydroxyaldehyde dimethyl acetals **5** bearing a quaternary stereogenic center – α-substituted acrolein **1** scope. All reactions were performed on 0.25 mmol scale (see Supporting Information for detailed reaction conditions).

established one-pot reaction cascade (Scheme 3). It was found that the replacement of a benzyl group with unfunctionalized alkyl chains of different length had no major influence on the reaction efficiency (Scheme 3, compounds **5c**-**e**). To our delight, the reaction enantioselectivity increased. Interestingly, α-branched alkyl chains were also well-tolerated as demonstrated in the synthesis of **5f**. Furthermore, the possibility to introduce various functional group in the side-chain of **1** was examined. Reactions proceeded efficiently for the α-substituted acroleins **1f-h** containing either triple bond, ether moiety or protected amine group (Scheme 3, compounds **5g-i**). However, for aldehydes bearing heteroatom-containing alkyl chains in the α-position **1g**,**h** the enantioselectivity of the cascade was decreased (Scheme 3, compounds **5h**,**i**).

Having studied the scope of the method with regard to the α-substituted acroleins **1a-h**, the next task was to incorporate two adjacent stereogenic centers (with at least one being a quaternary) into target β-amino-α-hydroxyaldehyde dimethyl acetals **5** (Scheme 4). In order to accomplish this goal different α,β-disubstituted- and β,β-disubstituted-α,β-

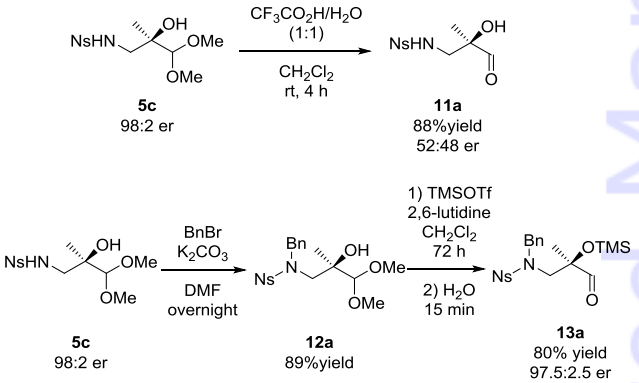
unsaturated aldehydes **1i-l** were subjected to the aziridination reaction under previously optimized conditions. Subsequent sodium-methoxide-initiated



Scheme 4. Enantioselective synthesis β-amino-α-hydroxyaldehyde derivatives **5** or **6** bearing an adjacent tertiary and quaternary carbon atoms. All reactions were performed on 0.25 mmol scale (see Supporting Information for detailed reaction conditions).

rearrangement performed in the one-pot fashion afforded desired products. Interestingly, careful analysis of the ^{1}H NMR spectra revealed that the corresponding azetidines **6** were formed as major products of the rearrangement. This indicated that when the substituent is present in the β-position of the starting aldehyde **1** the intramolecular reaction pathway in the last stage of the cascade started to dominate (Scheme 2, path b). Only in the case of 1-cyclohexene-1-carboxaldehyde **1l** the corresponding dimethyl acetal **5m** was predominantly formed. Importantly, in all of the cases reaction proceeded smoothly affording **5** or **6** in high yields. Furthermore, both diastereoselectivity and enantioselectivity of the cascade was high or excellent. These results indicated the usefulness of the developed one-pot cascade in accessing higher molecular and stereochemical complexity.

Notably, the absolute configuration of the products **5** and **6** was established by taking into account the well-established mechanism of the iminium-ion mediated aziridination reaction[9] and stereospecific character of the sodium-methoxide-initiated rearrangement[5f,11a,b] (see Scheme 2 for a detailed mechanism discussion). The relative configuration of the additional stereogenic center present in the *N,O*-acetals **6** was confirmed by the NOE experiment. With the configurational assignments accomplished, the possibility to deprotect the aldehyde moiety in **5** was attempted. Therefore, dimethyl acetal **5c** was selected as a model reactant. Initially, **5c** was directly subjected to hydrolytic acetal cleavage under classical acidic conditions (Scheme 5, top). The reaction proceeded efficiently affording **11a** in a high 88% yield. Disappointingly, the enantiomeric enrichment of **11a** proved very low indicating that the reaction proceeded with a racemization of the quaternary stereogenic center presumably via dehydratation-hydratation mechanism (S_N1-type reactivity) proceeding with the formation of a stable tertiary carbocation. Therefore, a different route was devised (Scheme 5, bottom). It involved initial protection of the nitrogen atom with a benzyl group to afford **12a**. Subsequent treatment of **12a** with TMSOTf afforded after an aqueous workup **13a** in excellent yield.[13] Notably, the stereoselectivity



Scheme 5. Preparation of β-amino-α-hydroxyaldehydes **11** and **13** via a cleavage of acetal moiety

induced at the stage of aminocatalytic cascade was fully preserved through the protection/deprotection reactions sequence.

In conclusion, a novel asymmetric organocatalytic strategy for the preparation of β-amino-α-hydroxyaldehydes was developed. It was based on the aminocatalytic one-pot reaction cascade involving enantioselective aziridination followed by the sodium methoxide initiated rearrangement. The choice of appropriate aziridinating reagent allowed for the reaction to proceed with the chemo- and stereoselective formation of nosyl-protected β-amino-α-hydroxyaldehyde dimethyl acetals. The protocol for the deprotection of aldehyde moiety proceeding with the maintenance of optical purity of a starting acetal was established. The developed cascade offers a facile, efficient and general entry to a new group of biologically relevant β-amino-α-hydroxyaldehydes

with a quaternary stereogenic center that can serve as useful building blocks for organic synthesis.

Experimental Section

General procedure for the one-pot reaction cascade

An ordinary screw-cap vial was charged with a magnetic stirring bar, catalyst **2d** (0.2 equiv, 0.05 mmol, 29.9 mg), sodium acetate (1.5 equiv, 0.375 mmol, 30.8 mg), toluene (1.5 mL) and aldehyde (1.0 equiv, 0.25 mmol). Subsequently, the mixture was cooled to 0 °C and 2-nitro-*N*-(tosyloxy)benzenesulfonamide **3d** (1.2 equiv, 0.30 mmol, 111.6 mg) was added and the reaction mixture was stirred overnight or 24 h at 0 °C. Next, methanolic solution of sodium methoxide (0.5 M, 2 equiv, 0.5 mmol, 1 mL) was added and stirring was maintained for additional 6 or 24 h. Reaction was quenched with water (15 mL), extracted with dichloromethane (3x15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Crude product was purified by the flash chromatography on silica gel.

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References

[1] a) B. Ernst, G. W. Hart, P. Sinaÿ, P., Eds. *Carbohydrates in Chemistry and Biology*, Wiley-VCH, New York, 2000; b) K. C. Nicolaou, N. J. Bockovich, in *Bioorganic Chemistry Carbohydrates*, S. M. Hecht, Ed. Oxford Univ. Press, New York, 1999, pp 134; c) P. Vogel, in *Glycoscience*, B. O. Fraser-Reid, K. Tatsuta, J. Thiem, Eds. Springer, Berlin, 2001, vol. 2, pp 1023; d) S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949; e) S. Ogawa, in *Carbohydrate Mimics: Concepts and Methods*, Y. Chapleur, Ed.; Wiley-VCH: Weinheim, 1998, pp 87; f) A. Berecibar, C. Grandjean, A. Siriwardena, *Chem. Rev.* **1999**, *99*, 779; g) M.; Sollogoub, P. Sinaÿ, in *The Organic Chemistry of Sugars*, D. E. Levy, P. Fügedi, Eds.; CRC Press: Boca Raton, 2006, pp 349.

[2] a) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152; b) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752; c) M. Markert, R. Mahrwald, *Chem. Eur. J.* **2008**, *14*, 40; d) M. Markert, U. Scheffler, R. Mahrwald, *J. Am. Chem. Soc.* **2009**, *131*, 16642; e) J. Młynarski, B. Gut, *Chem. Soc. Rev.* **2012**, *41*, 587.

[3] a) P. Compain, O. R. Martin, Eds. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley-VCH: Weinheim, 2007; b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem., Int. Ed.* **1996**, *35*, 1380; c) I. Hemeon, A. J. Bennet, *Synthesis* **2007**, 1899; d) F. Pfrengle, H.-U. Reissig, *Chem. Soc. Rev.* **2010**, *39*, 549.

[4] a) P. O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326; b) D. Nilov, O. Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169; c) J. A. Bodkin, M. D. McLeod, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733; d) M. Bruncko, G. Schlingloff, K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483; e) K. L. Reddy, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 1207.

[5] For selected examples, see: a) B. M. Trost, M. L. Crawley, C. B. Lee, *Chem. Eur. J.* **2006**, *12*, 2171; b) K. M. Akhoon, D. C. Myles, *J. Org. Chem.* **1997**, *62*, 6041; c) U. Scheffler, R. Mahrwald, *J. Org. Chem.* **2012**, *77*, 2310; d) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2011**, *17*, 3768; e) M. R. Witten, E. N. Jacobsen, *Org. Lett.* **2015**, *17*, 2772; f) K. Shibatomi, K. Kitahara, T. Okimi, Y. Abe, S. Iwasa, *Chem. Sci.* **2016**, *7*, 1388; g) Yuji Kawato, Akino Kubota, Hiromi Ono, Hiromichi Egami, and Yoshitaka Hamashima, *Org. Lett.*, 2015, 17 (5), pp 1244–1247; h) R. de la Campa, I. Ortin, D. J. Dixon, *Angew. Chem. Int. Ed.* **2015**, *54*, 4895.

[6] For selected examples, see: a) A. Steven, L. E. Overman, *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; b) G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, C. Ayats, S. V. Ley, *Angew. Chem. Int. Ed.* **2007**, *46*, 7633; c) A. W. G.; Burgett, Q.; Li, Q.; Wei, P. G. Harran, *Angew. Chem. Int. Ed.* **2003**, *42*, 4961; d) K. C.; Nicolaou, M.; Bella, D. Y.-K.; Chen, X.; Huang, T.; Ling, S. A. Snyder, *Angew. Chem. Int. Ed.* **2002**, *41*, 3495.

[7] For selected, recent reviews, see: a) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969; b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473; d) *Quaternary Stereocenters – Challenges and Solutions for Organic Synthesis*, J. Christoffers, A. Baro, Eds.; Wiley-VCH: Weinheim, 2005.

[8] For a review, see: M. Bella, T. Gasperi, *Synthesis* **2009**, 1583.

[9] For the aziridination of the α-substituted acroleins, see: a) A. Desmarchelier, D. Pereira de Sant'Ana, V. Terrasson, J. M. Campagne, X. Moreau, C. Greck, R. Marcia de Figueiredo, *Eur. J. Org. Chem.* **2011**, 4046; b) I. G. Molnár, E.-M. Tanzer, C. Daniliuc, R. Gilmour, *Chem. Eur. J.* **2014**, *20*, 794; c) L. Deiana, P. Dziedzic, G.-L. Zhao, J. Vesely, I. Ibrahem, R. Rios, J. Sun, A. Córdova, *Chem. Eur. J.* **2011**, *17*, 7904; d) L. Deiana, G.-L. Zhao, S. Lin, P. Dziedzic, Q. Zhang, H. Leijonmarck, A. Córdova, *Adv. Synth. Catal.* **2010**, *352*, 3201; for a seminal report on aziridination of enals, see: e) J. Vesely, I. Ibrahem, G. L. Zhao, R. Rios, A. Córdova, *Angew. Chem. Int. Ed.* **2007**, *46*, 778; f) for a review on organocascade reactivity, see: D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.

[10] a) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248; b) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54*, 13860.

[11] For stereospecific NaOMe-initiated rearrangement, see: a) Ł. Albrecht, H. Jiang, G. Dickmeiss, B.

Gschwend, S. G. Hansen, K. A. Jørgensen, *J. Am. Chem. Soc*. **2010**, *132*, 9188; b) O. Achmatowicz, Jr., A. Sadownik, R. Bielski, *Pol. J. Chem.* **1985**, *59*, 553; for examples of NaOMe-initiated rearrangement using α-chloro- or α-bromoaldehydes as starting materials, see: c) C. L. Stevens, E. Farkas, B. Gillis, *J. Am. Chem. Soc.* **1954**, *76*, 2695; d) C. L. Stevens, B. T. Gillis, *J. Am. Chem. Soc.* **1957**, *79*, 3448; e) A. Kirrmann, R. Muths, J.-J. Riehl, *Bull. Soc. Chim. Fr.* **1958**, 1469; f) J.-L. Kraus, G. Sturtz, *Bull. Soc. Chim. Fr.* **1974**, 943; g) K. Griesbaum, G. O. Lie, H. Keul, *J. Org. Chem.* **1984**, *49*, 679.

[12] H. Jiang, N. Holub, K. A. Jørgensen, *Proc. Nat. Acad. Sci.* **2010**, *107*, 20630.

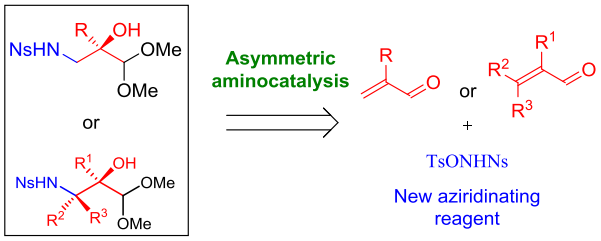
[13] H. Fujioka, Y. Sawama, N. Murata, T. Okitsu, O. Kubo, S. Matsuda, Y. Kita, *J. Am. Chem. Soc.* **2004**, *126*, 11800.

COMMUNICATION

Asymmetric Synthesis of β-Amino-α-hydroxyaldehyde Derivatives Bearing a Quaternary Stereogenic Center

Eur. J. Org. Chem. **Year**, *Volume*, Page – Page

Piotr Drelich, Anna Skrzyńska, and Łukasz Albrecht*



A stereocontrolled synthesis of β-amino-α-hydroxyaldehyde derivatives with a fully substituted stereogenic center in the α-position with respect to the aldehyde group is presented. The developed one-pot reaction cascade involves aminocatalytic aziridination (with a new aziridinating reagent introducing a nosyl group at the nitrogen atom) followed by the sodium-methoxide-initiated rearrangement.