Organic LETTERS

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d^0a^3 Synthon Equivalents for the Stereocontrolled Synthesis of Functionalized 1,4-Amino Alcohol Precursors

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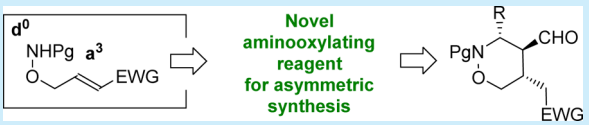
Supporting Information

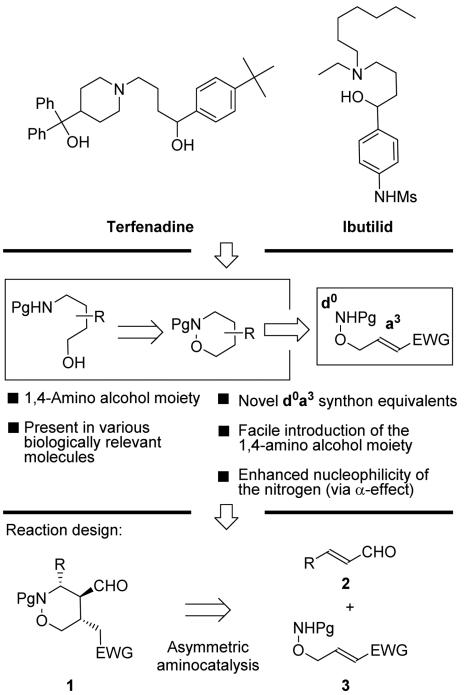
ABSTRACT: This study demonstrates the design, synthesis, and first application of novel aminooxylating reagents that serve as a useful d^0a^3 synthon equivalents for organic synthesis. It has been demonstrated that their reaction with α,β-unsaturated aldehydes performed under aminocatalytic conditions provides a straightforward access to polysubstituted tetrahydro-1,2-oxazine derivatives, direct precursors of functionalized 1,4-amino alcohols. Target tetrahydro-1,2-oxazine derivatives have been obtained with high yields (up to 89%) and with excellent stereocontrol (up to >20:1 dr, > 99.5:0.5 er). Furthermore, the synthetic usefulness of tetrahydro-1,2-oxazines obtained has been demonstrated in various selective transformations.



The quest for the development of stereoselective methods leading to biologically active molecules or privileged structural motifs, which can serve as useful building blocks, constitutes a highly relevant topic in contemporary organic chemistry.[1] One particularly visible trend within this research area is related to the use of chiral catalysts to control stereochemical reaction outcomes.[2] Since the turn of the millennium, asymmetric organocatalysis, where simple non-racemic organic molecules are employed as catalysts, has emerged as an effective tool widely employed in stereocontrolled synthesis.[3−5]

The amino alcohol moiety represents a privileged structural motif widely distributed in nature and present in various molecules relevant for the life-science industry, including amino sugars, iminosugars, sphingolipids, and sphingoids.[6] Therefore, the development of methods for their stereoselective preparation constitutes an important, yet challenging, task in modern organic synthesis.[7] In continuation of our interest[8] in the stereocontrolled synthesis of aminohydroxylated products, we became particularly interested in functionalized 1,4-amino alcohols as this structural motif is present in biologically relevant molecules (for selected examples, see Scheme 1, top).[9] Interestingly, these important building blocks are readily available from the corresponding tetrahydro-1,2-oxazines via the N−O bond cleavage.[10] However, stereocontrolled methods for the preparation of tetrahydro-1,2-oxazines are limited and rely mostly on the application of nitroso-Diels−Alder reaction as the key step.[11] Therefore, the task of designing a readily available reagent allowing access to functionalized, enantiomerically enriched tetrahydro-1,2-oxazines was undertaken. We envisioned that a possible route to these compounds might rely on the application of γ-aminooxy-α,β-unsaturated compounds. This novel group of aminooxylating reagents should be readily available and has certain advantages. First, they can be considered as d^0a^3 synthon equivalents. Therefore, they should be capable of reacting with Michael acceptors in a cascade manner involving aza-Michael/Michael reactions. Second, the nucleophilicity of the nitrogen should be enhanced due to the presence of the oxygen atom in the direct neighborhood (α-effect), thus making it more prone to undergo the desired reactivity.

Scheme 1. Importance of 1,4-Amino Alcohols and the Synthetic Objectives of Our Study



Herein, we present our studies on the application of novel aminooxylating reagents in the stereocontrolled synthesis of polysubstituted tetrahydro-1,2-oxazine derivatives **1**. Amino-

Received: April 26, 2017

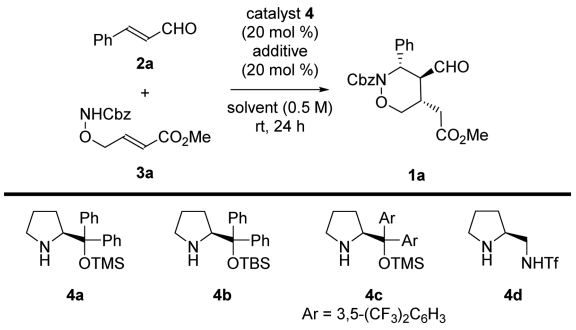
DOI: 10.1021/acs.orglett.7b01268
Org. Lett. XXXX, XXX, XXX−XXX

catalytic cascade activation mode of α,β-unsaturated aldehydes **2** via sequential iminium ion/enamine formation was selected as a model organocatalytic activation as it usually provides high levels of stereoinduction.[5] The developed strategy benefits from high efficiency, broad substrate scope, and offers a straightforward access to direct precursors of 1,4-amino alcohols.

Optimization studies were initiated using cinnamaldehyde **2a** and γ-aminooxy-α,β-unsaturated ester **3a** as model reactants (Table 1). Initially, the reaction was performed at room temperature in $CHCl_3$ in the presence of diphenylprolinol trimethylsilyl ether **4a**[12] as the catalyst (Table 1, entry 1). To our delight, it was found that the designed compound **3a** could serve as an efficient aminooxylating reagent in the stereocontrolled domino reaction leading to the formation of tetrahydro-1,2-oxazine **1a**. Notably, the cascade proceeded with excellent stereoselectivity. However, the reaction yield had to be improved. Disappointingly, neither the catalyst screening (Table 1, entries 1–4) nor the solvent optimization (performed with the catalyst **4a**, Table 1, compare entries 1, 5–7) led to the improvement of the chemical efficiency of the reaction. Interesting results were obtained when the additive screening was performed (Table 1, entries 8–12). It was found that both acidic (benzoic acid, BA, Table 1, entry 10) and basic additives (NaOAc, Table 1, entry 11) increased the conversion. Therefore, the use of an additive containing both acidic and basic moieties (4-(dimethylamino)benzoic acid, PDMBA, Table 1, entry 12) was attempted. To our delight, in the presence PDMABA the reaction was accomplished within 24 h, affording **1a** with excellent yield as a single stereoisomer.

With the optimization studies accomplished, the scope and limitations of the developed synthetic strategy was studied. Initially, different cinnamaldehyde derivatives **2** were evaluated in the reaction cascade. To our delight, the reaction proved to be unbiased toward both the electronic properties and the position of the substituents on the aromatic ring in **2** (Table 1, entries 1–12). The yields were high, and both the enantio- and diastereoselectivity of the cascade were excellent, providing the tetrahydro-1,2-oxazines **1a–l** as single stereoisomers in all of the cases. Furthermore, the reaction proceeded efficiently for aliphatic α,β-unsaturated aldehydes **2m–o** (Table 2, entries 13–16). Notably, the presence of different functional groups was tolerated in their side chain (phenyl group or double bond, compounds **1o,p**), further expanding the scope of the developed methodology (Table 2, entries 15 and 16). The possibility of replacing a protecting group at the nitrogen atom proved possible as demonstrated in the synthesis of Boc-protected tetrahydro-1,2-oxazine **1q** (Table 2, entry 17). Finally, the reaction cascade was fully scalable as it could be performed at 5 mmol scale, obtaining comparable results (Table 2, compare entries 1 and 18).

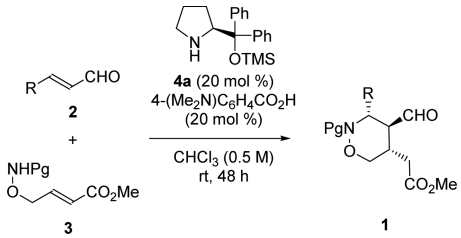
Table 1. Enantio- and Diastereoselective Synthesis of Tetrahydro-1,2-oxazines 1: Optimization Studies[a]



	solvent	cat. (additive)	conv[b]	dr[c]	er[d]
1	$CHCl_3$	**4a** (−)	51	>20:1	>99.5:0.5
2	$CHCl_3$	**4b** (−)	22	nd	nd
3	$CHCl_3$	**4c** (−)	<5	nd.	nd
4	$CHCl_3$	**4d** (−)	<5	nd	nd
5	CH_2Cl_2	**4a** (−)	48	>20:1	>99.5:0.5
6	toluene	**4a** (−)	27	>20:1	>99.5:0.5
7	CH_3CN	**4a** (−)	46	>20:1	>99.5:0.5
8	$CHCl_3$	**4a** (PNBA)[e]	21	nd	nd
9	$CHCl_3$	**4a** (BA)[e]	72	>20:1	>99.5:0.5
10	$CHCl_3$	**4a** (NaOAc)	59	>20:1	>99.5:0.5
11	$CHCl_3$	**4a** (DABCO)	44	>20:1	>99.5:0.5
12	$CHCl_3$	**4a** (PDMABA)[e]	>90 (88)	>20:1	>99.5:0.5

[a]Reactions performed on a 0.1 mmol scale using **2a** (2.0 equiv) and **3a** (1.0 equiv) in 0.2 mL of the solvent for 24 h. [b]Conversion as determined by ^{1}H NMR of a crude reaction mixture. The isolated yield is given in parentheses. [c]Determined by ^{1}H NMR of a crude reaction mixture. [d]Determined by a chiral stationary phase HPLC. [e]PNBA = 4-$NO_2C_6H_4CO_2H$. BA = $C_6H_4CO_2H$. PDMABA = 4-(Me_2N)-$C_6H_4CO_2H$.

Table 2. Enantio- and Diastereoselective Synthesis of Tetrahydro-1,2-oxazines 1: Reaction Scope[a]



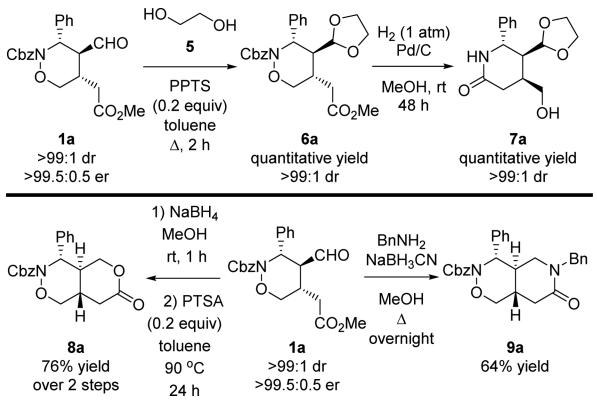
	R^1	Pg	yield (%)	dr[b]	er[c]
1	Ph	Cbz	88 (**1a**)	>20:1	>99.5:0.5
2	4-$NO_2C_6H_4$	Cbz	55 (**1b**)	>20:1	>99.5:0.5
3	4-CNC_6H_4	Cbz	58 (**1c**)	>20:1	>99.5:0.5
4	4-$CF_3C_6H_4$	Cbz	73 (**1d**)	>20:1	>99.5:0.5
5	4-BrC_6H_4	Cbz	87 (**1e**)	>20:1	>99.5:0.5
6	4-ClC_6H_4	Cbz	88 (**1f**)	>20:1	>99.5:0.5
7	3-ClC_6H_4	Cbz	86 (**1g**)	>20:1	>99.5:0.5
8	4-$CH_3C_6H_4$	Cbz	84 (**1h**)	>20:1	>99.5:0.5
9	4-$CH_3OC_6H_4$	Cbz	80 (**1i**)	>20:1	>99.5:0.5
10	2-$CH_3OC_6H_4$	Cbz	82 (**1j**)	14:1	>99.5:0.5
11	3,4-$(CH_3O)_2C_6H_3$	Cbz	77 (**1k**)	>20:1	>99.5:0.5
12	1-Naphthyl	Cbz	64 (**1l**)	8:1	99:1
13	Me	Cbz	63 (**1m**)	>20:1	>99.5:0.5
14	Hex	Cbz	68 (**1n**)	>20:1	>99.5:0.5
15	$PhCH_2CH_2$	Cbz	58 (**1o**)	>20:1	>99.5:0.5
16	Z-3-Hexenyl	Cbz	67 (**1p**)	>20:1	97:3
17	Ph	Boc	89 (**1q**)	>20:1	95:5
18[d]	Ph	Cbz	82 (**1a**)	>20:1	>99.5:0.5

[a]Reactions performed on a 0.2 mmol scale using **2a** (2.0 equiv) and **3a** (1.0 equiv) in 0.4 mL of $CHCl_3$ for 48 h. [b]Determined by ^{1}H NMR of a crude reaction mixture. [c]Determined by a chiral stationary-phase HPLC directly on the aldehyde or after the transformation of the aldehyde into the corresponding alcohol or 1,3-dioxolane (for details, see the Supporting Information). [d]Reaction performed on a 5 mmol scale using 10 mol % of the catalyst **4a**.

DOI: 10.1021/acs.orglett.7b01268
Org. Lett. XXXX, XXX, XXX−XXX

Functionalized 1,2-tetrahydroxazines **1** obtained could serve as versatile building blocks as demonstrated in selected selective transformations (Scheme 2). In the beginning, cleavage of the

Scheme 2. Synthetic Applications of Tetrahydro-1,2-oxazine 1a

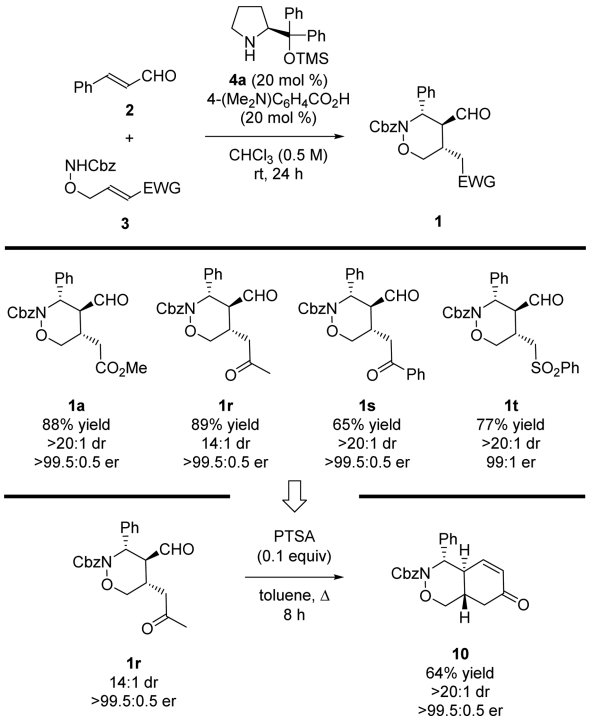


N−O bond was attempted (Scheme 2, top). However, initial experiments showed that the aldehyde moiety had to be protected prior to the cleavage. The acetal formation was realized under standard reaction conditions, yielding **6a** that was subjected to hydrogenolysis. Under these conditions, both the deprotection of the nitrogen atom and the N−O bond cleavage occurred. Initially formed 1,4-amino alcohol spontaneously cyclized to give δ-lactam **7a** in a fully chemoselective manner. Notably, a transformation of **1a** to **7a** could be performed without purification of any intermediate increasing the attractiveness of the methodology. The usefulness of the 1,2-tetrahydroxazines **1** obtained was further confirmed in a chemoselective transformation of **1a** into bicyclic δ-lactone **8a** and δ-lactam **9a** (Scheme 2, bottom). Chemoselective reduction of the aldehyde moiety followed by acid-promoted intramolecular transestrification led to a δ-lactone **8a**. The formation of δ-lactam **9a** was initiated through the reductive amination of **1a** followed by spontaneous lactamization.

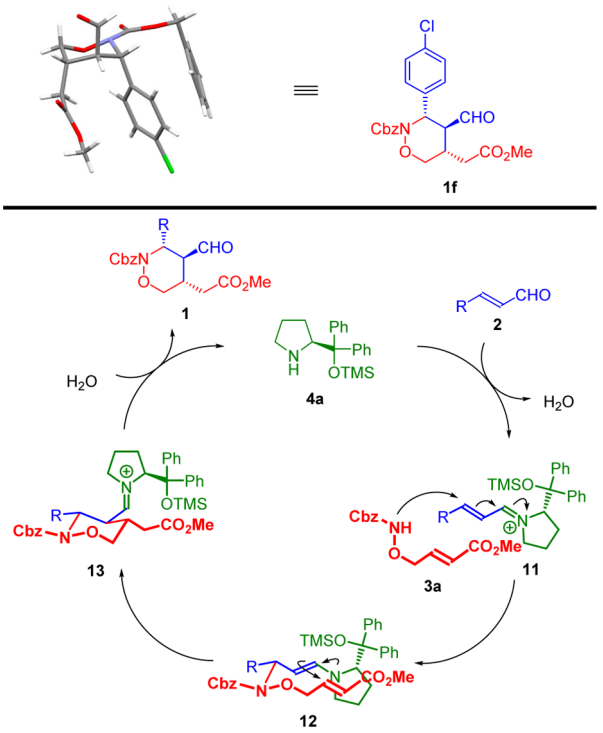
Further scope studies were focused on the utilization of various γ-aminooxy-α,β-unsaturated compounds **3** (Scheme 3). Reactions proceeded efficiently for aminooxylating reagents **3c−e** bearing different electron-withdrawing substituents on the double bond including methyl or phenyl ketone and sulfone moieties. Importantly, the introduction of various electron-withdrawing groups created new functionalization possibilities. For instance, methyl ketone **1r** could participate in the acid-promoted intramolecular aldol reaction, providing cyclohex-2-en-1-one derivative **10** in 67% yield. Notably, only (3*S*,4*S*,5*S*)-**1r** underwent cyclization leaving the other diastereomer of **1r** intact.

In order to assign the absolute configuration of the products **1**, X-ray analysis of **1f** was performed (Scheme 4, top).[13] On the basis of the obtained results, a plausible reaction mechanism was proposed (Scheme 4, bottom). The catalytic cycle was initiated by the condensation of the aminocatalyst **4a** with the corresponding α,β-unsaturated aldehyde **2** to give the reactive iminium ion **11** that underwent the aza-Michael reaction with the aminooxylating reagent **3**. The reaction occurred in a diastereoselective manner from the side opposite to the bulky substituent originating from the aminocatalyst **4a**. It was postulated that the subsequent, enamine-mediated intramolecular Michael addition proceeded through the chairlike transition state **12** to afford a six-membered heterocyclic ring in **13** with all

Scheme 3. Enantio- and Diastereoselective Synthesis of Tetrahydro-1,2-oxazines 1: Reaction Scope



Scheme 4. Enantio- and diastereoselective synthesis of tetrahydro-1,2-oxazines 1 − mechanistic considerations



substituents occupying equatorial positions. Hydrolytic cleavage of the catalyst **4a** liberated the product **1** and furnished the catalytic cycle. Notably, in this reaction PDMABA acts as an amphiprotic cocatalyst facilitating proton transfers.

In conclusion, we have designed a new group of aminooxylating reagents that serve as general d^0a^3 synthon equivalents.

DOI: 10.1021/acs.orglett.7b01268
Org. Lett. XXXX, XXX, XXX−XXX

Their usefulness in the stereocontrolled synthesis of tetrahydro-1,2-oxazines **1** via an aminocatalytic reaction cascade has been demonstrated for the first time. The developed method benefits from the broad scope and excellent stereocontrol. Furthermore, due to the presence of various functional groups in the heterocyclic ring, the obtained products are capable of participating in various chemoselective transformations with the N−O bond cleavage leading to 1,4-amino alcohol derivatives being the most relevant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. Screening details, experimental procedures, characterization of the products, NMR data, and CIF information (PDF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01268.

Screening details, experimental procedures, characterization of the products, NMR data, and X-ray data (PDF)
X-ray data for compound **1f** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was financially supported by the Ministry of Science and Higher Education, Poland, within the "Iuventus Plus" programme realized in the period 2015-2017, project no. 0008/IP3/2015/73. Thanks are expressed to Dr. Jakub Wojciechowski (Faculty of Chemistry, Lodz University of Technology) for performing X-ray analysis.

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(13) CCDC 1530190 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.orglett.7b01268
Org. Lett. XXXX, XXX, XXX−XXX