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Communication

A new, modular approach towards 2-(1-hydroxyalkyl)oxazolines, effective bidentate chiral ligands

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Abstract

Addition of β-hydroxyisonitriles towards aldehydes gives rise to hydroxyalkyl oxazolines, an interesting class of bidentate chiral ligands. This concept allows a very easy ligand tuning and optimization of the ligand structure as illustrated in a first example.

Keywords: Asymmetric catalysis; Addition; Isonitriles; Ligands; Ligand acceleration

Oxazolines are an important class of heterocyclic compounds, not only because of their widespread incidence in (mainly marine) natural products [1], but also as chiral building blocks in organic synthesis. Especially Meyers et al. [2] developed efficient chiral auxiliaries based on oxazolines in the 1970s. But also in the 'post auxiliary era' the oxazolines enjoy great popularity. Taking into account that in biological systems oxazolines are decisively involved in the complexation of metal ions such as Cu^{2+} and Zn^{2+} [3], it is not surprising that they find also application as building blocks for chiral ligands [4]. In most cases the oxazolines were combined with a second coordinating group giving rise to bidentate ligands. Besides bisoxazolines [5], especially phosphine oxazolines [6] and phosphite oxazolines [7] are applied in a wide range of catalytical processes, which were discussed in detail in the reviews cited. Phosphite oxazolines such as **A** and **B** (Fig. 1) give nice results in Cu-catalyzed $ZnEt_2$-additions towards enones [8], in Pd-catalyzed allylic alkylations [9] as well as in catalytic hydrogenations [10]. The same reactions were also investigated with the amino derivative **C** [11]. All these ligands can easily be obtained from hydroxy- or aminoalkyl oxazolines. In principle, these functionalized oxazolines should be themselves good bidentate ligands. But surprisingly, for this class of ligands only a few applications are reported in the literature so far. While few reports describe Et_2Zn additions to aromatic aldehydes or imines in the presence of ligands from type **D** [12], we are aware of only one application of ligands of type **E** for the phenylation of 4-chlorobenzaldehyde [13]. This caused our interest in a straightforward synthetic approach towards these hydroxyalkyl oxazolines (**E**), to use them either for the synthesis of phosphite oxazolines (**A**) or directly as bidentate ligands.

Most oxazoline syntheses are based either on a cycloaddition of a metallated isonitrile with an aldehyde [14] or on a condensation of a suitable carboxylic acid derivative with a β-amino alcohol [2]. Via this last approach hydroxyalkyl oxazolines **E** with two stereogenic centers can be obtained from optically active α-hydroxy acids.

Unfortunately, this synthetic pathway requires relatively drastic reaction conditions and gives moderate yields in many cases [15]. This protocol is also limited with respect to the substitution pattern because of the availability of the chiral α-hydroxy acids. While methyl- and phenyl-substituted derivatives can easily be obtained from lactic or mandelic acid, other derivatives require more synthetic efforts.

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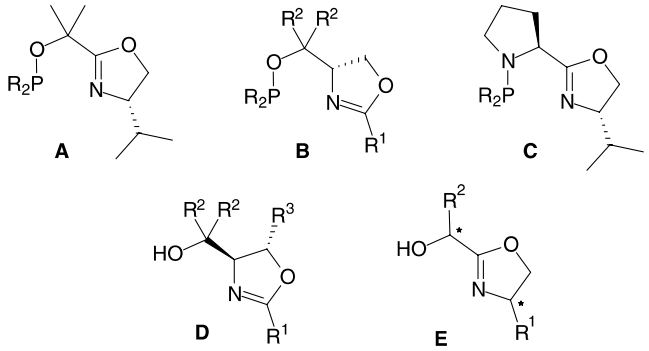
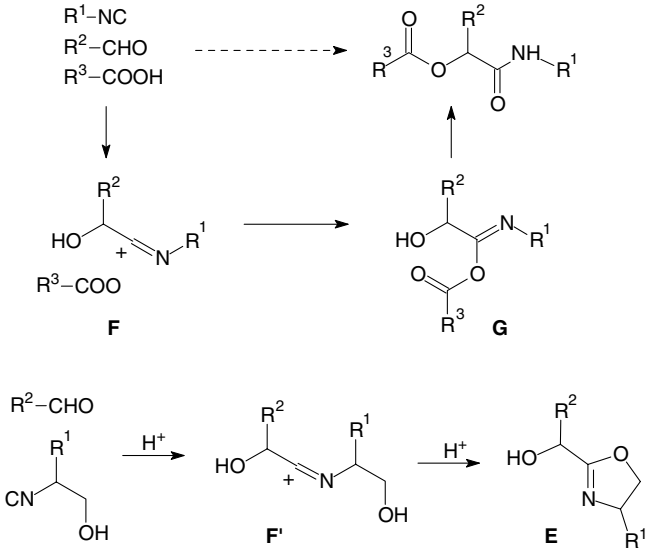


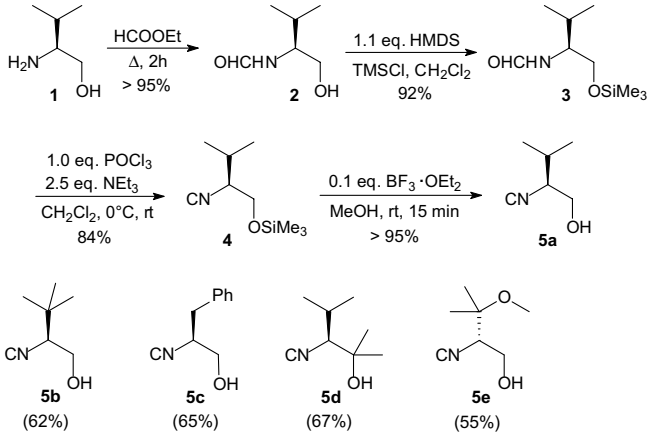
Fig. 1. Hydroxy- and phosphite oxazolines.

To have more flexibility with respect to variations of the substitution pattern, what should be indispensable for an efficient ligand screening, we decided to develop a new synthetic approach towards this class of ligands. In combinatorial chemistry, multicomponent reactions are extremely popular, and the isonitrile-based Passerini and Ugi reactions play a dominant role [16]. This becomes understandable by having a close look onto the mechanism of these reactions (Scheme 1). The first step is an activation of the carbonyl group via protonation followed by the addition of the isonitrile giving rise to acylimidoyl cation **F**. Addition of the carboxylate provides the intermediate **G**, which then undergoes a Mumm rearrangement to yield the expected product. By using a non-nucleophilic acid and an isonitrile with an additional β-hydroxy functionality, one might expect a cyclization of the corresponding intermediate **F′** directly to hydroxyalkyl oxazoline **E**.

Therefore, we focused our synthetic efforts on the synthesis of such hydroxyisonitriles which should be accessible easily from amino alcohols. The synthesis is illustrated exemplary for the isopropyl derivative **5a** (Scheme 2).



Scheme 1. Passerini reaction and its modification for the synthesis of hydroxyalkyl oxazolines.

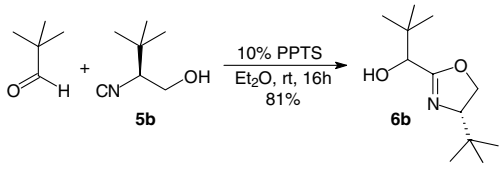


Scheme 2. Synthesis of hydroxyisonitriles.

Starting from valinol **1** the formamide **2** was obtained by refluxing **1** in ethyl formiate for 2 h in nearly quantitative yield as a crystalline solid [17]. Attempts to get **5a** directly from the formamide provided the isonitrile in yields as low as 20%. This problem could be solved by converting this functionality into the corresponding silyl ether **3** employing hexamethyl disilazane (HMDS), which then underwent a clean isonitrile formation. These two steps could be performed as a one-pot procedure as well. The silylated isonitrile **4** was deprotected in almost quantitative yield. In analogy, a range of other isonitriles **5b**–**5e** was obtained. Their overall yields from the corresponding amino alcohols are given in parentheses. Interestingly, protection of the hydroxy group was not necessary with derivative **5d**.

With isonitrile **5a** in hand, we optimized the subsequent oxazoline formation using various proton and Lewis acids. The best results in the reaction with pivalaldehyde were obtained in the presence of the relatively mild pyridinium *p*-toluenesulfonate (PPTS), which gave rise to oxazoline **6a** in 66% yield. By using isonitrile **5b** the yield could be increased to 81% (Scheme 3), even with the sterically demanding pivalaldehyde. The results obtained with the other isonitriles investigated are given in Fig. 2. It is worth mentioning that there is no loss of enantiomeric purity throughout the synthesis with respect to the stereocenter resulting from the amino alcohol.

Fortunately, we were able to separate the hydroxyalkyl oxazolines, which were formed as 1:1 diastereomeric mixtures, easily via chromatography into the diastereomers. The relative configurations for all compounds could be assigned by comparing their chromatographic data to that of **6a**, for which an X-ray structure of the (*S*,*S*)-diastereo-



Scheme 3. Synthesis of 2-(1-hydroxyalkyl)oxazoline **6b**.

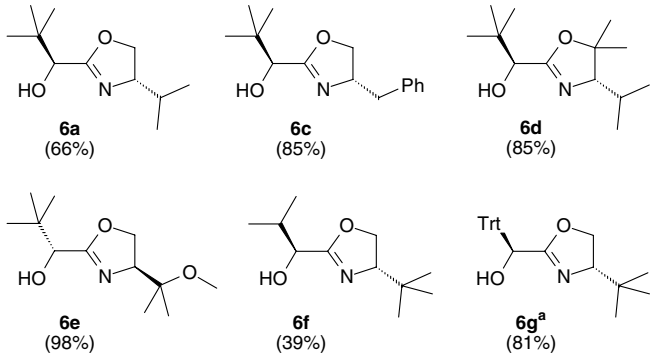


Fig. 2. Synthesis of hydroxyalkyl oxazolines **6**. [a]Abbreviation: Trt = triphenylmethyl.

mer was obtained. The stereoisomers were then subjected to our test reaction. As a standard reaction for ligand evaluation we chose the addition of $ZnEt_2$ towards benzaldehyde. In the reaction with ligand **6b** we made an interesting observation (Table 1). While the (*R*,*S*)-ligand (entry 1) gave rise to the (*R*)-alcohol with moderate ee (mismatched case), the corresponding (*S*,*S*)-ligand (entry 2) provided the (*S*)-configured alcohol with excellent ee (matched case). Kinetic studies (GC) indicated that with (*S*,*S*)-**6b** the reaction was almost complete after 30 min, while with (*R*,*S*)-**6b** nearly no reaction was observed. This caused us to use the diastereomeric mixture (obtained in the oxazoline synthesis) directly as a ligand. And indeed, the results obtained were comparable to those obtained with pure (*S*,*S*)-**6b**, making this ligand concept highly attractive.

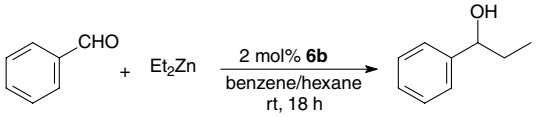
To prove its generality we first reacted the prepared isonitriles (Scheme 2) with pivalaldehyde to vary the substituent in the oxazoline moiety (Fig. 2). The yields were generally high, except for the already mentioned valine derivative **6a**, what can be explained by the high volatility of the ligand. Next, we varied the aldehyde component. Isobutyraldehyde derived oxazoline **6f** also appeared to be quite volatile and could only be isolated in a poor yield, whereas for **6g** in contrast, the yield was high. All isomeric mixtures could be separated by column chromatography, giving rise to stereochemically pure samples.

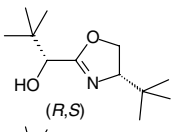
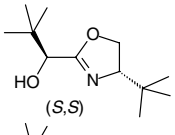
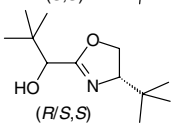
The matched ligands were investigated in the $ZnEt_2$ addition (Table 2). As expected, the ligand with the sterically demanding *t*-butyl group (**6b**) gave the best ee's, but the influence of the oxazoline substituent was not dramatic (entries 1–4). All other ligands gave ee's between 80% and 90%, and they all showed a comparable reactivity and complete consumption of the aldehyde under the standard conditions. A much stronger influence on the stereochemical outcome of the reaction was observed for the exocyclic substituent. For example, replacing the *t*-butyl group by an isopropyl group (**6f**) resulted in a selectivity drop of 66% (Table 1, entry 2 vs. Table 2, entry 6). Interestingly, the ligand with the lowest selectivity also showed the lowest reactivity leading to an incomplete consumption of the starting material after 18 h. A quarternary center at the exocylic substituent thus seems to be crucial for both good reactivity and good selectivity, probably for steric reasons. The good result for **6g** with the bulky trityl group supports that thesis (entry 6).

In conclusion, we could show that a modification of the Passerini reaction allows a straightforward and efficient approach towards new chiral ligands. This concept allows a very easy ligand tuning and optimization of the ligand structure as illustrated in a first example. In the reaction investigated a strong ligand acceleration was observed for the matched ligand, but not the mismatched one, what allows the application of the chiral ligand as diastereomeric mixture. Kinetic studies as well as further applications of these hydroxyalkyl oxazolines as chiral ligands are currently under investigation.

General procedure for hydroxyalkyl oxazoline formation. PPTS (20 mg) was added to a solution of the hydroxyisonitrile (1.0 mmol) and the corresponding aldehyde (1.5 mmol) in ether (1 ml). The mixture was allowed to stir at room temperature overnight, before it was subjected directly to column chromatography (silica, eluent: hexanes/ether).

Table 1
Et_2Zn-Addition in the presence of ligand **6b**



Entry	Ligand[a]	Conversion [%]	ee [%][b]	Conf.
1	 (*R*,*S*)	88	23	(*R*)
2	 (*S*,*S*)	100	94	(*S*)
3	 (*R*/*S*,*S*)	100	92	(*S*)

[a] Relative configurations assigned by analogy to the X-ray structure of **6a**.

Table 2
Evaluation of hydroxyalkyl oxazolines **6** in the $ZnEt_2$ addition

Entry	Ligand[a]	Conv. (%)	ee (%)[b]	Configuration
1	**6a**	100	91	(*S*)
2	**6c**	100	84	(*S*)
3	**6d**	100	88	(*S*)
4	**6e**	100	85	(*R*)
5	**6f**	80	28	(*S*)
6	**6g**	100	93	(*S*)

[a] Stereochemically pure samples employed. Relative configurations assigned by analogy to the X-ray structure of **6a**.

[b] Determined by GC (column: CP-Cyclodextrin-β).

The separated diasteromeres were obtained as colorless crystals or oils and should be stored under argon in the refrigerator.

Acknowledgements

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