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Enantioselective Synthesis of 2-Isoxazolines by a One-Flask Conjugate Addition/Oxime-Transfer Process

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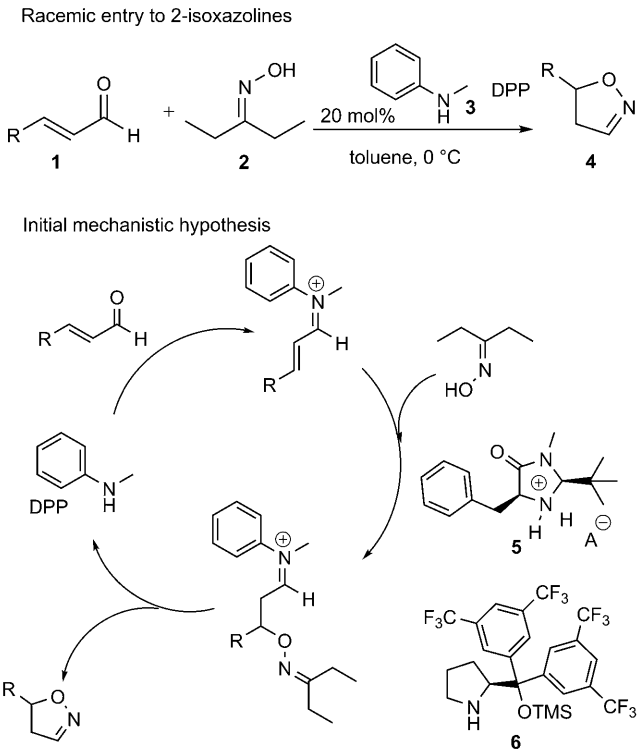
Asymmetric access to 2-isoxazolines, facile precursors to both aldol- and 1,3-aminoalcohol-type structural subunits, is an important objective in synthetic methodology.[1] The 1,3-dipolar cycloaddition between nitrile oxides and alkenes is by far the most popular method for the synthesis of the 2-isoxazoline ring. Unfortunately, these cycloadditions are generally not directly amenable to catalytic asymmetric synthesis.[1] Indeed, the number of catalytic methods used to prepare the 2-isoxazoline ring system is considerably smaller, and there seems to be no general solution to the problem. Although good selectivities have been attained by using Lewis acids such as Zn^{II}–tartrate complexes[2] or Mg^{II}–bisoxazolines,[3] the substrate scope has been limited owing to the necessity of having a second metal coordination site on the alkene substrate. Recently, Kündig and co-workers reported a ruthenium catalyst that appeared to overcome this limitation, but the substrate scope was still very restricted.[4] In addition to cycloadditions, a catalytic asymmetric cyclization of β,γ-unsaturated oximes has been reported,[5] but only modest selectivities have been attained with this method so far. Herein, we report a new catalytic enantioselective method to prepare 5-substituted 2-isoxazolines that applies a small organic catalyst as the source of chirality and enables the use of different α,β-unsaturated aldehydes as starting materials.

Recently, we disclosed a reaction for the preparation of 3-unsubstituted 2-isoxazolines in which aniline salts such as **3** (Scheme 1) catalyzed the condensation of α,β-unsaturated aldehydes and oximes to produce these rare heterocycles.[6]



Scheme 1. Mechanistic hypothesis for the racemic formation of 2-isoxazolines. For previous work see reference [6].

Access to these ring systems through, for example, 1,3-dipolar cycloadditions, is difficult because fulminic acid[7] or pregenerated silyl nitronates[8] are required as the dipolarophile components.

We first hypothesized that this reaction proceeded through an oxime conjugate addition/transoximation cascade and that the catalyst would accelerate both steps in this sequence. Support for this order of events was obtained from ^{1}H NMR spectroscopy experiments. When a mixture of crotonaldehyde (**1a**) and anisaldehyde oxime (**7**) was treated with the trifluoroacetic acid (TFA) salt of **5**, the con-

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version of the aldehyde to 2-isoxazoline (**4a**) appeared to be preceded by the formation of the conjugate addition intermediate **8** (Figure 1). Our double iminium catalytic hypothesis was further supported by Jørgensen, who reported an iminium-catalyzed asymmetric conjugate addition of oximes to aldehydes by using catalyst **6**,[9] and by Dawson and Jencks, who described the use of aniline catalysis in oxime ligation and semicarbazone formation reactions.[10]

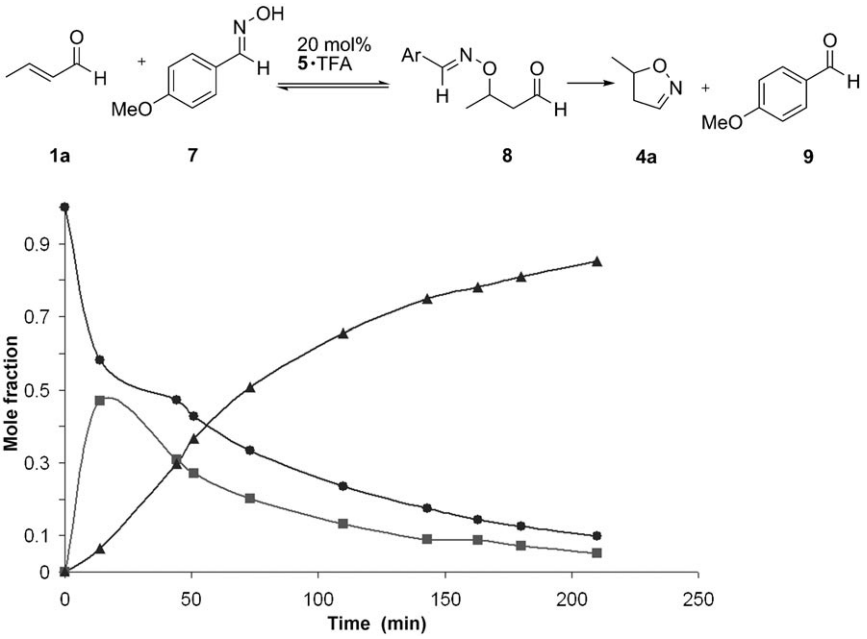


Figure 1. Conversion of **1a** to 2-isoxazoline in $CDCl_3$ in the presence of the TFA salt of **5**. Ar = *p*-methoxyphenyl (●: **1a**, ■: intermediate, and ▲: product).

However, to our disappointment, we were not able to produce optically active 2-isoxazolines by using our method and chiral catalysts **5** or **6**.[11] With catalyst **5**, only racemic 2-isoxazolines were obtained when moderately strong acids such as TFA or diphenylphosphate (DPP) were used as cocatalysts. In contrast, catalyst **6** was considerably less effective for this transformation in combination with TFA or DPP. With weaker acids such as chloroacetic acid as cocatalysts, compound **5** and a number of different *N*-alkylanilines were able to catalyze the first step of the reaction, the conjugate addition reaction of an oxime to the unsaturated aldehyde, but the rate of cyclization was retarded.

These results, however, did not explain why the 2-isoxazolines obtained with **5**·TFA were almost completely racemic. We hypothesized that any initially generated enantiomeric excess (*ee*) might be lost because the first step is likely to be reversible and the second step, the cyclization step, is relatively slow compared with the conjugate addition. In this case, thermodynamic equilibrium is reached with regard to the first step before the cyclization occurs, and thus, the product is obtained as a racemic mixture.[12] However, with aliphatic oximes, the rate of cyclization is faster, and in some cases no conjugate addition intermediate can be detected in the ^{1}H NMR spectra. In these cases, it is unlikely that the complete lack of enantioselectivity could be explained by the difference in the reaction rates. At this point, we were uncertain whether our initial hypothesis, the double iminium activation mechanism, was operating at all in this reaction.

Interestingly, when a mixture of aldehyde **1b** and oxime **10** was treated with a catalytic amount of *N*-methylaniline, no reaction could be observed. Instead, upon addition of different acid catalysts to the reaction mixture, the 2-isoxazoline product was generated according to the plots shown in Figure 2. The sigmoidal shape of the conversion plot implies that a new, potent catalyst is generated during an induction period. Both the length of this induction period and the potency of the catalytic species depend on the acid strength, and a positive correlation between reaction rate and the acid strength was observed.[13] These results suggested that the presence of a strong acid in the reaction mixture also induced the formation of similar catalytic species in the reactions catalyzed by **5**, and that

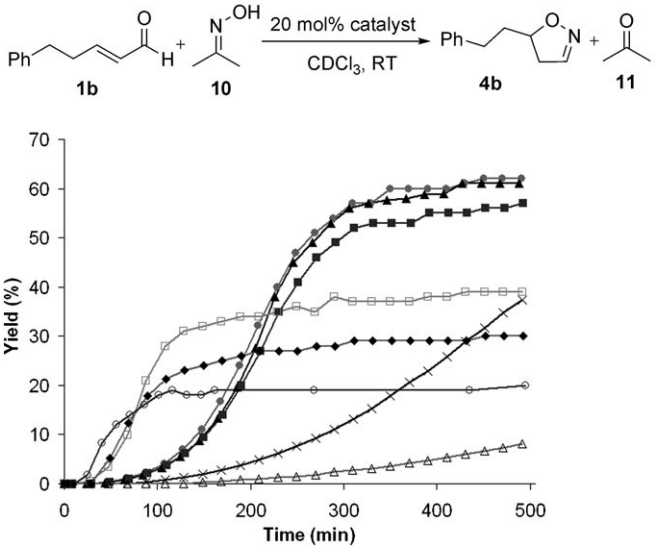
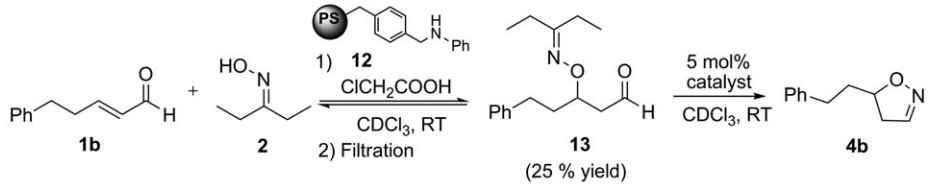


Figure 2. Acid-induced catalysis of 2-isoxazoline formation (●: trichloroacetic acid, ▲: diphenyl phosphate, ■: TFA, □: bis(nitrophenyl)phosphate, ◆: methanesulfonic acid, ○: *p*-TsOH, ×: dichloroacetic acid, and △: chloroacetic acid).

this unknown species was probably responsible for the production of the racemic products.

Although the identity of the intervening catalyst remains unknown, the acid experiment also raised the question of whether the 2-isoxazoline formation was actually dependent on the acidity of the medium. Accordingly, we analyzed the effect of different catalysts on the cyclization step. To generate the delicately unstable conjugate addition intermediates, we used the commercially available, polystyrene-bound *N*-benzylaniline base along with chloroacetic acid as the catalyst. This system enabled us to remove the catalyst components together with the majority of the oxime starting material from the reaction mixture by simple filtration through a pad of basic alumina. Although only approximately 25% conversion to adduct **13** was obtained, it could be reliably cyclized to the corresponding isoxazoline **4b** with different acid catalysts. Strong acids such as DPP displayed the fastest rates for the cyclization step (Figure 3).



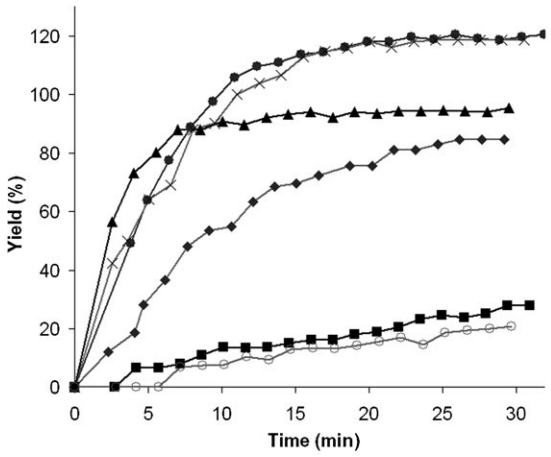


Figure 3. Conversion of intermediate **13** to **4b** in the presence of different acid catalysts. ^{1}H NMR spectroscopic yields are based on the initial concentration of intermediate **13**. The acid-induced formation of **13** from the remaining starting materials **1b** and **2** is responsible for conversions that are higher than 100%. The yields were determined by ^{1}H MNR spectroscopy (●: *p*-TsOH, ×: methanesulfonic acid, ▲: diphenylphosphate, ◆: TFA, ■: *N*-methylanilinium DPP, and ○: dichloroacetic acid).

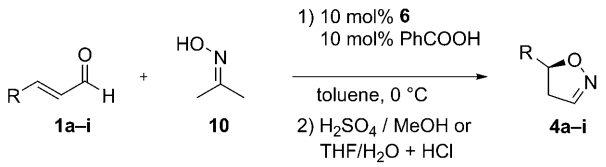
Importantly, salt **3** turned out to be a less effective catalyst for the cyclization step than any of the acids tested, whereas *N*-methylaniline alone was totally inactive. The success of the aniline salts as a catalyst in the reaction can be accounted for by the relatively high acidity of these salts combined with their ability to catalyze the conjugate addition step.[14]

Taken together, these results suggested a two-stage approach to the catalytic asymmetric synthesis of 2-isoxazolines. In the first stage, a mild, enantioselective catalyst should be used to promote the conjugate addition step with a hydrolytically labile oxime unit. In the second stage, a rapid quench with a strong acid stops the conjugate addition and promotes fast cyclization to the 2-isoxazolines.[15] For the first stage, we used a modification of the Jørgensen oxime conjugate addition protocol.[9] Pleasingly, this hypothesis was proven experimentally. Thus, treatment of aldehydes with acetone oxime, together with catalytic amounts of **6** and PhCOOH in toluene at 0°C for 3.5 h, and subsequent brief treatment of the reaction mixture with either 2.3 M H_2SO_4 in MeOH or a mixture of aqueous HCl in THF at 0°C afforded the desired isoxazolines in moderate yields and high enantioselectivities (Table 1).[16,17]

The isolated yields of this process appear to be limited by the competing decomposition of the starting materials in the process, as well as the K_{eq} value of the initial addition step.[17] Thus, further conjugation in the aldehyde completely suppresses the reaction, and no reaction was observed with cinnamaldheyde. Steric bulk also slightly lowers the yield (Table 1, entry 3). Aside from the previous examples, the substrate scope seems to be fairly broad and, generally, all aldehydes that withstand the cyclization conditions are viable substrates. Aldehydes that have potentially acid-labile PMB or Cbz groups (Table 1, entries 5, 8, and 9) and unsaturated esters (Table 1, entry 7) are readily tolerated. The use of acetone oxime facilitates rapid cyclization as well as easy removal of the ketone byproduct, and results in high *ee* values. The aldehyde oxidation level is preserved during the process, in contrast with previously reported approaches to asymmetric conjugate addition of oxygen nucleophiles.[9a,19]

In conclusion, after the analysis of the factors responsible for catalysis of each step of our oxime-transfer-based synthesis of 2-isoxazolines, we have developed a general catalytic protocol for the asymmetric synthesis of 2-isoxazolines by using the Jørgensen catalyst (**6**) as the source of enantioselectivity. The process considerably extends the usefulness of the original racemic process and creates a catalytic entry to a class of compounds that has not been easily available before. Further studies to explore the limits of the process and the chemistry of the products are underway.

Table 1. Substrate screen for the asymmetric formation of 2-isoxazolines.



1a–i 10 4a–i

Entry	R	Yield [%][a]	*ee* [%]
1	Me **1a**	39[b]	86
2	Ph **1b**	63	91
3	**1c**	45	94
4	Ph O **1d**	54	91
5[c]	PMBO **1e**	52	90
6[d]	TBDPSO **1f**	57	92
7	MeO_2C **1g**	47	88
8[e]	Bn N Cbz **1h**	55	86
9[e]	Bn N O Cbz **1i**	59	91

[a] Yields refer to pure, isolated products. [b] Yield determined by ^{1}H NMR spectroscopy after 3 h.[18] [c] PMP = *p*-methoxybenzyl. [d] TBDPS = tert-butyldiphenylsilyl. [e] Cbz = carbobenzyloxy

Experimental Section

General procedure for the asymmetric synthesis of 2-isoxazolines with the MeOH/H_2SO_4 cyclization conditions: The aldehyde (0.5 mmol, 100 mol%) and acetone oxime (110 mg, 1.5 mmol, 300 mol%) were added to a solution of amine **6** (29.9 mg, 0.05 mmol, 10 mol%) and benzoic acid (6.1 mg, 0.05 mmol, 10 mol%) in toluene (0.25 mL) at 0°C. After stirring the reaction mixture at 0°C for the indicated period of time, a precooled (0°C) solution of H_2SO_4 (0.21 mL) in MeOH (1 mL, 2.3 M H_2SO_4) was added and the resulting solution was stirred for 15 min at 0°C. A saturated aqueous solution of $NaHCO_3$ (1 mL) was added and the mixture was extracted with EtOAc (2×5 mL). The layers were separated and, if necessary (as indicated by TLC), the aqueous layer was completely basified by the addition of a saturated aqueous solution of $NaHCO_3$, then back-extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography to afford the products.

Acknowledgements

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Keywords: amines · asymmetric catalysis · cyclization · enantioselectivity · isoxazolines

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[11] Attempts to convert **1a** to the corresponding 2-isoxazoline by using acetone oxime with 20 mol% of catalyst **5** together with various acids resulted in racemic products at room temperature. When the reaction was conducted at −20°C and sulfonic acids (MsOH or *p*-TsOH) were used as cocatalysts, moderate (ca. 60%) *ee* values were obtained, but the yields were below 20%.

[12] It should be noted that a perfectly enantioselective catalyst could not be responsible for the nearly complete racemization of the intermediate. However, equilibration with a less-than-perfect catalyst will unavoidably result in the erosion of enantiomeric purity.

[13] The yield of the 2-isoxazoline product significantly decreased when strong acids were used. ^{1}H NMR spectroscopic analysis of the crude reaction mixtures indicated that the only significant side products appeared to be polymeric. No discrete side-product peaks could be discerned in the ^{1}H NMR spectra and the decomposition of **1b** was most reliably detected with the use of an internal standard (see the Supporting Information).

[14] Apparently, the salts resulting from the combination of relatively weak bases, such as anilines or imidazolidinones, with moderately strong acids, such as TFA or diphenylphosphoric acid, are acidic enough to activate cyclization. Stronger bases, such as pyrrolidine or its derivatives, form salts that are weaker acids and thus poor catalysts for the cyclization process.
[15] Previously reported examples of acid-promoted oxime transfer reactions require harsher conditions and longer reaction times, see: a) P. A. Jacobi, M. Martinelli, E. C. Taylor, *J. Org. Chem.* **1981**, *46*, 5416–5417; b) G. M. Shutske, *J. Org. Chem.* **1984**, *49*, 180–183.
[16] Other catalysts were also screened for this transformation. The diphenyl analoge of **6** (Hayashi catalyst see: Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215) afforded the product in similar yield and enantioselectivity (63% yield, 90% *ee*). In contrast, the MacMillan catalyst 5·$ClCH_2COOH$ gave a significantly lower yield and enantioselectivity (40% yield, 45% *ee*).
[17] The THF/H_2O/HCl system typically displayed slightly higher yields of the isoxazoline product. However, the isolated products were often contaminated with minor impurities that complicated the HPLC analysis.
[18] The yield of **4a** is largely limited by competing polymerization of **1a** in the reaction conditions.
[19] Examples of asymmetric conjugate additions of oxygen nucleophiles to enals are rare. Addition of salicylaldehydes to enals preserves the aldehyde oxidation state but does not preserve the original functionality, see: a) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763; b) H. Sundén, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Cordova, *Chem. Eur. J.* **2007**, *13*, 574–581.

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