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Synthesis of 2-Isoxazolines: Enantioselective and Racemic Methods Based on Conjugate Additions of Oximes

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Abstract: The formation of 3-unsubstituted 2-isoxazolines by means of condensation reactions between α,β-unsaturated aldehydes and oximes proceeds readily in the presence of catalytic amounts of anilinium salts. Mechanistically, the process involves a fast conjugate addition of the oxime and a slower intramolecular oxime-transfer reaction. The rate of oxime transfer was found to correlate with the acidity of the catalyst. This finding enabled us to discover an enantioselective process in which the fragile conjugate-addition product generated in the first stage is rapidly cyclized into the stable isoxazoline under acidic conditions, with conservation of enantiomeric excess. In summary, herein we describe synthetically useful protocols for accessing 3-unsubstituted 2-isoxazolines in both the enantioselective and racemic manner. The mechanism of the condensation reaction catalyzed by the anilinium salt was also investigated by NMR spectroscopy experiments in which the effect of differently substituted aldehydes and oximes as well as water on the reaction rate was studied. The results point to the rate-limiting elimination of water from the 3-hydroxy-2-isoxazolidine intermediate.

Keywords: acidity · amines · cyclization · enantioselectivity · isoxazolines

Introduction

Chiral secondary amine catalysts, often in combination with various acids, have been shown to be efficient catalysts for numerous transformations in the recent years.[1] Particularly significant advances in iminium- as well as enamine-catalyzed enantioselective transformations were made in 2000. These involved the use of proline and imidazolidinone heterocycles as catalysts in aldol, conjugate-addition, and Diels–Alder reactions.[2] A number of studies have shown that these catalysts, and particularly the imidazolidinones and diarylprolinol derivatives, activate α,β-unsaturated aldehydes to act as electrophiles with uncharged nucleophiles in a highly asymmetric manner, presumably by forming more reactive iminium-ion intermediates.[2b,3]

Our initial interest in these catalysts grew from the demand for the invention of new asymmetric conjugate-addition protocols for heteroatom nucleophiles, especially those of O-nucleophiles to unsaturated carbonyl compounds. The conjugate additions of oxygen-containing nucleophiles are well-established processes with unsaturated esters and ketones,[4] even though catalytic asymmetric protocols[5] for these additions are still rare.[6] The well-documented difficulty associated with these additions is the usually low reactivity of the hydroxyl functionality that demands kinetic activation of the reactants. The more fundamental problem, however, is related to the thermodynamic instability of the products since they readily revert back to the starting materials under equilibrating conditions. The thermodynamic instability of the products is emphasized in the case of unsaturated aldehydes, which are also prone to acetal and hemiacetal formation with the alcohol nucleophiles in the presence of basic or acidic activation of the reaction partners. Not surprisingly, only a few studies on conjugate additions of oxygen nucleophiles to unsaturated aldehydes,[7] and virtually no examples of enantioselective catalysis, were published at the time of the inception of our study. The products of these additions can be viewed as (protected) aldol products

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of acetaldehyde and acceptor aldehydes. These aldol reactions remain extremely challenging and have been successful only with a limited number of acceptor aldehydes, mostly aromatic aldehydes.[8] With this in mind, we felt that there would be definite use and need for the development of alternate processes based on conjugate additions.

Since the initiation of our study, both alcohols[9] and oximes[10] have been successfully used as nucleophiles in asymmetric addition to enals. However, the aldehyde oxidation state was not preserved in the oxime additions, and the isolation of the fragile oxime adducts was possible only after reduction of the aldehydes to the corresponding alcohols. Oximes and other oxygen nucleophiles have also been used as components in many creative cascade reactions[11] in which the initial conjugate-addition products are further processed in subsequent reactions. Surprisingly, stabilization of the aldehyde oxidation state by internal oxime transfer has not been used in asymmetric catalysis. In this paper, we present the research that resulted in the development of two new synthetic protocols that utilize the oxime-transfer process for the synthesis of 3-unsubstituted 2-isoxazolines both in the racemic[12] and enantioselective[13] manner (Scheme 1).

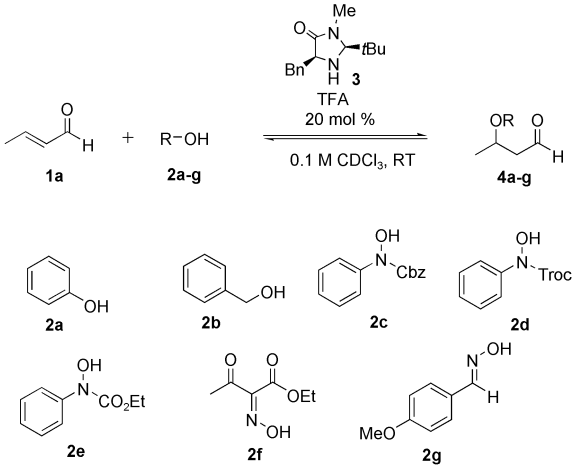
The protocols involve two distinct reaction steps, an oxime conjugate-addition and oxime-transfer reaction, which, depending on the catalyst, may be conducted separately or as a one-flask cascade. These methods are complementary to the known methods to synthesize these compounds[14] and represent the first catalytic asymmetric method for the synthesis of 3-unsubstituted 2-isoxazolines.[15]

Results and Discussion

Initial studies: Based on literature precedents,[5a] we reasoned that the character of the oxygen nucleophile would play a strong role in the success of iminium-catalyzed conjugate-addition reactions to enals. Relatively hard nucleophiles, such as alcohols, would not be ideal candidates for the reaction, since direct 1,2-addition to the iminium carbon might compete effectively with the desired 1,4-addition. Thus we hypothesized that the insertion of an α-heteroatom adjacent to the nucleophilic oxygen atom could, in addition to its documented effect of raising the relative nucleophilicity of such species,[16] also steer the reactivity of the nucleophile in favor of the conjugate-addition process.

The reactivity of different oxygen nucleophiles was investigated by monitoring their reactions with crotonaldehyde in the presence of the MacMillan imidazolidinone/trifluoroacetic acid (TFA) catalyst/co-catalyst system (Table 1).

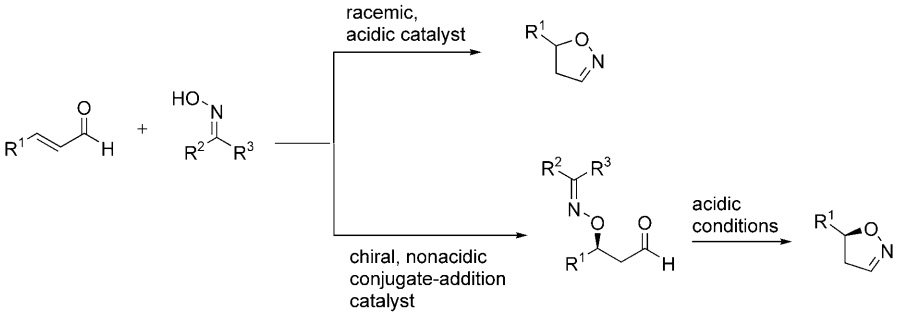
Table 1. Conjugate addition of crotonaldehyde with different oxygen nucleophiles.[a]



Nucleophile	t [min]	Yield [%][b]
2a	–	0
2b	20	6
2c	20	24
2d	20	26
2e	20	21
2f	180	36
2g	15	28

[a] Cbz = carbobenzyloxy, Troc = carbo(2,2,2-trichloroethyl)oxy. [b] NMR spectroscopic yields (conversion to product) for **4a–g** were determined by ^{1}H NMR spectroscopy using the catalyst as the internal standard. Conditions: 0.1 mmol **1a**, 0.1 mmol **2**, 1 mL $CDCl_3$.

Direct monitoring of the reactions by ^{1}H NMR spectroscopic experiments revealed that the conversions to conjugate-addition products in the tested conditions were relatively low in all cases. We were unable to isolate these addition products, and they could only be detected by ^{1}H NMR spectroscopy, but not by TLC. Nevertheless, the ^{1}H NMR spectroscopic study revealed several features that are characteristic to these reactions. First, as expected, α nucleophiles gave faster reactions and higher conversions. Second, the conversions typically reached a plateau that we expected to represent the equilibrium of the addition in the reaction conditions. Third, an exception to this behavior was observed with oxime **2g**. Under these condi-



Scheme 1. Two protocols for 2-isoxazoline formation presented herein.

tions, the reaction proceeded to give 2-isoxazoline **5a** and anisaldehyde **6** as the major products (Figure 1).

Based on this conversion plot, we assumed that isoxazoline **5a** is generated by means of an intramolecular cyclization reaction of intermediate **4g**. The formation of **4g** most likely proceeds by means of a conjugate addition between the oxime **2g** and the enal **1a** catalyzed by an imidazolidinonium salt. Interestingly, oxime **2f** was ineffective in this transformation.[17] As such, a range of oximes was screened to reveal the structural requirements of the isoxazoline-formation process. These studies are summarized in Figure 2.

In general, aliphatic oximes such as acetone oxime **7a** or pivalaldehyde oxime **7b** displayed higher rates towards isoxazoline formation when compared to aromatic oximes. However, in all cases the final yields (determined by NMR spectroscopy) of the product were typically only around 50%, despite the fact that no significant side products could be identified by ^{1}H NMR spectroscopy.

Studies with the imidazolidinone catalyst: To improve the yields, the reaction conditions were optimized. The optimization was conducted using *trans*-hex-2-enal and acetone oxime as the reactants.[18]

First, a temperature screen indicated that optimal yields could be obtained by running the reaction at 0°C. Lowering the temperature further simply decreased the reactivity but did not improve the yields, whereas at higher temperatures, faster rates but lower NMR spectroscopic yields were observed. The side reactions responsible for erosion of the yields at higher temperatures are most likely polymerization processes since no definite low-molecular-weight side products could be detected by NMR spectroscopic studies.

The reaction medium was found to have a significant impact on the yields. These experiments are summarized in Table 2. In general, nonpolar solvents such as toluene afforded the highest rates and yields.

Further optimization studies revealed that using a slight excess amount (110–120 mol%) of the enal afforded optimal yields, and lower yields were obtained when larger excess amounts of either reagent were used. Curiously, the order or reagent addition seemed to have a small, but noticeable, effect on the final yield as well. The best results were obtained when

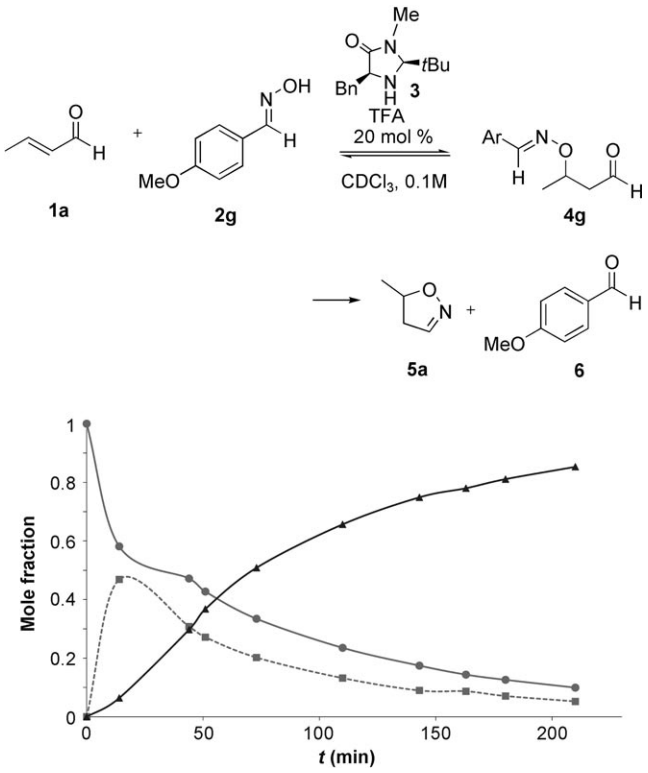


Figure 1. Formation of intermediate **4g** (■) and isoxazoline **5a** (▲) from crotonaldehyde **1a** (●) and oxime **2g**.

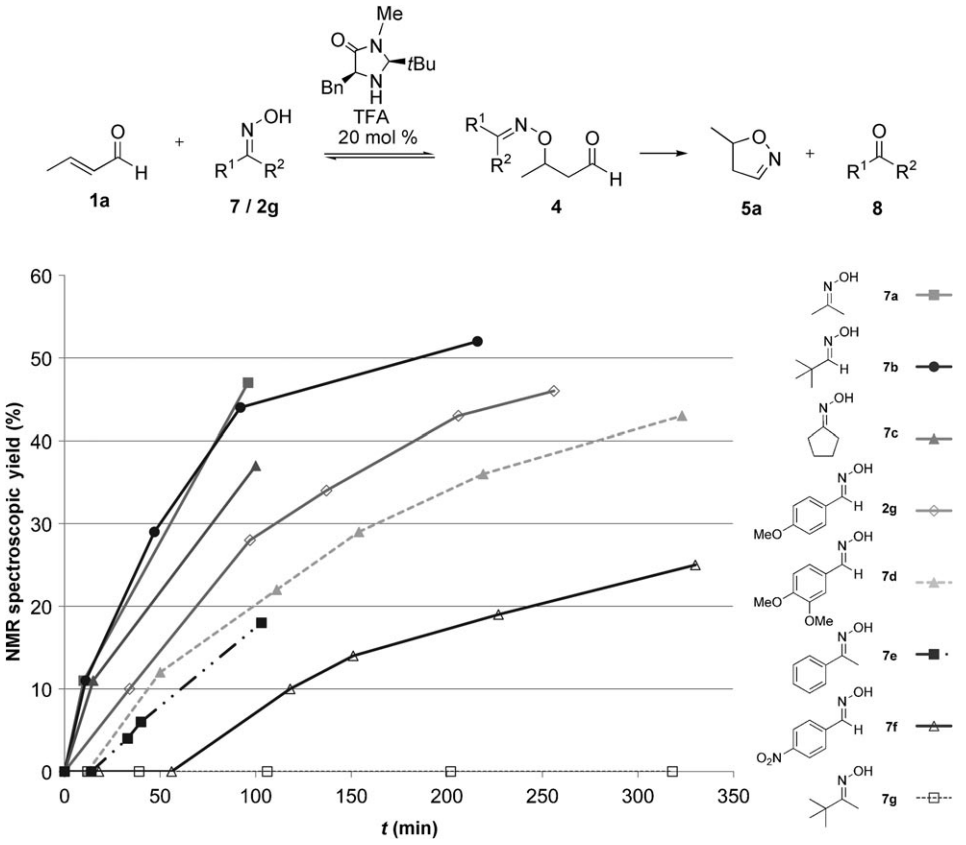
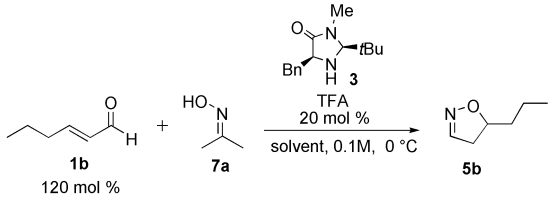


Figure 2. Formation of isoxazoline **5a** with different oximes. Conditions: crotonaldehyde 0.1 mmol, oxime 0.1 mmol, and catalyst 0.02 mmol in $CDCl_3$. Catalyst was used as the internal standard.

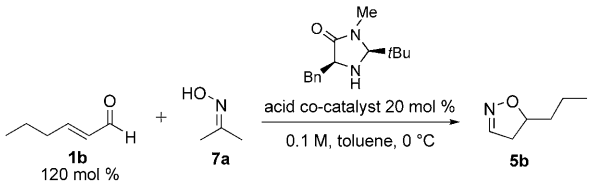
Table 2. Solvent effect on isoxazoline formation.

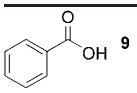
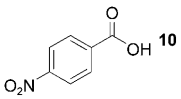
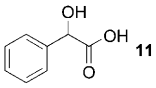
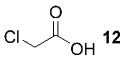
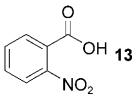
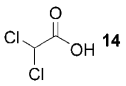
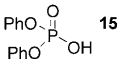
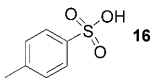


Solvent[a]	Yield [%] (1 h)[b]	Yield [%] (3 h)[b]	Yield [%] (22 h)[b]
MeCN	0	0	20
MeOH	0	0	0
THF	0	0	12
diethyl ether	7	10	30
toluene	26	40	73
$CHCl_3$	18	30	61
CH_2Cl_2	16	29	54

[a] Conditions: 0.12 mmol **1b**, 0.10 mmol **7a**, 0.020 mmol catalyst, 1 mL solvent. [b] NMR spectroscopic yields (conversion to product) were determined by ^{1}H NMR spectroscopy experiments from aliquots of the reaction mixture diluted with $CDCl_3$. Catalyst was used as the internal standard.

Table 3. Effect of co-acid on enantiomeric excess using the imidazolidinone catalyst.[a]



Acid	Yield [%] (17 h)[b]	*ee* [%][c]
 **9**	0	n.d.[d]
 **10**	5	n.d.
 **11**	13	n.d.
 **12**	12	n.d.
 **13**	10	−10
 **14**	46	−5
 **15**	76	8
 **16**	34	36

[a] Conditions: 0.12 mmol **1b**, 0.10 mmol **7a**, 0.02 mmol catalyst, and 0.02 mmol co-acid, 1 mL toluene. [b] NMR spectroscopic yield (conversion to product), as determined by ^{1}H NMR spectroscopy. Catalyst was used as the internal standard. [c] Enantiomeric excess was measured with GCMS. [d] n.d. = not determined.

catalyst and aldehyde were mixed prior to addition of the oxime. However, gradual addition the oxime did not improve the process.

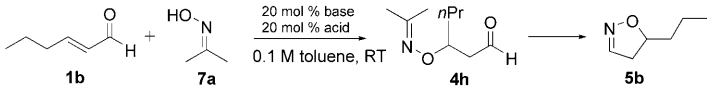
Surprisingly, under otherwise optimal conditions, the chiral oxazolidinone catalyst afforded a nearly racemic isoxazoline product. Attempts to improve the enantiomeric excess (*ee*) values by varying the acid co-catalyst component did not improve this result: the use of *p*-toluene sulfonic acid (*p*TsOH) raised the *ee* value to 36%, but NMR spectroscopic yields were disappointingly low, and similar results were obtained with many other co-acids (Table 3). At lower temperatures (−20°C), somewhat higher *ee* values (60%) were obtained with *p*TsOH **16** and related sulfonic acids ((+)-camphorsulfonic acid, 1- and 2-naphthylsulfonic acids), but the conversions remained poor (<20%).

Development of the racemic process: Having initially failed to discover the enantioselective process, a catalyst screen was conducted to find a cheaper and simpler amine catalyst for the synthesis of 2-isoxazolines in racemic form. Although the majority of secondary amine iminium-ion catalysts published in the literature are chiral, some nonchiral amines have also been used.[19] The studies with achiral amines are presented in Table 4. Aliphatic secondary amines (**22**–**27**), secondary anilines (**28a**–**28d**), and primary anilines (**29a**, **29b**) were screened. All amines were combined with four different acids of different pK_a. In addition, diphenylphosphate (DPP) was tested as it had performed very similary with TFA in other mechanistically related reactions studied in our laboratory.[19b]

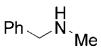
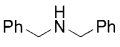
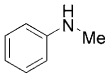
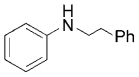
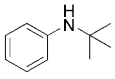
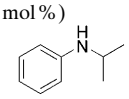
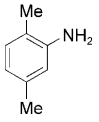
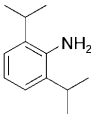
The amine/acid screen revealed that different secondary anilines, in combination with DPP, typically afforded superior results. With several amines, the reaction failed to proceed further from the initial conjugate-addition product with both weakest (chloroacetic acid) and strongest (methanesulfonic acid) acid co-catalysts. In these cases, the isoxazoline formation was suppressed. Based on these results, we selected the salt of *N*-methylaniline and DPP for further studies as both components were cheap and commercially available.

The other reaction parameters were reoptimized for the *N*-methylanilinium diphenylphosphate catalyst. Fine-tuning the structure of the aliphatic oxime[20] was helpful since oximes such as 3-pentanone oxime and methyl isopropyl ketone oxime gave slightly better yields than acetone oxime. 3-Pentanone oxime was thus selected as the oxime source as it gave the best combination of reaction rate and yield. The effect of reaction concentration was also evaluated. In general, a concentration of 0.2–0.4 M appeared to be optimal, as the lower (<0.1 M) concentration resulted in a lower reaction rate, and higher concentration (1 M) resulted in a lower yield. Although increasing the concentration has a positive impact on the reaction equilibrium and rate, it also accelerates intermolecular side reactions, thereby resulting in lower overall yields. In some cases, oximes of the initial conjugate addition products could be detected as side products.

Table 4. Racemic catalyst/co-catalyst screen.[a]



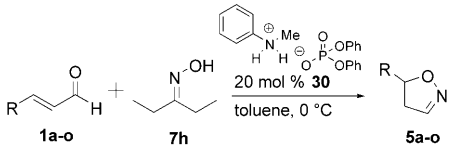
1b 7a 4h 5b

		17	18	19	20	21
22		1 h: 18% **4h** 3 h: 26% **4h**	1 h: trace of **5b** 3 h: 10% **5b**	1 h: 20% **4h** 3 h: 15% **4h**	n.d.[b]	1 h: trace of **5b** 3 h: trace of **5b**
23		1 h: 8% **4h** 3 h: 18% **4h**	1 h: trace of **5b** 3 h: trace of **5b**	1 h: 23% **4h** 3 h: 17% **4h**	1 h: 9% **4h** 3 h: 14% **4h**	n.d. 3 h: trace of **5b**
24		1 h: 10% **4h** 3 h: 13% **4h**	1 h: 9% **5b** 3 h: 20% **5b**	1 h: 4% **4h** 3 h: 12% **5b**	1 h: trace of **4h** 3 h: trace of **4h**	1 h: 16% **4h** 3 h: trace of **5b**
25		1 h: 6% **4h** 3 h: 11% **4h**	1 h: 6% **4h** 3 h: n.d	1 h: 15% **4h** 3 h: 18% **4h**	1 h: 18% **4h** 3 h: 26% **4h**	n.d.
26		1 h: no product 3 h: 5% **4h**	1 h: 11% **5b** 3 h: 21% **5b**	n.d.	n.d.	1 h: 16% **4h** 3 h: 10% **4h**, 15% **5b**
27		n.d.	n.d.	n.d.	n.d.	1 h : 10% **5b** 20 h: 27% **5b**
28a		1 h: 22% **4h** 3 h: 16% **A**, trace of **5b**	1 h: 42% **5b** 3 h: 57% **5b**	1 h: trace of **5b** 3 h: n.d.	1 h: 12% **4h** 3 h: 14% **4h**	1 h: 55% **5b** 3 h: 74% **5b**
28b		1 h: 14% **4h** 3 h: 17% **4h**	1 h: 42% **5b** 3 h: 42% **5b**	1 h: n.d. 3 h: 22% **5b**	1 h: trace of **4h** 3 h: 13% **4h**	1 h: 53% **5b** 3 h: 68% **5b**
28c (10 mol%)		n.d.	n.d.	n.d.	n.d.	3 h: no product 3 d: 28% **5b**
28d		n.d.	n.d.	n.d.	n.d.	3 h: 33% **5b**
29a		1 h: 11% **5b** 3 h: 22% **5b**	1 h: 44% **5b** 3 h: 51% **5b**	1 h: 8% **5b** 3 h: 40% **5b**	1 h: 9% **4h** 3 h: 15% **4h**	1 h: 54% **5b** 3 h: 55% **5b**
29b		1 h: 21% **5b** 3 h: 36% **5b**	1 h: 51% **5b** 3 h: 48% **5b**	n.d.	n.d.	1 h: 60% **5b** 3 h: 55% **5b**

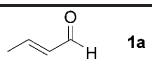
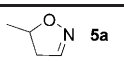
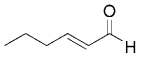
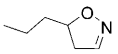
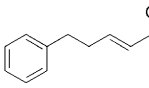
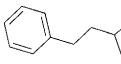
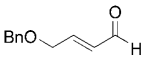
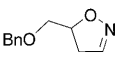
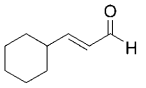
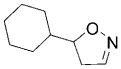
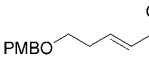
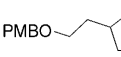
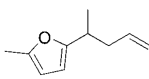
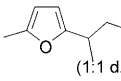
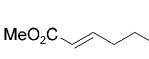
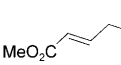
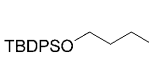
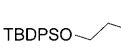
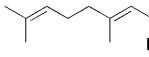
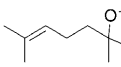
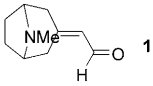
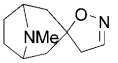
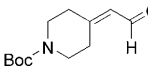
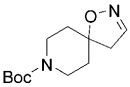
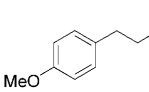
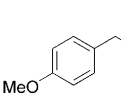
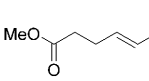
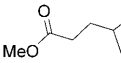
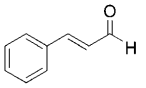
[a] Conditions: 0.12 mmol **1b**, 0.10 mmol **7a**, 0.020 mmol catalyst, 0.020 mmol acid, and 1 mL toluene. Catalysts were used as the internal standards. [b] n.d. = not determined.

After finding satisfactory conditions for the reaction, the generality with respect to the α,β-unsaturated aldehydes was explored (Table 5). These experiments revealed that the reaction is general to the α,β-unsaturated aldehydes that bear no further conjugation to the C=C bond. For example, cinnamaldehyde and (2*E*,4*E*)-hexa-2,4-dienal were unreactive, and the reaction with (*E*)-methyl 4-oxobut-2-enoate was slow. Other substrates that bear a γ-sp^3-carbon atom are well tolerated. Sensitive substrates (Table 5, entries 4 and 8) gave reasonable yields, and acid labile functionalities such as *tert*-butyldiphenylsilyl ether (TBDPS) and *tert*-butylcarbamate (Boc) (entries 9, 12) readily withstand the reaction conditions. Notably, sterically demanding substrates that bear two β-substituents are viable substrates for the reaction; they afford the isoxazolines in good yields (entries 11–14). However, the tropinone-derived enal (entry 12) gave a sluggish reaction, presumably due to the presence of a competing tertiary amine group, and addition of more acid did not help.

Table 5. Synthesis of racemic 2-isoxazolines with *N*-methylanilinium phosphate catalyst (**30**).[a]



1a-o 7h 5a-o

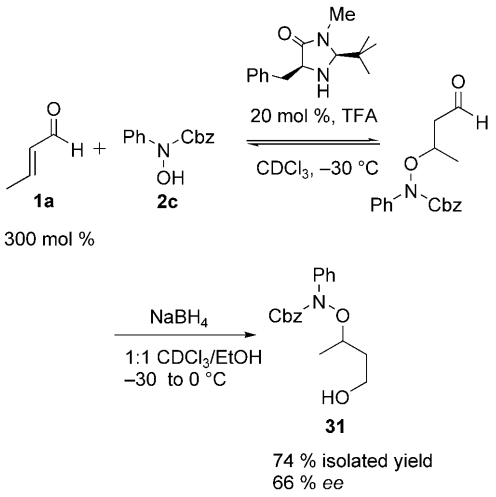
Entry	Aldehyde	Product	*t* [h]	Yield [%][b]
1	 **1a**	 **5a**	6.5	55[c]
2	 **1b**	 **5b**	6.0	80[b]
3	 **1c**	 **5c**	6.5	86
4	 **1d**	 **5d**	15.5	63
5	 **1e**	 **5e**	6.5	73
6	 **1f**	 **5f**	7.0	73
7	 **1g**	 **5g** (1:1 d.r.)	14.5	83
8	 **1h**	 **5h**	15.0	73
9	 **1i**	 **5i**	7.5	82
11	 **1j**	 **5j**	15.0	83
12	 **1k**	 **5k**	–	0[e]
13	 **1l**	 **5l**	4.0	85
14	 **1m**	 **5m**	14.0	69
15	 **1n**	 **5n**	15.0	82
16	 **1o**		no reaction	

[a] Bn = benzyl, PMBO = *para*-methoxybenzyloxy. [b] Yields refer to isolated and chromatographically purified products. [c] The reaction was performed in $CHCl_3$ using 10 mol% of **30** on a 20 mmol scale using acetaldehyde oxime as oxime reactant. Yield refers to distilled product. [d] NMR spectroscopic yield after 6 h is given. *p*-Bromoanisole was used as the internal standard. [e] Similar results were obtained without added acid and with 1 equiv of TFA or acetic acid.

In addition to 3-pentanone oxime, other oximes may be good alternative reagents in special cases. For the reaction with crotonaldehyde (Table 5, entry 1), acetaldehyde oxime was used as the oxime donor as the acetaldehyde by-product was slowly condensing to crotonaldehyde in the reaction conditions. Using volatile oxime also enabled the purification of the product isoxazoline by direct distillation from the reaction mixture. As an alternative to 3-pentanone oxime, cyclohexanone oxime gave similar yields in some cases but the reaction rates are faster (see below). The advantage of 3-pentanone, however, lies in its slightly higher volatility.

Development of the enantioselective process: The next logical objective was to return to the development of the enantioselective version of the reaction, especially since only a very few methods for the catalytic synthesis of enantiomerically enriched 2-isoxazolines have been disclosed.[15] In our initial attempts, the MacMillan imidazolidinone catalyst salts typically gave good conversions but only very low enantiomeric excess (Table 3). Based on the hypothesis that the reaction proceeds in two steps, the conjugate-addition step and the cyclization step, we first suspected that the low enantioselectivity is attributed to rapid equilibration and deterioration of the enantioselectivity in the conjugate-addition step. Equilibration of the conjugate-addition product with an imperfect catalyst could eventually lead to complete racemization of this intermediate before the cyclization step. However, we had observed that the imidazolidinone/TFA catalyst was indeed able to catalyze the oxygen conjugate-addition reaction of a different but equally reactive oxygen nucleophile, *N*,*N*-diprotected hydroxylamine **2c** (Table 1), to crotonaldehyde under similar conditions with moderate enantiomeric excess (Scheme 2).[21] As such, at least at cold temperatures, the conjugate-addition step does not give racemic products.

During the studies that probed the effect of different acid and amine combinations to the reaction rate (Table 4), we had also observed that the acid component alone was able to promote isoxazoline formation without any added amine catalyst. When these reactions were closely monitored by



Scheme 2. Enantioselective conjugate addition with *N*-hydroxycarbamate.

NMR spectroscopy, sigmoidal conversion curves were observed (Figure 3). No immediate buildup of the conjugate-addition product intermediate was observed in these reactions; instead, the rate of the reaction accelerated after an acid-dependent induction period.[22] As such, the overall reaction appeared to be catalyzed by a secondary catalyst generated during the reaction. It is therefore possible that a secondary catalyst formed during the reaction could also be responsible for the generation of the racemic products.

This result also indicated that the catalytic pathway that leads to isoxazoline formation was perhaps more complicated than initially assumed. To study the cyclization step separately, the conjugate-addition product was prepared by using a polymer-supported *N*-benzylaniline and chloroacetic acid co-catalyst. Both catalyst components were removed from the solution by filtrating the solution through a plug of basic alumina. This afforded a crude solution that contained the conjugate-addition product and that could be used to probe the effect of different acid-catalyst candidates by using ^{1}H NMR spectroscopy (Figure 4).

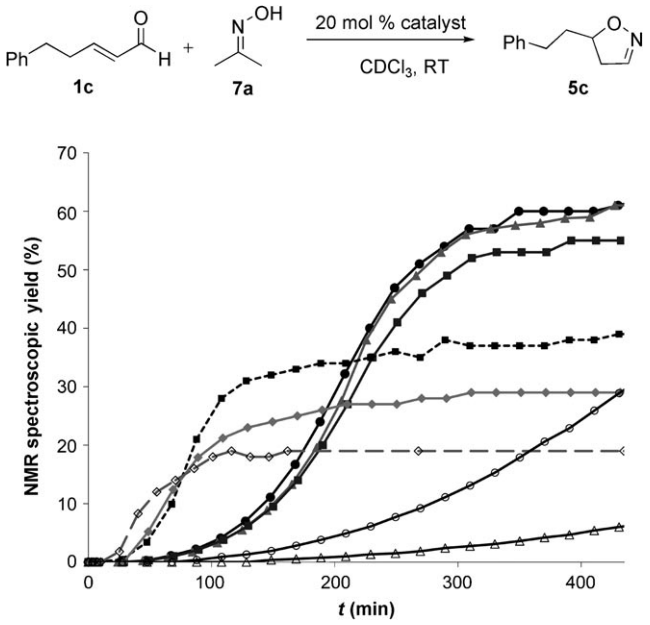


Figure 3. Formation of 2-isoxazoline in the presence of acid catalysts (trichloroacetic acid (●), diphenyl phosphate (▲), TFA (■), bis(4-nitrophenyl)phosphate (■), methanesulfonic acid (◆), *p*-TsOH (◇), dichloroacetic acid (○), chloroacetic acid (△)). *p*-Bromoanisole was used as the internal standard.

These results indicated that the cyclization of aldehyde **33** to isoxazoline takes place very rapidly under acidic conditions. No induction period was observed, and the cyclization appears to be mediated solely by the acids. The *N*-methylanilinium salt was less effective, and *N*-methylaniline failed to promote the reaction at all. These results also explained why some amine salts failed to produce the isoxazoline products in the earlier amine/co-acid screen (Table 4). Amines that are too basic suppress the isoxazoline-cyclization process by neutralizing the strong acids required for the process. The decisive factor in the cyclization activity appears to be the acidity of the amine salt.

Given that the cyclization of the conjugate-addition intermediate proceeds readily under strongly acidic conditions, we concluded that any enantioselective oxime conjugate-addition process should be applicable to the asymmetric synthesis of 2-isoxazolines if the unstable conjugate-addition product could be cyclized effectively. In a timely coincidence, the Jørgensen group had cleverly solved the problem of asymmetric oxime conjugate addition by using their own trimethylsilyl (TMS)-diarylprolinol catalyst **34**. However, the products were isolable only after $NaBH_4$ reduction to the corresponding alcohols. As such, we adapted the conditions used by Jørgensen and co-workers to the conjugate-addition step. Acetone oxime was used instead of the benzaldehyde oxime used in the original method, due to its low molecular weight and ease of hydrolysis. Several different acidic conditions for the conversion of the resulting conjugate-addition intermediates to 2-isoxazolines were screened. As summarized in Table 6, a brief exposure of the initial conjugate-addition reaction mixtures to strongly acidic conditions such as 3.2 M H_2SO_4 in methanol or 1.7 M HCl in aqueous THF resulted in the rapid formation of enantiomerically enriched 2-isoxazolines in good enantioselectivities and >60% yields. A control experiment with $NaBH_4$ (Table 6, entry 15) indicated that these cyclization conditions preserved the conjugate-addition product with the same efficiency and *ee* values as the $NaBH_4$ workup. Although benzaldehyde oxime gave better enantioselectivities (entry 6), the overall yield was inferior to that obtained with acetone oxime.[23] The high *ee* value and the moderate yield of the product are largely determined in the conjugate-addition step, and the cyclization step is fast enough to preserve the initially generated enantiomeric excess when strong acids are used in protic conditions to cyclize the conjugate-addition product. Nonprotic cyclization conditions appeared to deteriorate the *ee* values. Other catalyst combinations did not afford better results.[24]

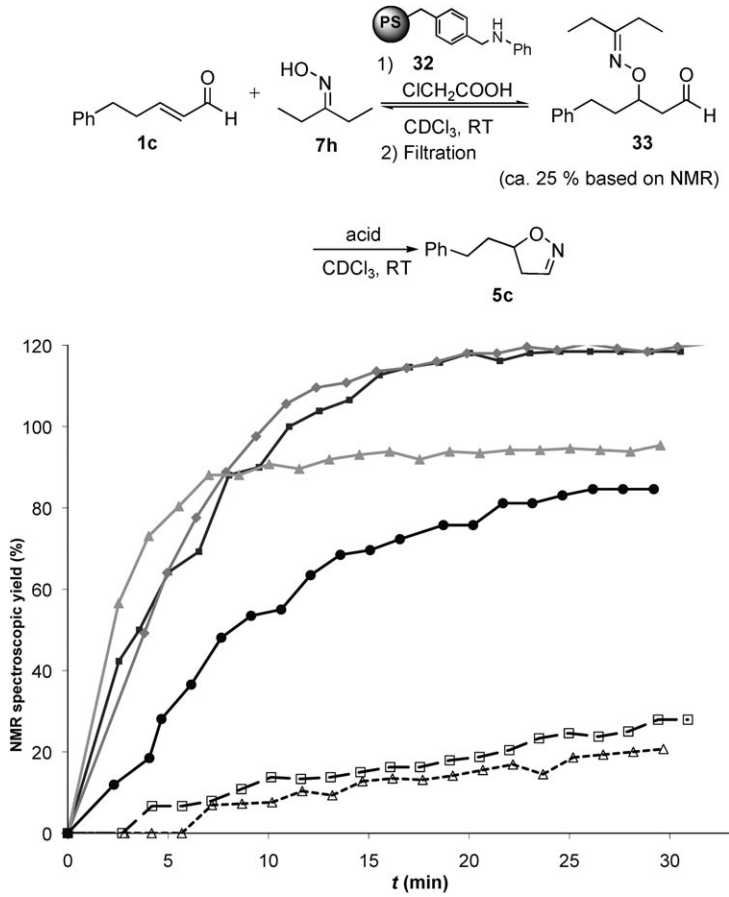
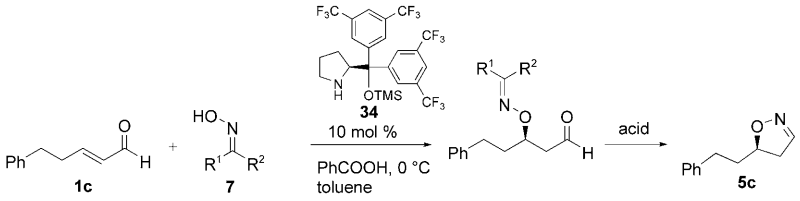


Figure 4. Conversion of intermediate **33** to **5c** in the presence of different acids (methanesulfonic acid (■), *p*-TsOH (◆), diphenyl phosphate (▲), TFA (●), dichloroacetic acid (△), *N*-methylaniline-DPP (□)). The NMR spectroscopic yield of **5c**, based on the initial concentration of intermediate **33**, is reported. *p*-Bromoanisole was used as the internal standard. The acid-induced formation of **33** from the remaining starting materials **1c** and **7h** is likely responsible for conversions that are higher than 100%.

Table 6. Screen of acidic cyclization conditions and comparison with reductive quench ($NaBH_4$, entry 15).



Entry	R^1, R^2	Acid[a]	Yield [%][b]	*ee* [%]
1	Me, Me	2.36 M H_2SO_4 (aq)	60	88
2	Et, Et	2.3 M H_2SO_4 (aq)	54	87
3	Me, Me	2 M HCl (aq)	48	91
4	Et, Et	2 M HCl (aq)	47	86
5	Me, Me	2.3 M H_2SO_4/MeOH	55	92
6	H, Ph	2.3 M H_2SO_4/MeOH	14	98
7	H, $C(CH)_3$	2.3 M H_2SO_4/MeOH	10	93
8	Me, Me	THF/H_2O + H_2SO_4 (2 mmol, 400 mol%)	64	90
9	Me, Me	THF/H_2O + *p*TsOH (2 mmol)	52	92
10	Me, Me	THF/H_2O + H_3PO_4 (2 mmol)	46	86
11	Me, Me	THF/H_2O + TFA (2 mmol)	68	86
12	Me, Me	THF/H_2O + HCl (2 mmol)	65	92
13	Me, Me	$MeSO_3H$ (300 mol%)	25	90
14	Me, Me	Et_2O/HCl (dry, 5 M)	45	80
15	Me, Me	$NaBH_4$/MeOH	60[c]	91

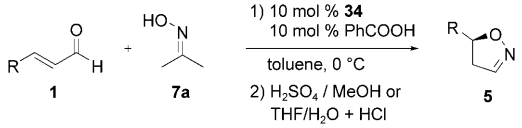
[a] 1 mL of the solution was used. [b] Isolated yield of 2-isoxazoline. [c] Isolated yield of the corresponding alcohol.

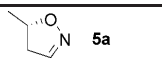
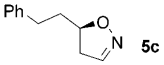
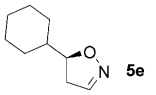
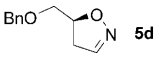
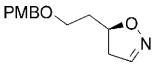
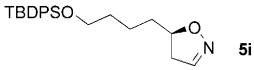
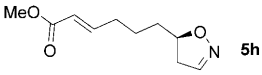
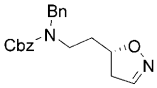
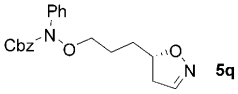
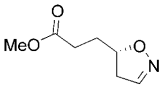
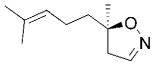
The substrate scope of the enantioselective isoxazoline protocol was examined with a range of different α,β-unsubstituted enals (Table 7). Gratifyingly, a wide range of functionalities seemed to tolerate the acidic cyclization conditions, including *para*-methoxybenzyl (PMB) ethers (Table 7, entry 4), carbamates (entry 8), and unsaturated esters (entry 7). Crotonaldehyde turned out to be challenging substrate, possibly due to side reactions. Interestingly, geranial **1j** was also a competent substrate (entry 11); it afforded the product in average yield but lower enantioselectivity, probably as a consequence of the smaller energy difference between the reactive (*E*)- and (*Z*)-iminium ions. Importantly, reactions run at a slightly larger scale (2 mmol) and with a larger excess amount of the oxime reagent (4.5 equiv) and longer reaction time (5 h) increased the yields in all cases (entries 2–4, 6–8, and 11) by around 10–15%.[20]

When the enantioselective process was scaled up to 2–5 mmol, we encountered inconsistencies in the product *ee* values with aldehydes **1c**, **1d**, and **1e**. After extensive experimentation, including examination of the reaction conditions, reagents, reaction times, and both the chemical and optical purity of the commercial catalyst, careful purification of the amine catalyst afforded consistently good enantioselectivities. The overall yields, however, were not typically affected by the impurities.[20]

Mechanistic discussion: We propose that the overall mechanism for the 2-isoxazoline formation predominantly follows a pathway along which the conjugate-addition product formed in a fast reaction between aldehyde and the oxime cyclizes to

Table 7. Enantioselective synthesis of different optically active 2-isoxazolines with the diarylprolinol catalyst **34**.



Entry	Product	Yield [%][a]	*ee* [%]
1	 **5a**	39[b]	86
2[c]	 **5c**	72	94
3[c]	 **5e**	65	91–97
4[c]	 **5d**	60	95
5	 **5f**	52	90
6[c]	 **5i**	69	94
7[c]	 **5h**	72	94
8[c]	 **5p**	59	92
9	 **5q**	59	91
10	 **5n**	70	90
11[c]	 **5j**	58	69

[a] Isolated yields. [b] NMR spectroscopic yield. *p*-Bromoanisole was used as the internal standard. [c] Reaction conducted on a 2 mmol scale (2.0 mmol aldehyde, 9.0 mmol oxime, and 0.20 mmol of the chromatographically purified catalyst).

2-isoxazoline in the presence of catalysts. The conjugate-addition reaction of oximes likely involves iminium ions as reactive intermediates. This mechanism is supposedly operational in the presence of anilinium salts as well.

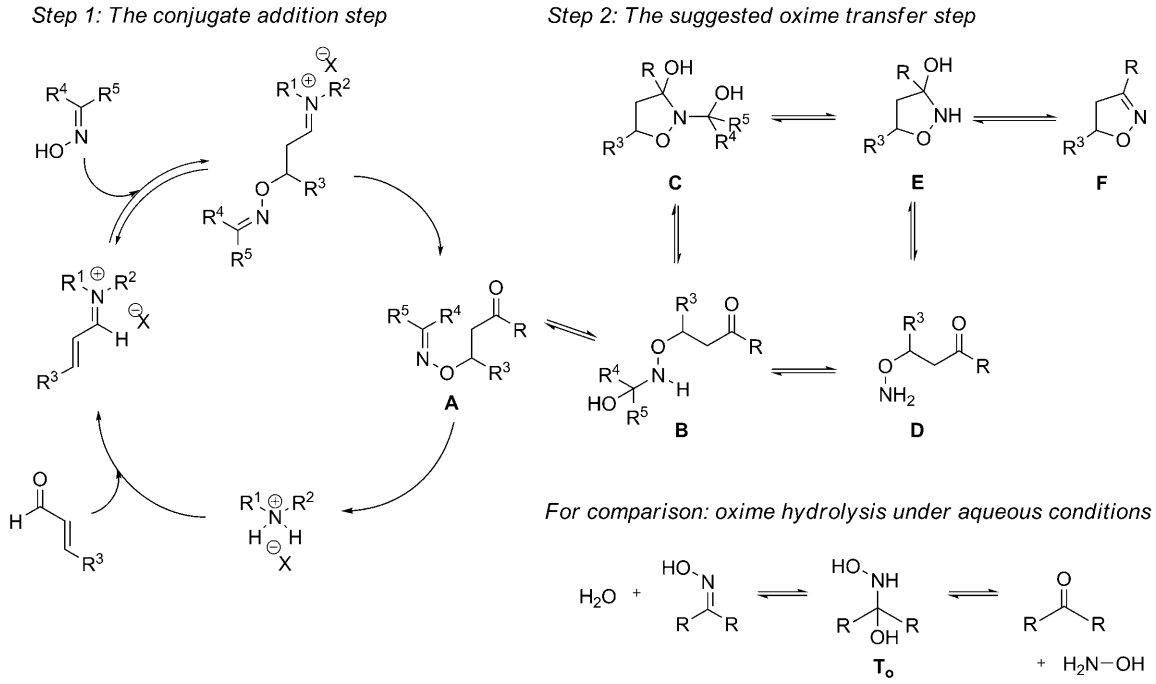
The cyclization reaction to 2-isoxazoline appears to be an intramolecular oxime-transfer reaction that mechanistically consists of sequential oxime hydrolysis and oxime-formation reactions (Scheme 3). Related oxime-transfer reactions have been previously reported for several different substrates in aqueous acidic conditions.[25]

More O'Ferrall, Jencks, and Sayer have conducted thorough studies of oxime hydrolysis[26] and formation[27] reactions in aqueous media. Both reactions have been shown to proceed by means of a carbinolamine intermediate $\mathbf{T}_0$ (Scheme 3). For the formation of *p*-chlorobenzaldehyde *O*-methyloxime, the pH of the solution determines the rate-determining step (rds). At low pH (0–2), the attack of the nucleophile to the aldehyde is the rds, and above pH 5, the elimination of the water molecule from the carbinolamine intermediate $\mathbf{T}_0$ is rate-limiting.[27b] In the intermediate pH range, the proton-transfer reactions that lead to the carbinolamine intermediate have been shown to have kinetic significance. In oxime hydrolysis, on the other hand, the nucleophilic attack of water to the oxime has been shown to limit the reaction at high pH, whereas the elimination of the hydroxylamine limits the reaction rate in acidic conditions.[26c] These results of these studies are used as the basis for the following discussion.

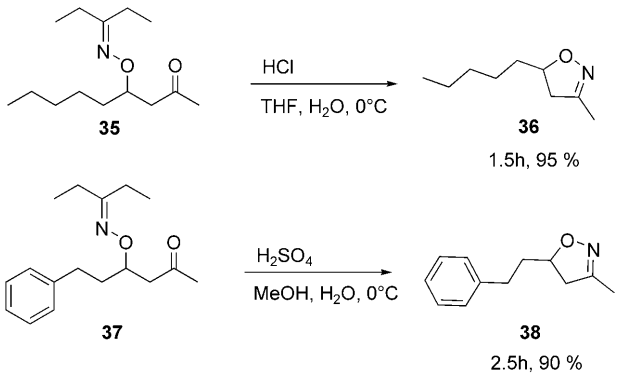
The mechanism of the oxime transfer likely involves intermediates that are similar to those observed in the studies of oxime formation and hydrolysis reactions. In our enantioselective process, we used strongly acidic protic conditions for the cyclization step. Based on the mechanistic studies mentioned above, the overall rate of oxime transfer in these conditions is likely determined by the rates of the elimination reactions in the proposed intermediates **B** and **C** (which correspond to the elimination of hydroxylamine in oxime hydrolysis) or by the rates of cyclization of the proposed intermediates **B** or **D** (which correspond to the nucleophilic attack in the formation of $\mathbf{T}_0$). This hypothesis is supported by the cyclization experiments conducted with isolated β-oxime ketones **35** and **37** that indicated slower cyclization rates with ketones compared to the aldehyde conjugate-addition intermediates. Even though a direct comparison of the cyclization rates in these conditions is not reliable due to difficulties in standardizing the experimental conditions for both substrates (aldehyde and ketone), these results imply that the initial attack of water is not likely to be the rds under these conditions. Although the reaction is slower with ketones, it should be noted that the cyclization still proceeds to give high yields of the corresponding 3-substituted isoxazolines. As such, the conjugate-addition/oxime-transfer route is not restricted to aldehydes, and could be used to prepare 2-isoxazolines from α,β-unsaturated carbonyl compounds (Scheme 4).

Mechanistically, the process catalyzed by anilinium salt in which the isoxazoline is formed in aprotic conditions represents a different case. To the best of our knowledge, the formation and hydrolysis of oximes has not been studied in aprotic media. The situation differs from aqueous protic media significantly in two ways. First, water is available only in catalytic quantities from the aldehyde–iminium equilibrium between the catalyst and enal. Second, the reaction conditions are only moderately acidic as the only acid is the catalytic anilinium salt (cf. Figure 4 in which different acids are compared). Under these conditions, the most likely rate-limiting steps are the formation of **B** and the dehydration of **E**. The possible nucleophilic cyclization (**B** to **C** and **D** to **E**) and elimination steps (**B** to **D**, **C** to **E**) resemble the steps involved in the enamine–iminium equilibrium and are usually considered to be fast in similar conditions.[28]

We examined the effect of added water and both oxime and aldehyde structure to the rate of anilinium-salt-catalyzed isoxazoline formation.[20] Upon addition of 10, 20, 50, and 75 mol % of water to the reaction mixture, a small rate-



Scheme 3. Proposed mechanistic pathway for the formation of the intermediate **A** and the subsequent oxime-transfer reaction.



Scheme 4. Acid-promoted cyclization of ketone substrates.

accelerating effect was observed in the reaction between *trans*-hex-2-enal and 3-pentanone oxime, but no further acceleration could be seen beyond 50 mol% of water, presumably due to saturation of the reaction mixture.[20] The effect of oxime structure on the reaction rate was evident already in the preliminary tests of the reaction. Both aldehyde and ketone oximes proved to be reactive, but increasing the steric hindrance or introduction of electron-withdrawing substituents in the *para* position of benzaldehyde oximes decreased the reaction rate.[29] Finally, experiments that compared the reaction rates of 3-pentanone oxime with differently substituted aldehydes demonstrated a clear accelerating effect of additional aldehyde β-substitution (Figure 5). Exocyclic enals such as cyclohexylideneacetaldehyde (**1r**) and **1l** turned out to be particularly reactive substrates, and geranial **1j** and **1m** also reacted faster than structurally similar **1c**.

The results of water and oxime structure experiments would suggest the step **A**→**B** as the rate-limiting step. If this were the case, β,β-disubstitution of the aldehyde would not be expected to have a significant effect on the rate unless the rate differences were simply caused by concentration differences between the reactive intermediates **A** with different aldehydes. To probe these differences, the conjugate-addition steps between different enals and a particularly slowly cyclizing oxime, *p*-nitrobenzaldehyde oxime, were examined (Figure 5).[30] Although the equilibrium concentrations of the intermediates were higher with exocyclic enals **1r** and **1l** compared to other substrates,[31] the structurally very similar pair **1m** and **1c** behaved differently. The β,β-disubstituted substrate **1m** cyclizes faster than the β-monosubstituted substrate **1c**, although the equilibrium concentrations of the intermediates **4m** are smaller compared to **4c**. It is thus reasonable to assume that the rate-limiting step occurs later in the cyclization pathway, and the observed effects with water and different oximes are incorporated into the overall rate at earlier stages of the sequence, presumably through equilibration.

Based on the established reaction pathways[26,27] (see above) for the intermolecular oxime formation and hydrolysis, the breakdown rates of the tetrahedral intermediates **B**, **C**, or **E** (Scheme 3) were the likely candidates for the rate-limiting step of the intramolecular oxime-transfer reaction. We probed the relative breakdown rates of the tetrahedral intermediate **B** or **C** by comparing the reaction rates of anilinium-catalyzed 2-isoxazoline formation between 3-pentanone oxime, acetone oxime, cyclopentanone oxime, and cyclohexanone oxime. Cyclohexanone oxime turned out to be a superior reagent to all other tested oximes in terms of rate

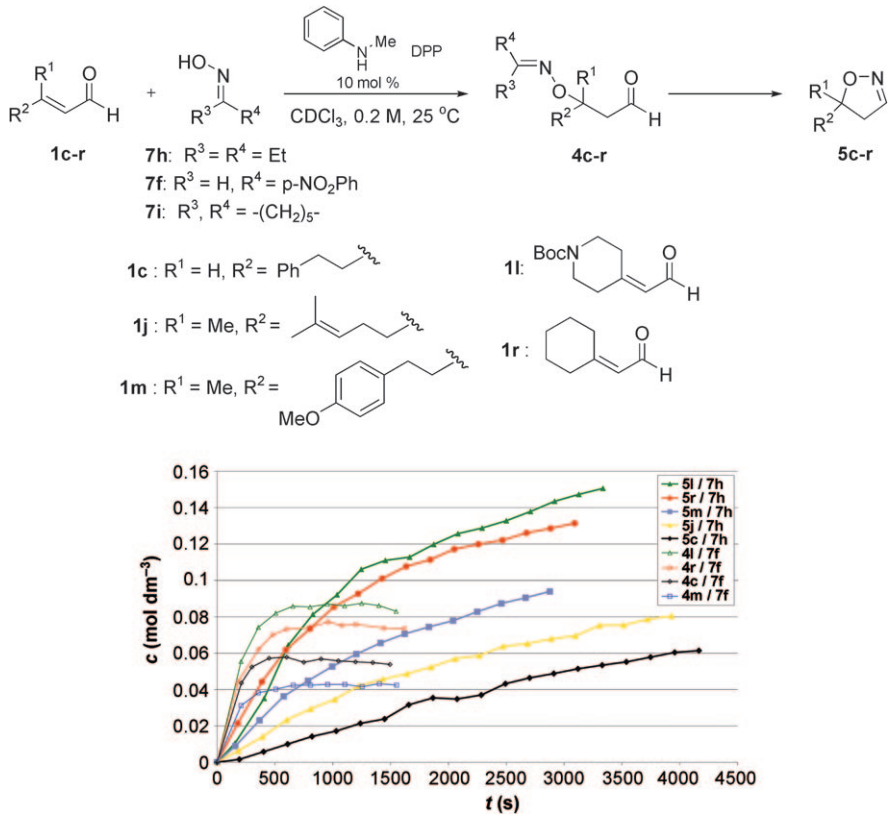


Figure 5. NMR spectroscopic yields of conjugate-addition intermediates (**4c**, **4l**, **4m**, and **4r**) and 2-isoxazolines (**5c**, **5j**, **5l**, **5m**, and **5r**) in the reactions of different enals (**1c**, **1l**, **1m**, and **1r**; 0.20 mmol, 100 mol%) with *p*-NO_2-benzaldehyde oxime (**7f**; 0.20 mmol, 100 mol%) or 3-pentanone oxime (**7h**; 0.20 mmol, 100 mol%). *p*-Bromoanisole or 3,5-bis(trifuoromethyl)bromobenzene were used as the internal standards.

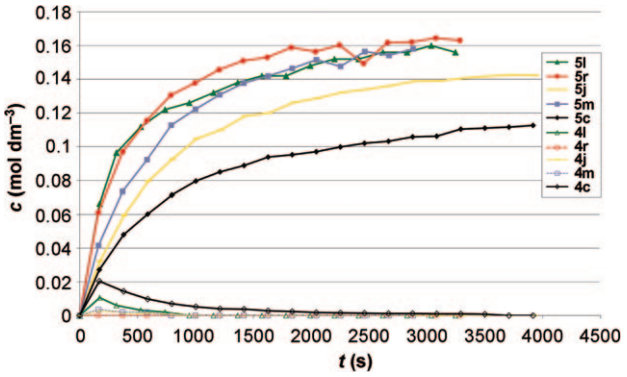


Figure 6. NMR spectroscopic yields of 2-isoxazolines (**5c**, **5j**, **5l**, **5m**, and **5r**) and the respective conjugate-addition intermediates (**4c**–**4r**) in the reactions of different enals (**1c**, **1j**, **1l**, **1m**, and **1r**, 0.20 mmol, 100 mol%) with cyclohexanone oxime (**7i**; 0.20 mmol, 100 mol%). *p*-Bromoanisole or 3,5-bis(trifuoromethyl)bromobenzene were used as the internal standards.

(Figure 6 and Supporting Information). According to Brown,[31] exocyclic double bonds should be more reactive in six-membered rings compared to similar acyclic or five-membered ring systems. As such, cyclohexanone oxime should show increased reactivity compared to acyclic ketone oximes in the nucleophilic addition step (**A**→**B**, Scheme 3) but decreased reactivity in the ketone elimination step (**C**→**E**). Thus, the increased relative rate observed with cyclohexanone oxime does not support the slow elimination of ketone from **B** or **C**. If the step **A**→**B** were rate-limiting, the rate differences between the cyclization of the β,β-disubstituted aldehyde such as **1m** and the β-monosubstituted aldehyde **1c** would be expected to be rather small. However, even with cyclohexanone oxime, the formation of **5m** (from the β,β-disubstituted aldehyde) is almost twice as rapid as the formation of **5c** (see Figure 6). This result leaves the rate-limiting breakdown of final intermediate **E** as the only possibility that accounts for the differing rates between both different aldehydes and oximes.[32] However, considering that the evidence for this is not direct and that the rate differences between different substrates and conditions are relatively small, it is entirely possible that the energies of cyclization intermediates as well as the barriers between them may also be small and, as a consequence, the overall reaction in different cases may be determined by several factors that depend on reagents. Also, other mechanisms that involve the participation of other nucleophiles, such as the aniline catalyst as the initiating nucleophile in the cyclization pathway, cannot be excluded by our present studies.[33]

Conclusion

We have developed a new method for the synthesis of the 3-unsubstituted 2-isoxazolines that takes advantage of the conjugate-addition reaction of oximes with enals. In the presence of acidic catalysts, the labile conjugate-addition intermediates directly cyclize to thermodynamically more stable 2-isoxazolines. The general strategy was shown to be applicable to the enantioselective synthesis of 3-unsubstituted 2-isoxazolines by the rapid acid-catalyzed cyclization of enantio-enriched conjugate-addition products. This protocol is the first general catalytic asymmetric method for the preparation of 3-unsubstituted 2-isoxazolines. The acid-mediated cyclization can also be applied to Michael adducts of oximes and α,β-unsaturated ketones to afford 3,5-disubstituted isoxazolines. Finally, the anilinium-catalyzed process displays

interesting substituent effects. These suggest that that the rate-limiting step in these processes might be the dehydration of the 3-hydroxy-2-isoxazolinidine intermediate.

Experimental Section

General: All moisture-sensitive reactions were carried out under an argon atmosphere in flame-dried glassware unless otherwise noted. Preparative 2-isoxazoline reactions were conducted in screw-cap glass vials or small flasks by using dry toluene as the reaction solvent, but without exclusion of air or moisture. The reaction temperatures refer to the temperatures of the cooling or heating baths.

When needed, nonaqueous reagents were transferred under argon by syringe or cannula and dried prior to use. THF and toluene used were obtained either by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system) or by distillation over sodium/benzophenone. Other solvents and reagents were used as obtained from suppliers unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light (254 or 366 nm) and by staining upon heating with standard vanillin, permanganate, ninhydrin, or cerium-phosphomolybdic acid solutions. For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted.

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 (^{1}H: 399.98 MHz; ^{13}C: 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ ($\delta=7.26$ ppm), $C_2H_2Cl_4$ ($\delta=5.98$ ppm), or CD_3CN ($\delta=1.94$ ppm) for ^{1}H NMR spectroscopy and ($\delta=77.0$, 73.7, 1.32 ppm) for ^{13}C NMR spectroscopy. In general, the NMR spectroscopic yields of the conjugate-addition products and the intermediates were determined by ^{1}H NMR spectroscopic experiments by using the integrals of the aldehyde peak ($\delta=9.55$–9.50 ppm, 1H) for the starting material, the aldehyde peak ($\delta=9.8$ ppm, 1H) for the intermediate, and the 5-H ($\delta\approx4.7$–4.6 ppm, 1H) or 4-H ($\delta\approx3.1$–3.0 and 2.6–2.5 ppm, both 1H) peaks for the isoxazoline. The integrals were compared against an internal standard (20 mol%, *p*-bromoanisole ($\delta=7.4$ (2H), 6.8 (2H), 3.8 ppm (s, 3H)) or 3,5-bis(trifluoromethyl)bromobenzene ($\delta=8.0$ (2H), 7.8 ppm (1H)). In the experiments described in Tables 1–4, the integrals of the starting materials and products were calibrated with catalyst peaks (for example, *tert*-butyl peak of **3** at $\delta=0.75$–0.80 ppm).

The enantiomeric excesses of the products were determined by HPLC using chiral stationary phases and the corresponding racemic samples as references. Melting points were determined in open capillaries using a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were recorded using a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were obtained using a Perkin–Elmer 343 polarimeter. High-resolution mass spectrometric data were obtained using a Micro-Mass LCT Premier Spectrometer by the Analytical Services of the Department of Chemistry.

Materials: All commercial reagents, unless otherwise noted, were used without further purification. 2,2,6,6-Tetramethylpiperidine *N*-oxide (TEMPO) was purified by sublimation. All oximes used in this study were prepared in our laboratory and purified by distillation or recrystallization from hydrocarbon solvents. When benzaldehyde oxime is referred to, only the *E* isomer (separated from the *Z* isomer by column chromatography) was used.

Geranial **1j** and 2-cyclohexylideneacetaldehyde **1r** used in the mechanistic studies were prepared from corresponding allylic alcohols as described by Koskinen and Kumpulainen.[34] The preparation and full characterization data of 2-isoxazolines not reported here have been reported in the preceding communications.[12,13] For the preparation and characterization data of other compounds involved, see the Supporting Information.

***N*-Methylanilinium diphenylphosphate (30)**: The catalyst was most conveniently used as a salt that was prepared from commercial diphenylphosphate and *N*-methylaniline. Diphenylphosphate (100 mol%) was dissolved in Et_2O (used as much as needed to ensure complete dissolution of DPP) at room temperature. The solution was cooled on an ice bath and *N*-methylaniline (105 mol%) was added. Stirring the solution on an ice bath resulted in precipitation of the salt that was filtered, washed well with Et_2O, and dried in vacuum. The salt was used as catalyst without further purification. For analytical purposes, the salt was recrystallized from EtOH/Et_2O. White solid; m.p. 78.5–79.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=11.34$ (br s, 2H), 7.30–7.19 (m, 13H), 7.10–7.0 (m, 2H), 2.70 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=152.6$, 152.5, 139.3, 129.7, 129.3, 127.6, 123.6, 121.7, 120.3, 120.25, 37.1 ppm; elemental analysis calcd (%) for $C_{19}H_{20}NO_4P$: C 63.9, H 5.6, N 3.9; found: C 64.0, H 5.6, N 3.7.

General synthetic procedure for racemic 2-isoxazolines using *N*-methylanilinium diphenylphosphate (30) catalyst:[20] Catalyst **30** (36 mg, 0.10 mmol, 20 mol%) was dissolved in toluene (2.5 mL) at room temperature and the solution was cooled to 0 °C. α,β-Unsaturated aldehyde (0.60 mmol, 120 mol%) was added, followed by 3-pentanone oxime (0.50 mmol, 100 mol%) (or cyclohexanone oxime; see notes in the Supporting Information). After the reaction was completed (based on consumption of the aldehyde or oxime, indicated by TLC or ^{1}H NMR spectroscopy) the reaction mixture was diluted with Et_2O (15 mL) and the resulting solution was washed with saturated $NaHCO_3$ (5 mL) and 5% aqueous oxalic acid (2×5 mL). Both basic and acidic aqueous phases were then back-extracted with Et_2O (6 mL, 2×5 mL, respectively). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated carefully in vacuo, and the resulting residue was purified by column chromatography.

*Compound **5g** (mixture of diastereomers 1:1)*: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (103 μL, $\rho=1.04$, 0.60 mmol, 120 mol%), 3-pentanone oxime (55 μL, $\rho=0.92$, 0.50 mmol, 100 mol%). Reaction time: 14.5 h. Eluent: gradient 8–30% methyl *tert*-butyl ether (MTBE) in hexanes. Yield: 80 mg (83%), yellow oil; $R_f=0.4$ (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): diastereomer 1: $\delta=7.10$ (t, $J=1.8$ Hz, 1H), 5.90 (d, $J=3$ Hz, 1H), 5.86–5.83 (m, 1H), 4.46 (dtd, $J_1=5.3$ Hz, $J_2=7.9$ Hz, $J_3=10.5$ Hz, 1H), 3.06–2.94 (m, 1H), 2.96 (ddd, $J_1=1.8$ Hz, $J_2=10.5$ Hz, $J_3=17.4$ Hz, 1H), 2.49 (ddd, $J_1=1.8$ Hz, $J_2=7.9$ Hz, $J_3=17.4$ Hz, 1H), 3.44 (s, 3H), 2.25 (d, $J=0.9$ Hz, 1H), 1.87 (ddd, $J_1=5.3$ Hz, $J_2=8.1$ Hz, $J_3=13.8$ Hz, 1H), 1.80 (ddd, $J_1=5.3$ Hz, $J_2=9.2$ Hz, $J_3=13.8$ Hz, 1H), 1.27 ppm (d, $J=7.0$ Hz, 3H); diastereomer 2: $\delta=7.10$ (t, $J=1.8$ Hz, 1H), 5.87–5.82 (m, 2H), 4.46 (m, 1H), 3.03 (ddd, $J_1=1.8$ Hz, $J_2=10.4$ Hz, $J_3=17.2$ Hz, 1H), 3.05–2.90 (m, 1H), 2.58 (ddd, $J_1=1.9$ Hz, $J_2=8.2$ Hz, $J_3=17.3$ Hz, 1H), 2.25 (d, $J=0.9$ Hz, 3H), 2.12 (td, $J_1=7.0$ Hz, $J_2=13.9$ Hz, 1H), 1.68 (ddd, $J_1=6.6$ Hz, $J_2=7.3$ Hz, $J_3=13.9$ Hz, 1H), 1.29 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=157.4$, 157.0, 150.4, 150.3, 146.0, 145.9, 105.7, 105.6, 105.1, 104.4, 77.2, 76.5, 41.8, 40.81, 40.78, 40.6, 30.7, 29.9, 20.1, 18.8, 13.5, 13.45 ppm; FTIR for the mixture of diastereomers (film): $\tilde{\nu}=2968$, 2824, 1601, 1567, 1453, 1436, 1220, 1020, 840, 784 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for [$C_{11}H_{15}NO_2$+Na]: 194.1181; found: 194.1178.

*Compound **5j***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (105 μL, $\rho=0.87$, 0.60 mmol, 120 mol%), 3-pentanone oxime (55 μL, 0.50 mmol, 100 mol%). Reaction time: 15 h. Eluent: gradient 10–20% EtOAc in hexanes. Yield: 70 mg (83%), colorless oil; $R_f=0.34$ (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.01$ (t, $J=1.7$ Hz, 1H), 5.07 (m, 1H), 2.81 (dd, $J_1=1.7$ Hz, $J_2=17.5$ Hz, 1H), 2.65 (dd, $J_1=1.7$ Hz, $J_2=17.5$ Hz, 1H), 2.03 (m, 2H), 1.67 (s, 3H), 1.66–1.62 (m, 2H), 1.59 (s, 3H), 1.34 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=145.6$, 132.0, 123.5, 84.5, 45.5, 39.9, 25.6, 25.4, 22.9, 17.6 ppm; FTIR (film): $\tilde{\nu}=2971$, 2928, 2858, 1673, 1600, 1439, 1376, 1296, 1112, 870 cm^{-1}; HRMS (ESI+): *m*/*z* calcd for [$C_{10}H_{17}NO$+H]: 168.1388; found: 168.1387.

*Compound **5l***: Prepared as described in the general procedure except that 100 mol% of both starting materials were used. Starting materials: α,β-unsaturated aldehyde (113 mg, 0.53 mmol, 106 mol%), 3-pentanone oxime (55 μL, 0.50 mmol, 100 mol%). Reaction time: 4 h. Eluent: gradient 30–40% EtOAc in hexanes. Yield: 105 mg (85%), white solid; m.p. 67–68 °C; $R_f=0.32$ (60% EtOAc in hexanes); ^{1}H NMR (400 MHz,

$CDCl_3$): $\delta = 7.09$ (t, $J = 1.8$ Hz, 1H), 3.67 (td, $J_1 = 4.5$ Hz, $J_2 = 13.6$ Hz, 2H), 3.34 (ddd, $J_1 = 3.3$ Hz, $J_2 = 10.2$ Hz, $J_3 = 13.6$ Hz, 2H), 2.71 (d, $J = 1.8$ Hz, 2H), 1.78 (m, 2H), 1.61 (ddd, $J_1 = 4.5$ Hz, $J_2 = 10.2$ Hz, $J_3 = 13.5$ Hz, 2H), 1.43 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.6$, 145.8, 81.8, 49.6, 45.8, 40.9, 35.5, 28.3 ppm; FTIR (film): $\tilde{\nu} = 2976$, 2934, 2871, 1694, 1603, 1473, 1454, 1422, 1366, 1269, 1246, 1234, 1176, 1149, 869 cm^{-1}; HRMS (ESI+): m/z calcd for [$C_{12}H_{20}N_2O_3$+Na]: 263.1372; found: 263.1371.

Compound ***5m***: Prepared as described in the general procedure except that 100 mol% of both starting materials were used. Starting materials: α,β-unsaturated aldehyde (102 mg, 0.50 mmol, 100 mol%), 3-pentanone oxime (55 μL, 0.50 mmol, 100 mol%). Reaction time: 14 h. Eluent: gradient 30–18% hexanes in CH_2Cl_2. Yield: 76 mg (69%), tan oil that solidifies upon standing; m.p. 50–51 °C; $R_f = 0.5$ (60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.13$–7.08 (m, 2H), 7.04 (t, $J = 1.8$ Hz, 1H), 6.85–6.80 (m, 2H), 3.78 (s, 3H), 2.83 (dd, $J_1 = 1.8$ Hz, $J_2 = 17.5$ Hz, 1H), 2.69 (dd, $J_1 = 1.8$ Hz, $J_2 = 17.5$ Hz, 1H), 2.66–2.60 (m, 2H), 1.93 (m, 2H), 1.41 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.8$, 145.7, 133.65, 129.1, 113.8, 84.3, 55.2, 45.7, 42.1, 29.6, 25.5 ppm; FTIR (film): $\tilde{\nu} = 2969$, 2932, 2836, 2059, 1884, 1611, 1583, 1513, 1459, 1440, 1376, 1301, 1245, 1178, 1035, 869, 822 cm^{-1}; HRMS (ESI+): m/z calcd for [$C_{13}H_{17}NO_2$+Na]: 242.1157; found: 242.1152.

Compound ***5n***: Compound **30** (36 mg, 0.10 mmol, 20 mol%) was added to a solution of α,β-unsaturated aldehyde **1n**[35] (85 mg, 0.60 mmol, 120 mol%) in toluene (2.5 mL) at room temperature. After the catalyst had dissolved (2 min), the reaction mixture was cooled to 0 °C and 3-pentanone oxime (55 μL, 0.50 mmol, 100 mol%) was added. After 15 h, the reaction mixture was diluted with Et_2O (15 mL) and the resulting solution was washed with saturated $NaHCO_3$ (5 mL) and 5% aqueous oxalic acid (2×5 mL). Both basic and acidic aqueous phases were back-extracted with Et_2O (10 mL, 2×5 mL, respectively) and again with EtOAc (2×10 mL, both) to recover the relatively polar product from the aqueous phase. The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to approximately 1 mL. Purification of the residue by column chromatography (50–60% MTBE in hexanes) afforded product **7n** (65 mg, 82%) as a colorless oil. $R_f = 0.21$ (70% MTBE in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$ (t, $J = 1.8$ Hz, 1H), 4.60–4.50 (m, 1H), 3.66 (s, 3H), 3.08 (ddd, $J_1 = 1.8$ Hz, $J_2 = 10.5$ Hz, $J_3 = 17.5$ Hz, 1H), 2.62 (ddd, $J_1 = 1.8$ Hz, $J_2 = 7.3$ Hz, $J_3 = 17.5$ Hz, 1H), 2.52–2.39 (m, 2H), 1.88 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.3$, 145.8, 77.2, 51.6, 40.5, 30.1, 29.9 ppm; FTIR (film): $\tilde{\nu} = 3076$, 2954, 1736, 1601, 1439, 1362, 1262, 1201, 1176, 845 cm^{-1}; HRMS (ESI+): m/z calcd for [$C_7H_{11}NO_3$+Na]: 180.0637; found: 180.0643.

General synthetic procedure for the enantioselective synthesis of 2-isoxazolines:[20] (*S*)-α,α-[Bis(3,5-bistrifluoromethyl)phenyl]-2-pyrrolidine methanol trimethylsilyl ether (0.20 mmol, 10 mol%, purified by column chromatography) and benzoic acid (0.20 mmol, 10 mol%) were dissolved in toluene (1 mL) at room temperature. α,β-Unsaturated aldehyde (2.0 mmol, 100 mol%) was added to this solution at 0 °C (an ice–water bath was used), and after 1 min, acetone oxime (9.0 mmol, 450 mol%) was then added. After stirring the reaction mixture for the indicated period of time, a precooled (0 °C) freshly prepared solution of concentrated H_2SO_4 (0.84 mL, 15.9 mmol, 800 mol%), methanol (3.8 mL), and water (0.2 mL) was added and the resulting solution was stirred vigorously for 15–20 min at 0 °C. Saturated aqueous $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with EtOAc (2×15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (EtOAc/hexanes).

*Compound (R)-****5c***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (320 μL, $\rho = 1.0$, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.2 h. Eluent: gradient: 20–25% EtOAc in hexanes. Yield: 253 mg (72%), colorless oil; $R_f = 0.35$ (40% EtOAc in hexanes); $[\alpha]_D = +138.9$ ($c = 1$, CH_2Cl_2, 94% *ee*); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.31$–7.27 (m, 2H), 7.21–7.18 (m, 3H), 7.12 (t, $J = 1.8$ Hz, 1H), 4.52 (ddt, $J_1 = 5.2$ Hz, $J_2 = 7.8$ Hz, $J_3 = 10.5$ Hz, 1H), 3.04 (ddd, $J_1 = 1.8$ Hz, $J_2 = 10.5$ Hz, $J_3 = 17.4$ Hz, 1H), 2.80 (ddd, $J_1 = 5.6$ Hz, $J_2 = 9.5$ Hz, $J_3 = 13.9$ Hz, 1H), 2.72 (ddd, $J_1 = 6.9$ Hz, $J_2 = 9.3$ Hz, $J_3 = 13.9$ Hz, 1H), 2.62 (ddd, $J_1 = 1.8$ Hz, $J_2 = 7.8$ Hz, $J_3 = 17.4$ Hz, 1H), 2.01 (dddd, $J_1 = 5.6$ Hz, $J_2 = 7.8$ Hz, $J_3 = 9.3$ Hz, $J_4 = 13.6$ Hz, 1H), 1.83 ppm (dddd, $J_1 = 5.2$ Hz, $J_2 = 6.9$ Hz, $J_3 = 9.5$ Hz, $J_4 = 13.6$ Hz, 1H). Analysis data corresponds to that published in the literature.[13] Enantiomeric purity was determined using HPLC analysis with a Daicel Chiralcel OD column (25 cm) along with a precolumn (5 cm). Eluent: 10% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; $\lambda = 230$ nm; major isomer: $t_r = 19.03$ min, minor isomer: $t_r = 20.87$ min. Conversion of (*R*)-**5c** to a known β-hydroxynitrile allowed the determination of the absolute configuration by chemical correlation.[13] The absolute stereochemistry of other compounds was assigned by analogy.

*Compound (S)-****5d***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (323 μL, $\rho = 1.09$, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.2 h. Eluent: gradient: 20–50% EtOAc in hexanes. Yield: 229 mg (60%), pale yellow oil; $R_f = 0.25$ (50% EtOAc in hexanes); $[\alpha]_D = +109.0$ ($c = 1$, CH_2Cl_2, 95% *ee*); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.37$–7.27 (m, 5H), 7.12 (t, $J = 1.8$ Hz, 1H), 4.71 (ddt, $J_1 = 5.1$ Hz, $J_2 = 7.2$ Hz, $J_3 = 10.8$ Hz, 1H), 4.58 (s, 2H), 3.58 (dd, $J_1 = 5.1$ Hz, $J_2 = 10.4$ Hz, 1H), 3.52 (dd, $J_1 = 5.0$ Hz, $J_2 = 10.4$ Hz, 1H), 3.04 (ddd, $J_1 = 1.8$ Hz, $J_2 = 10.8$ Hz, $J_3 = 17.6$ Hz, 1H), 2.90 ppm (ddd, $J_1 = 1.8$ Hz, $J_2 = 7.2$ Hz, $J_3 = 17.6$ Hz, 1H). Analysis data corresponds to that published in the literature.[13] The enantiomeric purity was determined by HPLC analysis using a Daicel Chiralpak IC column. Eluent: 10% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; $\lambda = 230$ nm; major isomer: $t_r = 33.9$ min, minor isomer: $t_r = 38.7$ min.

*Compound (R)-****5e***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (300 μL, $\rho = 0.92$, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.2 h. Eluent: gradient 20–25% EtOAc in hexanes. Yield: 203 mg (66%), colorless oil, $R_f = 0.38$ (50% MTBE in hexanes); $[\alpha]_D = +124.3$ ($c = 1.2$, CH_2Cl_2, 91% *ee*); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.08$ (t, $J = 1.8$ Hz, 1H), 4.23 (ddd, $J_1 = 6.9$ Hz, $J_2 = 8.8$ Hz, $J_3 = 10.8$ Hz, 1H), 2.92 (ddd, $J_1 = 1.8$ Hz, $J_2 = 10.8$ Hz, $J_3 = 17.5$ Hz, 1H), 2.69 (ddd, $J_1 = 1.8$ Hz, $J_2 = 8.8$ Hz, $J_3 = 17.5$ Hz, 1H), 1.90–1.83 (m, 1H), 1.79–1–70 (m, 2H), 1.69–1.56 (m, 2H), 1.47 (m, 1H), 1.30–1.09 (m, 3H), 1.08–0.91 ppm (m, 2H). Analysis data corresponds to that published in the literature.[13] Enantiomeric purity was determined by HPLC analysis using a Daicel Chiralpak AS column (25 cm) along with a precolumn (5 cm). Eluent: 10% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; $\lambda = 230$ nm; major isomer: $t_r = 19.8$ min, minor isomer: $t_r = 16.9$ min.

*Compound (R,E)-****5h***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (364 mg, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.3 h. Eluent: gradient 40–50% EtOAc in hexanes. Yield: 280 mg (71%), colorless oil; $R_f = 0.23$ (30% MTBE in hexanes); $[\alpha]_D = +105.2$ ($c = 1$, CH_2Cl_2, 94% *ee*); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.11$ (t, $J = 1.8$ Hz, 1H), 6.93 (td, $J_1 = 7.0$ Hz, $J_2 = 15.6$ Hz, 1H), 5.82 (td, $J_1 = 1.6$ Hz, $J_2 = 15.6$ Hz, 1H), 4.51 (ddt, $J_1 = 4.7$ Hz, $J_2 = 7.4$ Hz, $J_3 = 10.5$ Hz, 1H), 3.73 (s, 3H), 3.05 (ddd, $J_1 = 1.8$ Hz, $J_2 = 10.5$ Hz, $J_3 = 17.4$ Hz, 1H), 2.60 (ddd, $J_1 = 1.8$ Hz, $J_2 = 7.9$ Hz, $J_3 = 17.4$ Hz, 1H), 2.25 (m, 2H), 1.72–1.47 ppm (m, 4H). Analysis data corresponds to that published in the literature.[13] Enantiomeric purity was determined by HPLC analysis using a Daicel Chiralpak AS column (25 cm) along with a precolumn (5 cm). Eluent: 10% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; $\lambda = 220$ nm; major isomer: $t_r = 75.0$ min, minor isomer: $t_r = 61.5$ min.

*Compound (R)-****5j***: Prepared as described in the general procedure. Starting materials: α,β-unsaturated aldehyde (304 mg, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time 5.2 h. Eluent: gradient: 10–25% EtOAc in hexanes. Yield: 195 mg (58%). $[\alpha]_D = +47.9$ ($c = 1$, CH_2Cl_2, 69% *ee*) All other spectral data were identical to those of the racemic product. The enantiomeric purity was determined by HPLC analysis using a Daicel Chiralcel OD column (25 cm) along with a precolumn (5 cm). Eluent: 1% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; $\lambda = 220$ nm; major isomer: $t_r = 14.5$ min, minor isomer: $t_r = 16.1$ min.

*Compound (R)-****5i***: Prepared as described in the general procedure except that the following cyclization procedure and workup were con-

ducted. After the indicated reaction time, a cooled solution of 10 M HCl (0.8 mL) in THF (3 mL)/H_2O (1 mL) was added to the reaction mixture. The resulting solution was stirred for 20 min and diluted with H_2O (8 mL). The mixture was extracted with EtOAc (2×20 mL). Combined organic layers were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography. Starting materials: α,β-unsaturated aldehyde (733 mg, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.2 h. Eluent: gradient 15–25% EtOAc in hexanes. Yield: 530 mg (69%), colorless oil; R_f=0.23 (40% MTBE in hexanes); $[\alpha]_D$=+50.7 (c=1, CH_2Cl_2, 94% *ee*); ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.70–7–64 (m, 4H), 7.46–7.35 (m, 6H), 7.10 (t, J=1.8 Hz, 1H), 4.60–4.40 (m, 1H), 3.67 (t, J=6.3 Hz, 2H), 3.01 (ddd, J_1=1.8 Hz, J_2=10.5 Hz, J_3=17.3 Hz, 1H), 2.58 (ddd, J_1=1.8 Hz, J_2=8.0 Hz, J_3=17.3 Hz, 1H), 1.74–1.38 (m, 6H), 1.05 ppm (s, 9H). Analysis data corresponds to that published in the literature.[13] Enantiomeric purity was determined by HPLC analysis using a Daicel Chiralpak AS column (25 cm) along with a precolumn (5 cm). Eluent: 2% 2-propanol in hexanes; flow rate: 0.8 mL min^{-1}; λ=220 nm; major isomer: t_r=16.0 min, minor isomer: t_r=14.0 min.

*Compound (S)-**5n***: Prepared as described in the general procedure at a 0.5 mmol scale with the *R* enantiomer of the catalyst. Starting materials: α,β-unsaturated aldehyde (68 μL, ρ=1.05, 0.50 mmol, 100 mol%), acetone oxime (0.110 g, 1.50 mmol, 300 mol%). Reaction time: 4 h. Eluent: gradient: 50–60% MTBE in hexanes. Yield: 55 mg (70%). $[\alpha]_D$=−129.2 (c=1, CH_2Cl_2, 90% *ee*). All other spectral data were identical to those of the racemic product. The enantiomeric purity was determined by HPLC analysis using a Daicel Chiralcel AD column (25 cm) along with a precolumn (5 cm). Eluent: 1% 2-propanol in hexanes; flow rate: 0.8 mL min^{-1}; λ=230 nm; major isomer: t_r=74.4 min, minor isomer: t_r=63.2 min.

*Compound (S)-**5p***: Prepared as described in the general procedure with the *R* enantiomer of the catalyst. Starting materials: α,β-unsaturated aldehyde (647 mg, 2.0 mmol, 100 mol%), acetone oxime (0.66 g, 9.0 mmol, 450 mol%). Reaction time: 5.3 h. Eluent: gradient 30–50% EtOAc in hexanes. Yield: 375 mg (55%), pale yellow oil; R_f=0.17 (70% MTBE in hexanes); $[\alpha]_D$=−63.1 (c=1, CH_2Cl_2, 92% *ee*); ^{1}H NMR (85 °C, $C_2D_2Cl_4$, 400 MHz): δ=7.41–7.21 (m, 10H), 7.05 (t, J=1.7 Hz, 1H), 5.22 (s, 2H), 4.54 (ABq, $J_{A,B}$=15.5 Hz, $\Delta\nu$=24.7 Hz), 4.45 (m, 1H), 3.49–3.33 (m, 1H), 2.97 (dd, J_1=10.4 Hz, J_2=17.2 Hz, 1H), 2.55 (dd, J_1=7.6 Hz, J_2=17.2 Hz, 1H), 1.85 ppm (m, 2H). Analysis data corresponds to that published in the literature.[13] Enantiomeric purity was determined by HPLC analysis using a Daicel Chiralpak AS column (25 cm) along with a precolumn (5 cm). Eluent: 15% 2-propanol in hexanes; flow rate: 0.7 mL min^{-1}; λ=220 nm; major isomer: t_r=57.6 min, minor isomer: t_r=49.3 min.

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[30] The formation of 2-isoxazolines cannot be observed with *p*-NO_2-benzaldehyde oxime, within the timeframe of the experiment. Although these experiments cannot measure the equilibrium concentrations of the actual substrates, it should be noted that the concentrations of the intermediates with 3-pentanone and cyclohexanone oximes, viable substrates for the cyclization reaction, do follow the trend [**6c**] > [**6m**] or [**6c**] > [**6j**] during the reaction (see the Supporting Information).
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