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Stereodivergent Methodology for the Synthesis of Complex Pyrrolidines

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Abstract: The intramolecular reaction of oxime ethers and cyclopropane diesters results in the diastereoselective formation of substituted pyrrolo-isoxazolidines which serve as precursors to the ubiquitous pyrrolidine motif. A simple reversal of addition order of catalyst and substrate results in formation of two discrete diastereomers in a highly selective and predictable manner. The adducts are prepared in excellent yields from either enantiomer of an alkoxyamino-tethered cyclopropanediester, allowing efficient access to highly substituted homochiral pyrrolidines.

Introduction

Cyclopropanes constitute an important class of synthetic building blocks due to their rich chemical reactivity.[1] Specifically, those bearing electron-withdrawing substituents undergo ring opening with a variety of nucleophiles to afford heterocyclic products.[2] The pyrrolidine ring, in particular, is found in a myriad of natural products, and consequently, numerous methods exist to access this important heterocycle. However, several of these strategies often suffer from poor diastereoselectivity, efficiency, and generality when applied to the assembly of densely substituted pyrrolidines.[3] Currently, the most efficient method for assembling densely substituted enantiomerically enriched pyrrolidine rings is via the catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides with various olefins.[4] While the method has the potential to efficiently generate fully substituted pyrrolidine rings with good stereocontrol, it is generally limited to the use of aryl azomethine ylides and therefore results in formation of pyrrolidines with 2-aryl substitution. Isopropyl or cyclohexyl derivatives are notable exceptions; however, asymmetric induction is moderate for these examples.[5] 2,5-Trans-substituted pyrrolidines, such as those found in callosine (**1**)[6] and Abbott's influenza neuraminidase inhibitor A-315675 (**2**),[7] are especially difficult to synthesize in an efficient manner (Figure 1).[8] For example, approaches to A-315675 have relied on a linear construction of the pyrrolidine ring through a pyrrolinone intermediate.[9] Quinocarcin (**3**)[10] and allosecurinine (**4**)[11] are complex natural products containing a 2,5-cis-substituted pyrrolidine ring. An efficient method allowing access to either pyrrolidine diastereomer from a common starting material would constitute a fundamentally important contribution to the synthetic arsenal.

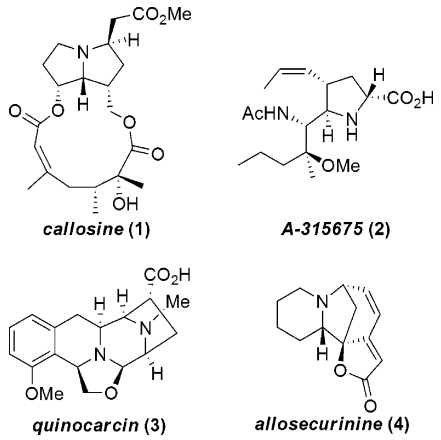

Figure 1.

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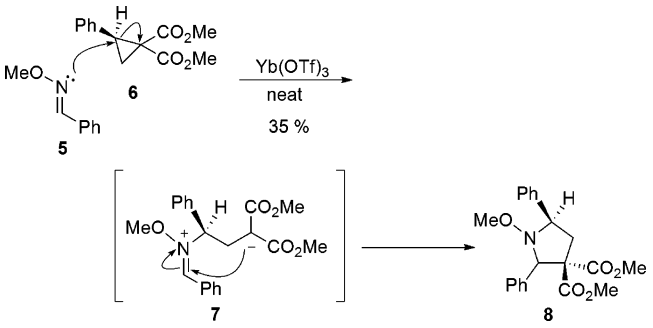
Recently, we have shown that nitrones[12] as well as imines[3q] react with cyclopropane diesters under $Yb(OTf)_3$ catalysis to afford tetrahydro-1,2-oxazines and 2,5-substituted pyrrolidines, respectively. However, the scope of the imine reaction was restricted to the use of aryl imines, whereas all aliphatic cases failed to react.

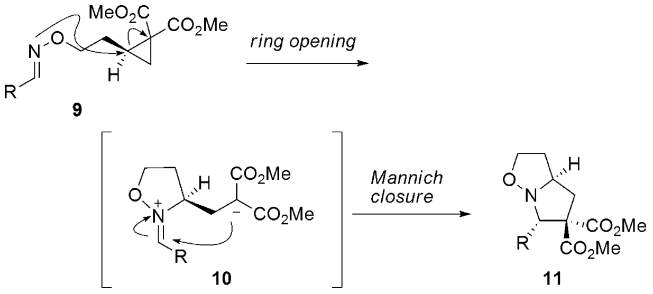
It cannot be overstated that a methodology limited to derivatives of benzaldehyde does not well serve natural product synthesis. As such, in our continuing studies on the reactivity of cyclopropane diesters, we considered whether the use of oxime ethers as nucleophiles in cyclopropane ring opening would lead to improved substrate scope given that the nucleophilicity of the oxime nitrogen should be increased by virtue of the alpha heteroatom.[13] However, it was quickly discovered that the bimolecular reaction had very limited scope, gave poor yields, and could only be effected under neat conditions (Scheme 1).

Given the observation that excessively high concentrations of substrates were needed to achieve any conversion to product, it was expected that an intramolecular variant would lead to improved reactivity as well as improved diastereoselectivity through a tighter transition state resulting from the high effective molarity inherent to intramolecular reactions.[14] Intramolecular ring opening would afford oxy-iminium species **10**, leading to bicyclic product **11** through Mannich ring closure (Scheme 2). In addition, given that homochiral cyclopropane diesters are readily prepared, we anticipated this method would allow access

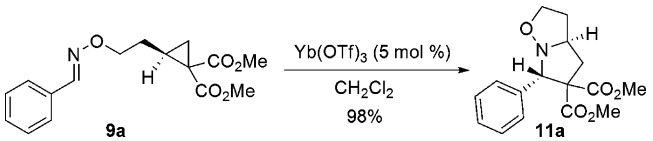
Scheme 1. Bimolecular Reaction of an Oxime Ether and a Cyclopropane Diester



Scheme 2. Intramolecular Oxime Ether/Cyclopropane Annulation



Scheme 3



to enantiopure pyrrolidines through pyrrolo-isoxazolidines such as **11**. In this report, we present the discovery of a stereospecific annulation reaction involving oxime ether-tethered cyclopropane diesters with broad substrate scope and exceptional diastereoselectivity, affording efficient access to either 2,5-trans- or 2,5-cis-substituted pyrrolidines from the same starting materials.

Results and Discussion

Synthesis of 2,5-*trans*-Pyrrolo-isoxazolidines. In the initial experiment, the oxime ether of benzaldehyde was prepared in racemic form and treated with 5 mol % $Yb(OTf)_3$ (Scheme 3). Gratifyingly, pyrrolo-isoxazolidine **11a** was obtained in nearly quantitative yield as a single diastereomer, which was assigned (vide infra) as the 2,5-trans isomer (pyrrolidine numbering).

With this spectacular result, we wished to probe the scope and stereochemistry of this new reaction and embarked on an asymmetric synthesis of cyclopropyl-alkoxylamine **17** which was required for oxime ether preparation (Scheme 4). Thus, commercially available (*S*)-butane triol was protected as the cyclic ketal, followed by benzylation of the primary alcohol. Deprotection and cyclic sulfate formation afforded **14** in 84% yield. Displacement of the sulfate with dimethylmalonate gave cyclopropane **15**,[15] which was elaborated to the *N*-phthaloyl-protected compound **16**. Hydrazine deprotection afforded the desired cyclopropyl-alkoxylamine **17** in excellent yield.[16]

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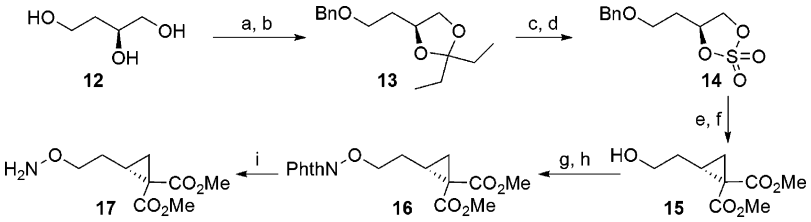
(15) Racemic **15** is easily prepared via hydroboration of readily available (+/−)-2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester. See Supporting Information.

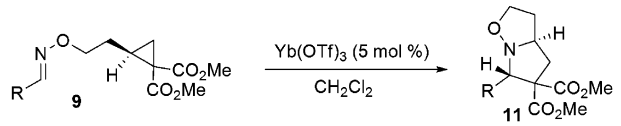
(16) This sequence is amenable to multigram scale. (*R*)-Butane triol is also commercially available.

Scheme 4. Synthesis of (*S*)-Cyclopropyl-alkoxylamine **17**[a]



[a] Conditions: (a) 3-pentanone, TsOH; (b) BnBr, NaH, THF (89%, 2 steps); (c) HCl, MeOH (100%); (d) $SOCl_2$, CCl_4, reflux; $RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4/MeOH/H_2O, 0 °C (84%); (e) dimethylmalonate, NaH, THF, reflux (71%); (f) H_2, Pd/C, MeOH; (g) TsCl, DABCO, CH_2Cl_2 (93%); (h) *N*-hydroxyphthalimide, DBU, DMF (74% recrystallized, % ee = >99%); (i) $N_2H_4 \cdot H_2O$, MeOH/CH_2Cl_2 (1:1) (92%).

Table 1. Diastereoselective Synthesis of 2,5-*trans*-Pyrrolo-isoxazolidines from *E*-Oxime Ethers

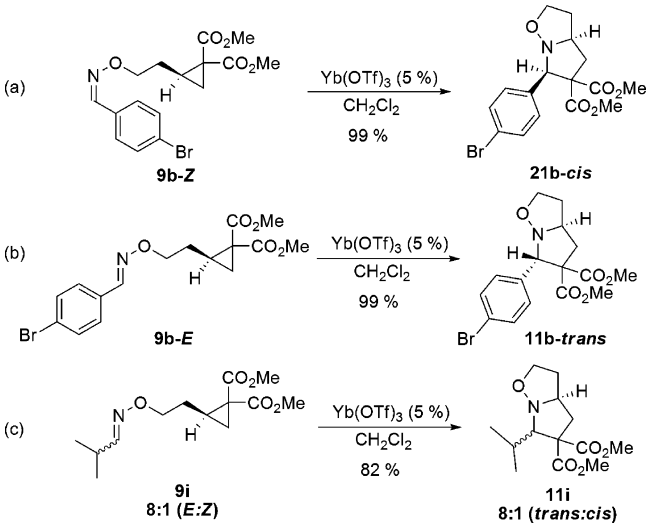


Entry/Class	Parent Aldehyde/Ketone	Product **11**	% Yield **11** (*trans:cis*)[a]
aryl/alkenyl			
a	benzaldehyde	**11a-f**	98
b	*p*-bromo-benzaldehyde		99[b, c]
c	*p*-methoxy-benzaldehyde		99
d	*p*-nitro-benzaldehyde		99
e	pyridine-2-carboxaldehyde		97
f	6-bromo-naphthalene-2-carboxaldehyde		99[b, c]
g	*trans*-cinnamaldehyde	**11g**	81 (10:1)
h	*trans*-2-Me-cinnamaldehyde	**11h**	85
aliphatic			
i	isobutyrylaldehyde	**11i, j**	82 (8:1)[d]
j	trimethylacetaldehyde		75[b, c]
k	**18**	**11k**	94 (20:1)[b, c]
dialdehyde			
l	pyridine-2,6-dicarboxaldehyde	**11l**	70[c]
m	glyoxal	**11m**	48[c, e]
		11m′	35[c, e]
ketone			
n	methyl benzoylformate	**11n**	98[b, c]

[a] Isolated yield of single diastereomer. Isomeric ratio determined by ^1H NMR analysis of crude mixture. [b] % ee > 99% for this representative example. See Supporting Information. [c] Enantiopure (*S*)-cyclopropyl-alkoxylamine 17 was employed. In all other cases, the racemic form was employed. [d] 8:1 (*E*:*Z*) mixture of oxime ethers was employed. Product isomers were inseparable. [e] 10:8:1 (*E*/*E*:*E*/*Z*:*Z*/*Z*) mixture of oxime ethers was employed.

With alkoxylamine **17** in hand, a number of cyclopropyl-oxime ethers were prepared from aryl, akenyl, or aliphatic aldehydes, and the major *E* isomers were obtained after flash chromatography. As depicted in Table 1, the scope of the reaction was found to be extremely broad and found to be compatible with oxime ethers derived from all classes of aldehydes. Electron-donating (Table 1, entry c) and -withdrawing (Table 1, entries b, d) aromatic oxime ethers cyclized in high yields to the corresponding 2,5-trans products **11** with exceptional diastereoselectivity. Pyridyl aldehyde was also well tolerated, affording the pyrrolo-isoxazolidine product in high yield and excellent diastereoselectivity (Table 1, entry e).

Scheme 5



α,β-Unsaturated oxime ethers were also found to be viable substrates (Table 1, entries g, h). Cyclization of the *E* isomers proceeded with complete diastereoselectivity in the case of the 2-methyl cinnamaldehyde derivative and good selectivity for the parent cinnamaldehyde derivative (10:1). Gratifyingly, aliphatic oxime ethers (Table 1, entries i−k) were useful substrates for this reaction. We were especially pleased to observe that alpha chiral (*R*)-2-silyloxy aldehyde **18** (Table 1, entry k) was a superb substrate for the annulation reaction. The bulky *tert*-butyl diphenylsilyloxy group effectively inhibits formation of the *Z* isomer, and cyclization of the crude oxime ether affords the product without racemization in excellent yield and high diastereoselectivity. The one-step, high-yielding assembly of product **11k** as a single homochiral diastereomer is remarkable given that the pyrrolidine core of such a compound would task current pyrrolidine-forming methodologies.

Interestingly, bis-aldehydes could also be employed (Table 1, entries l, m). Pyridine 2,6-dicarboxaldehyde was converted to the *E*/*E*-bis-oxime ether as the sole isomer. Cyclization of this substrate led to C_2-symmetric compound **11l** as a single diastereomer. Use of glyoxal, however, resulted in a mixture of oxime ether isomers, which converged to C_2-symmetric

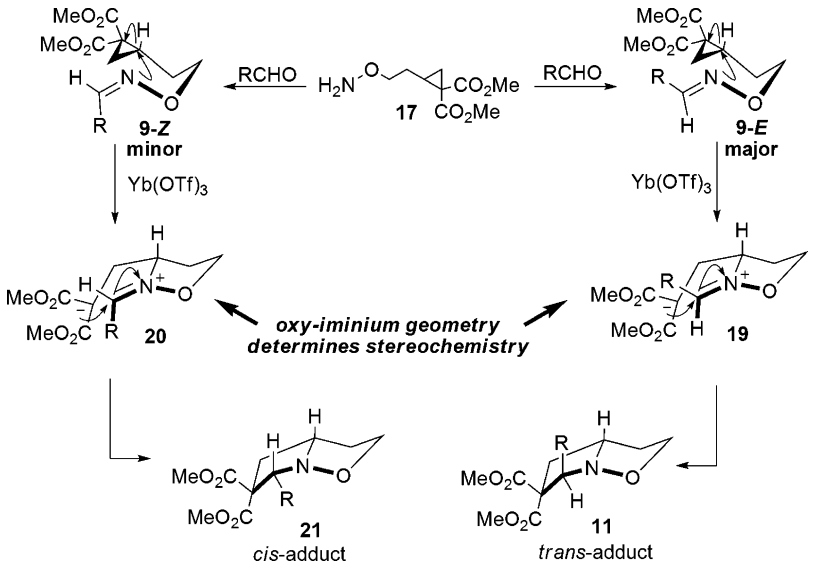


Figure 2. Proposed model for observed diastereoselectivity.

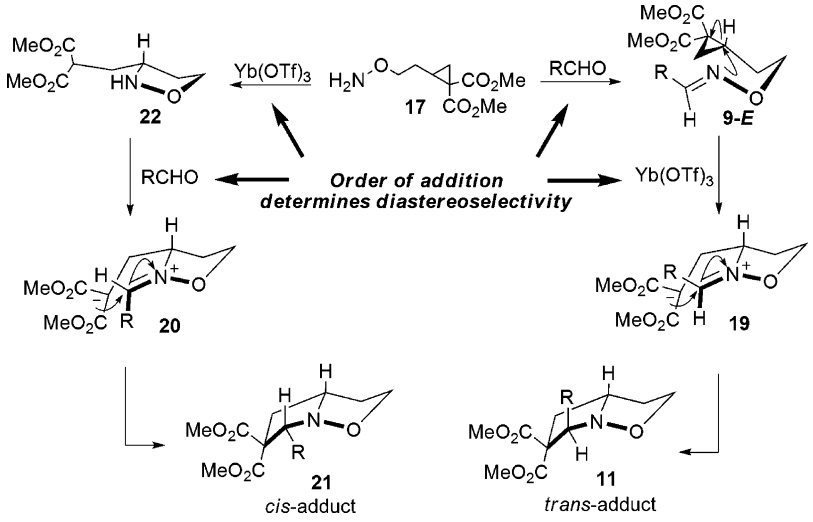


Figure 3. Modification allowing selective formation of *cis*- or *trans*-diastereomers.

diastereomer **11m** as well as diastereomer **11m′** in a ratio (7:5) comparable to that of the initial oxime ether mixture. Finally, the *Z*-enantiopure ketoxime of methyl benzoylformate (Table 1, entry n) was prepared and cyclized in high yield to enantiopure adduct **11n** bearing a tetrasubstituted stereogenic center.

In order to gain insight into the nature of the diastereoselectivity of the reaction, we investigated the annulation of the minor *Z* isomer of **9b** (Scheme 5). The *Z*-oxime ether of **9b** was treated with $Yb(OTf)_3$ and cyclized to the 2,5-cis diastereomer **21b** exclusively, while the *E*-oxime of **9b** cyclized to the trans product **11b**. In a separate experiment, an 8:1 (*E*:*Z*) mixture of oxime ether isomers **9i** derived from isobutyrylaldehyde was subjected to the same cyclization conditions and resulted in formation of an 8:1 (trans:cis) mixture of diastereomeric products (Scheme 5c and Table 1, entry i). These observations confirmed that the stereochemical outcome of the reaction was entirely dependent on the geometry of the initial oxime ether.

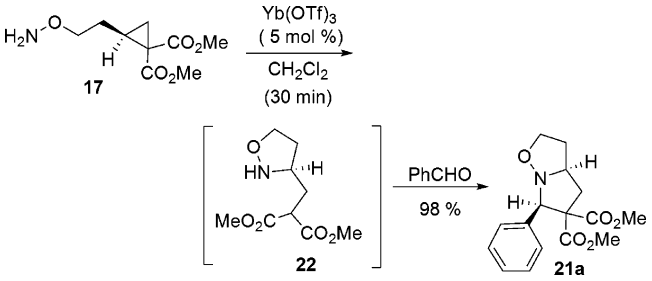
To confirm the absolute and relative configuration of the adducts, the enantiomerically pure *E*-oxime ether of 6-bromo-naphthalene-2-carboxaldehyde was cyclized to afford a crystalline compound suitable for X-ray analysis (Table 1, entry f). The crystal structure of **11f** revealed a 2,5-trans disposition of the substituents about the pyrrolidine moiety with inversion of configuration of the initial cyclopropane stereogenic carbon. The enantiomeric excess was determined for representative examples from each class of oxime ether and consistently found to be >99% (Table 1, entries b, f, j, k, n). Importantly, this confirmed that the reaction proceeds in all cases without racemization to afford enantiopure adducts.

Consistent with the observed diastereoselectivity is the mechanistic model depicted in Figure 2. Cyclization of *E*-oxime **9** proceeds likely through a stepwise mechanism,[17] affording *E*-oxy-iminium intermediate **19**. Mannich ring closure by the malonate nucleophile on the oxy-iminium re face leads to the trans-substituted product **11** in a stereospecific manner. In contrast, the minor *Z*-oxime isomer of **9** gives rise to the cis-substituted adduct **21** through *Z*-oxy-iminium intermediate **20**.

Synthesis of 2,5-*cis*-Pyrrolo-isoxazolidines. We recognized that a shortcoming to our annulation methodology was the fact that access to the *Z*-oxime ether, and consequently the 2,5-cis

(17) For mechanistic insight on the related nitrone cycloaddition with cyclopropane diesters, see: Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251−10253 and ref 12d.

Scheme 6



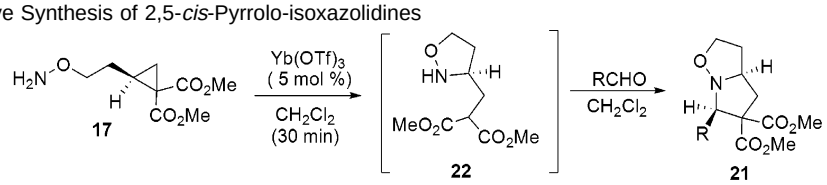
adduct, was as the minor product of oxime ether formation. In order to complement the existing method for 2,5-trans adduct formation, a means to selectively form the *Z*-oxy-iminium intermediate **20** (Figure 2) was required in order to gain access to the 2,5-cis adduct **21**. This dilemma was solved with the realization that generation of isoxazolidine **22** prior to reaction with an aldehyde would likely afford the requisite *Z*-oxy-iminium species **20** as the preferred geometry due to minimized A1,3 interactions[18] between the pendant malonate and R group (Figure 3). Mannich cyclization of this species then gives rise to the desired cis-substituted product **21**.

We were delighted to find that this was indeed the case. In the event, cyclopropyl-alkoxylamine **17** was treated with catalytic $Yb(OTf)_3$ to afford isoxazolidine **22** with complete conversion (Scheme 6). Benzaldehyde was then added to the same reaction pot, which resulted in production of the desired cis-substituted pyrrolo-isoxazolidine **21a** as a single diastereomer in 98% yield. *Importantly, this result confirmed that by simply reversing the order of addition of the substrate and catalyst the stereochemical outcome of the reaction could be controlled.*

Substrate scope for this new protocol was examined and also found to be extremely general. Electron-rich (Table 2, entry c) and electron-poor (Table 2, entries b, d) aromatic aldehydes cyclized cleanly and in high yields. Furyl and napthyl substrates were also well tolerated (Table 2, entries e−g). We were again pleased to observe that the reaction with linear or branched aliphatic aldehydes proceeded with exceptional diastereoselectivity. Remarkably, however, in all but one case (Table 2, entry o), the diastereocontrol was absolute with no detectable trace of the trans isomer. Especially gratifying was the observation that (*R*)-2-siloxy aldehyde **18** cleanly cyclized with excellent diastereoselectivity and in good yield (Table 2, entry o). In addition, the one-pot reaction proceeds without racemization to afford enantiopure products. The enantiomeric excess was determined for several adducts derived from differing classes of aldehydes (Table 2, entries g, m, o) and found to be >99% in all cases. Isolation of compound **22** was possible, and the ee of the tosylated derivative was found to be >99%, further demonstrating the conservation of enantiomeric integrity during the initial cyclization of **17** to **22**.

Cleavage of the Pyrrolo-isoxazolidine N−O Bond. To demonstrate the utility of the methodology to access highly substituted pyrrolidine rings, we turned our attention to N−O

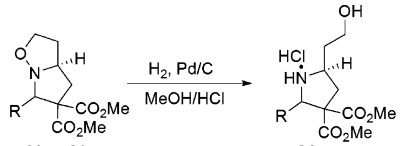
Table 2. Diastereoselective Synthesis of 2,5-*cis*-Pyrrolo-isoxazolidines

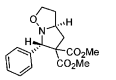
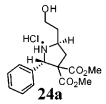
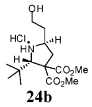
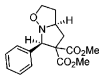
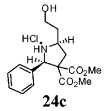
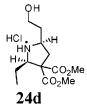


Entry/Class	Aldehyde	Product **21**	% Yield[a]
aryl/alkenyl			
a	benzaldehyde		98
b	*p*-bromo-benzaldehyde		88
c	*p*-methoxy-benzaldehyde		99
d	*p*-nitro-benzaldehyde		91
e	furyl-2-carboxaldehyde	**21a-g**	85
f	furyl-3-carboxaldehyde		81
g	6-bromo-naphthlene-2-carboxaldehyde		100[b, c]
h	*trans*-2-methyl-cinnamaldehyde	**21h**	50
aliphatic			
i	**23**	**21i**	55 (72 brsm)
j	propionaldehyde		70
k	butyraldehyde		73
l	isobutyrylaldehyde		60
m	trimethylacetaldehyde	**21j-n**	82[b, c]
n	octanal		70
o	**18**	**21o**	89 (20:1)[c, d]

[a] Isolated yield. Only the *cis*-diastereomer was observed by ^1H NMR analysis of crude reaction mixture except where noted. [b] % ee > 99% for this representative example. See Supporting Information. [c] Enantiopure (*S*)-cyclopropyl-alkoxylamine **17** was employed. In all other cases, the racemic form was employed. [d] Cis:trans of crude mixture.

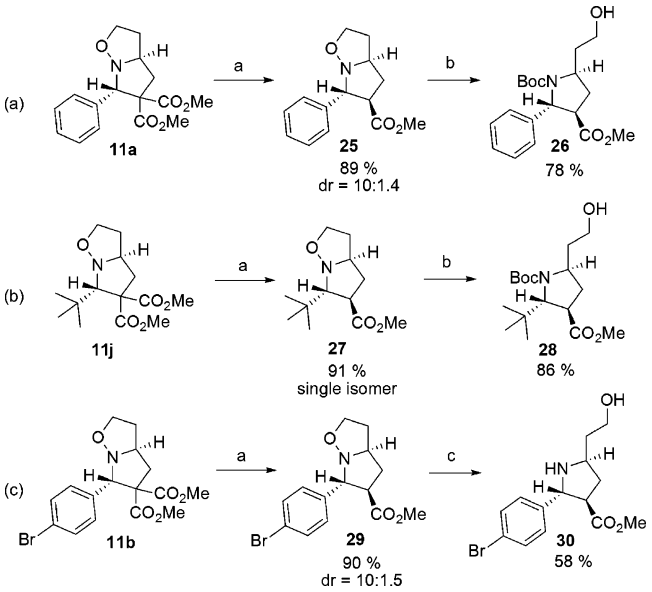
Table 3. Accessing the Pyrrolidine Ring: N−O Bond Cleavage[a]



Entry	Substrate	Product **19**	% Yield
2,5-trans-adducts			
a	 **11a**	 **24a**	98
b	 **11j**	 **24b**	99
2,5-cis-adducts			
c	 **21a**	 **24c**	99
d	 **21j**	 **24d**	99

[a] Pd/C (10 mol %), H_2 (1 or 4.4 atm), HCl, MeOH.

Scheme 7. Elaboration of *trans*-Adducts to Highly Substituted Pyrrolidines[a]



[a] Conditions: (a) NaCN, DMSO, 140 °C, 15 min, microwave; (b) $Pd(OH)_2/C$ (10 mol %), H_2 (1 atm), Boc_2O, MeOH; (c) Zn, AcOH.

bond cleavage. Hydrogenation of the adducts under standard conditions (Pd/C, MeOH, H_2, 1 atm) led to partial epimerization at C2. The *trans-tert*-butyl-substituted adduct **11j** was especially prone to isomerization due to severe diaxial interactions. Suppression of a likely retro-Mannich isomerization pathway was achieved by hydrogenation in methanolic HCl to afford diastereomerically pure pyrrolidine salts **24** (Table 3). Aromatic and aliphatic cis- or trans-adducts could be cleaved under these conditions; however, the cis-adducts required higher pressures of H_2.

As an alternative method to suppress retro-Mannich isomerization, the trans-adducts[19] could be diastereoselectivity dealkoxycarbonylated. Selected examples were subjected to Krapcho[20] conditions, affording the decarbonylated products in high yields and good diastereoselectivity, favoring the 2,3-trans-isomers (Scheme 7). Hydrogenation of the major diastereomer of **25** and **27** in the presence of Boc_2O then led to *N*-protected 2,3,5-substituted, diastereomerically pure pyrrolidines **26** and **28**. Compound **29** was elaborated to the corresponding pyrrolidine though Zn-mediated N−O bond cleavage to avoid debromination.

Conclusion

In summary, we discovered an annulation reaction involving oxime ether-tethered cyclopropanes which affords enantiopure pyrrolo-isoxazolidines in a highly diastereoselective and stereodivergent manner. Use of an alkyl tether in the reaction serves several purposes. Not only does it facilitate the reaction (the bimolecular case failed), but it allows for a pyrrolidine product with direct *N*-protection. Cleavage of the N−O bond then converts the protecting group into a handle, allowing further elaboration at the 5-position of the newly formed pyrrolidine. Altering the order of aldehyde and catalyst addition leads to the selective formation of either 2,5-cis- or 2,5-trans-substituted pyrrolidine products from the same starting materials. An extremely broad substrate scope has been demonstrated for both methods, and it is possible to access either 2,5-cis- or 2,5-trans-substituted pyrrolidines, including those with *branched alkyl substitution*, demonstrating the power of this new transformation. This methodology constitutes a highly efficient way to access pyrrolidine-based natural products and will be the subject of future reports from our laboratory.

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Supporting Information Available: Experimental procedures, full characterization for all new compounds, as well as cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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