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Intramolecular annulations of donor–acceptor cyclopropanes*

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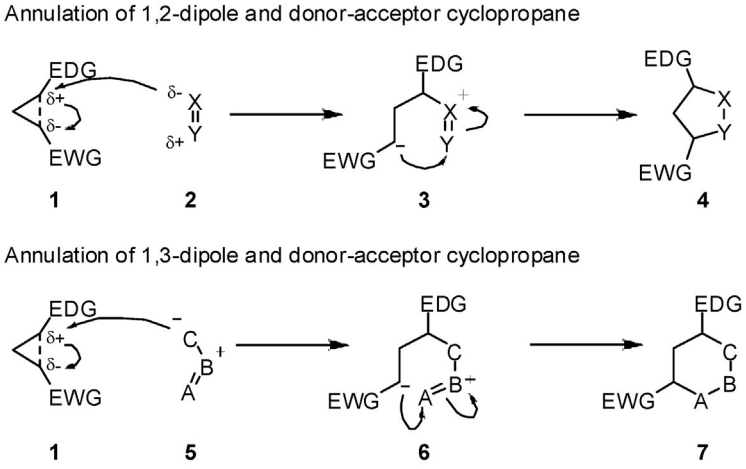
Abstract: The intramolecular reaction of donor–acceptor cyclopropanes with various dipoles and dipolar equivalents allows access to a variety of bicyclic adducts with good stereocontrol. The linkers can often be cleaved to provide stereodefined products.

Keywords: annulations; donor–acceptor cyclopropanes; heterocycles; intramolecular; pyrazolidine; pyrrolidine; tetrahydro-oxazine.

INTRODUCTION

Annulations of donor–acceptor cyclopropanes [1] with various dipoles (and dipolar equivalents) have received considerable attention in recent years as they allow rapid access to a variety of carbo- and heterocyclic products (Scheme 1). While there have been numerous intermolecular examples [2–16], there have been limited reports of intramolecular versions [17]. Intramolecularity would, in principle, allow for increased reactivity, control of diastereoselectivity, and the ability to form multiple rings in a single event [18]. Herein, we report recent examples of the reaction of 1,1-cyclopropanediesters tethered to nitrones, oxime ethers, and hydrazones, as well as transformations of the adducts and their application in total synthesis.



Scheme 1 Annulations of donor–acceptor cyclopropanes with 1,2- and 1,3-dipoles.

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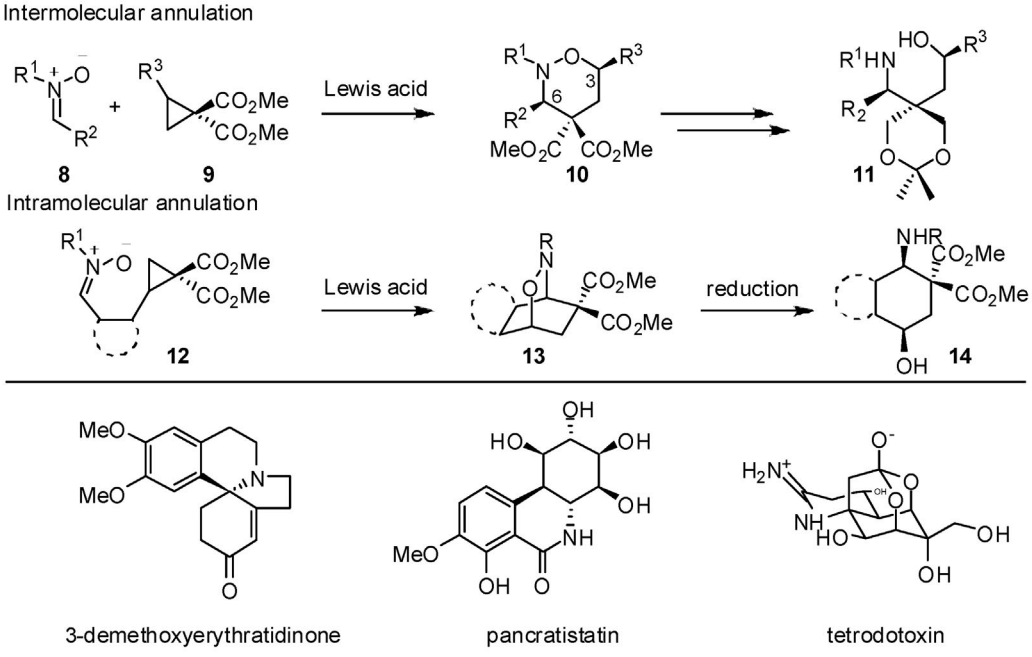
DISCUSSION

Reaction with nitrones

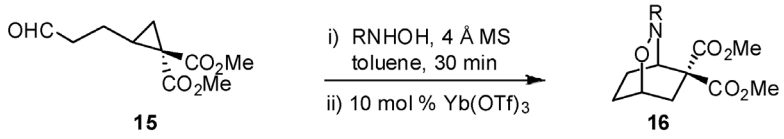
The intermolecular annulation of nitrones **8** and 1,1-cyclopropanediesters **9** to form tetrahydro-1,2-oxazines **10** was first reported by our group in 2003 [3i]. The reaction was found to proceed via a stepwise mechanism with initial S_N2-type ring-opening, at the cyclopropane carbon best able to stabilize a developing positive charge, followed by Mannich ring-closure. The reaction products are usually formed with excellent diastereoselectivity and bear a *cis* relationship between the C-3 and C-6 substituents [3c,d]. Soon after this initial report, a one-pot, three-component coupling protocol was developed with in situ generation of the nitrone, allowing for easy access to a variety of substituted tetrahydro-1,2-oxazines [3h]. Since these initial reports, this reaction has received interest from a number of groups allowing for the development of several enantioselective versions [3b,f]. We have recently extended this reaction to its intramolecular variant allowing for the formation of bridged bicyclic adducts **13**, which upon cleavage of the N–O bond yield stereodefined 1,4-*cis*-aminocyclohexanols **14**, a motif that is prevalent in a variety of natural products (Scheme 2) [17b].



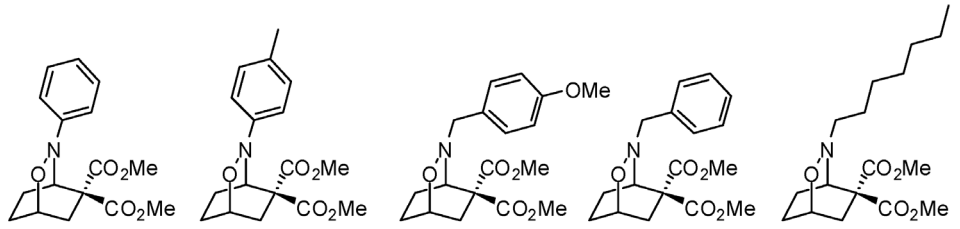
Scheme 2 Intramolecular annulation of nitrones and 1,1-cyclopropanediesters.

While initial attempts using a one-carbon linker between the aldehyde and cyclopropane were unfruitful, due to an undesired β-elimination pathway, the use of a two-carbon linker allowed formation of the desired bicyclic adducts in excellent yields (Table 1). Aldehyde **15** could be condensed with both aromatic and aliphatic hydroxylamines, to form the corresponding nitrone, which would undergo an intramolecular annulation to form the bicyclic tetrahydro-1,2-oxazine **16**. While maintaining the two-carbon tether length, a variety of alternative tethers could also be employed (Table 2). Unsaturation could be introduced through either an alkenyl tether, aromatic or heteroaromatic ring. The electronic nature of the aromatic tether was found to have little effect with electron-rich, neutral, and poor performing equally well.

Table 1 Reaction scope of saturated bicyclo-tetrahydro-1,2-oxazines.

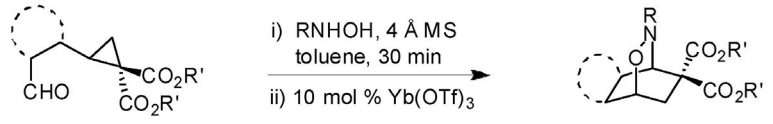


15 **16**

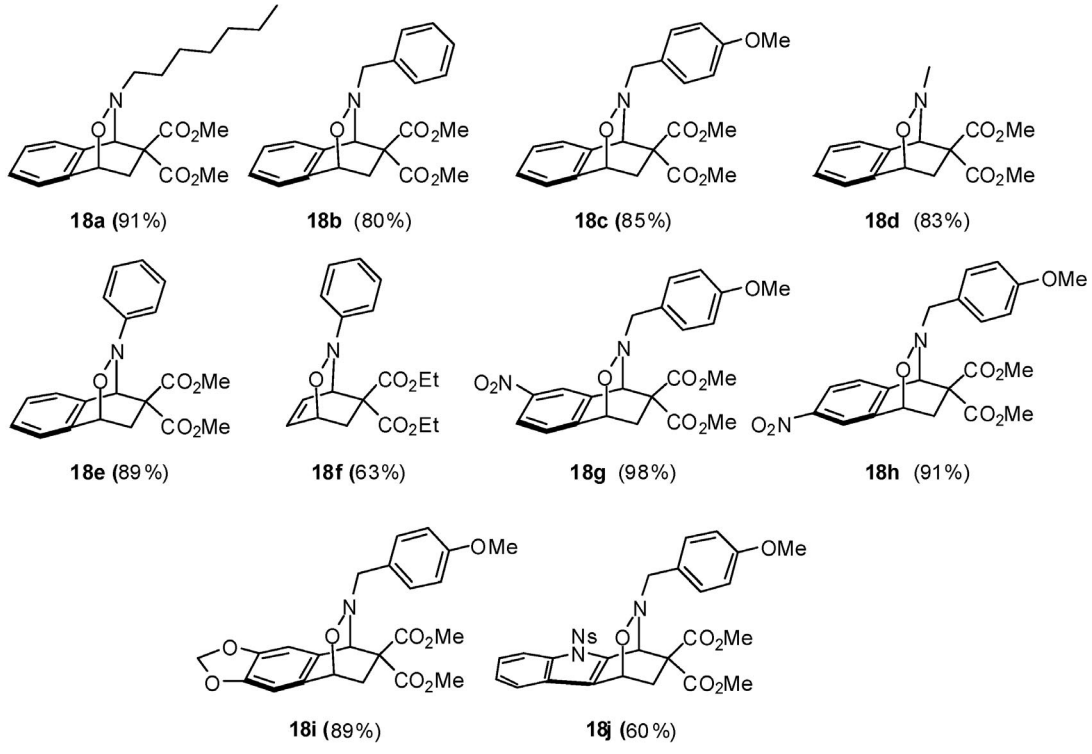


16a (92%) **16b** (92%) **16c** (84%) **16d** (89%) **16e** (82%)

Table 2 Reaction scope of unsaturated bicyclo-tetrahydro-1,2-oxazines.



17 R' = Me, Et **18**



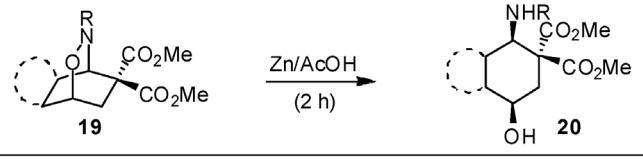
18a (91%) **18b** (80%) **18c** (85%) **18d** (83%)

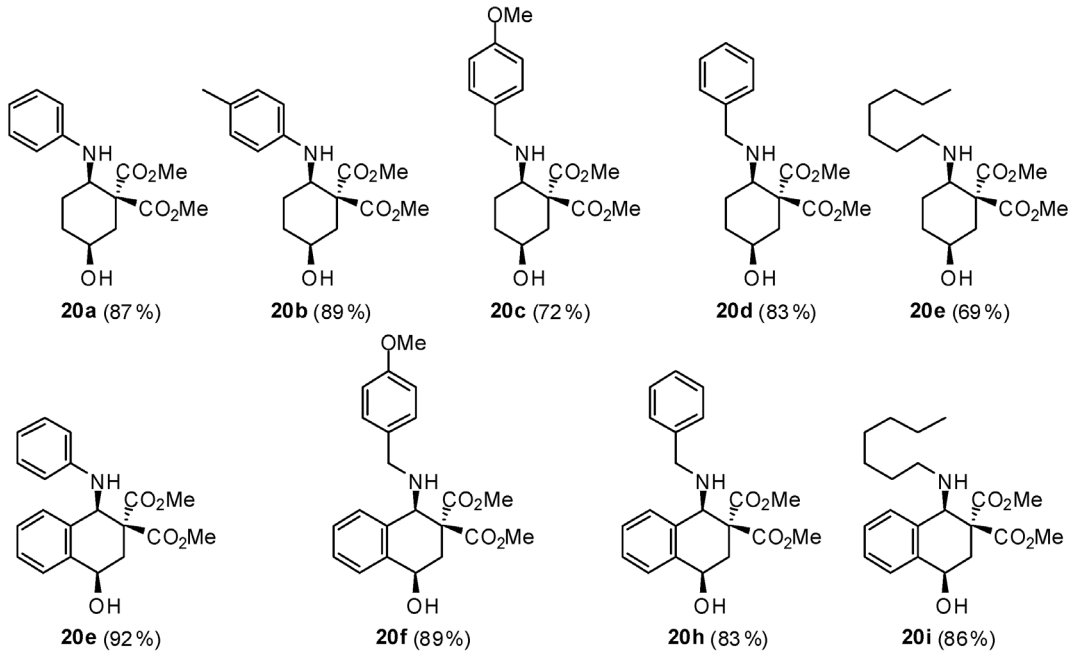
18e (89%) **18f** (63%) **18g** (98%) **18h** (91%)

18i (89%) **18j** (60%)

With access to a variety of bicyclic tetrahydro-1,2-oxazines, transformation of the adducts was next investigated. To this end, tetrahydro-1,2-oxazines **19** derived from both saturated and unsaturated tethers were subjected to N–O bond cleavage conditions to furnish the desired cyclic 1,4-aminoalcohols **20**. In all cases, regardless of the tether, the N–O bond was easily cleaved with Zn dust in glacial acetic acid in good to excellent yields (Table 3).

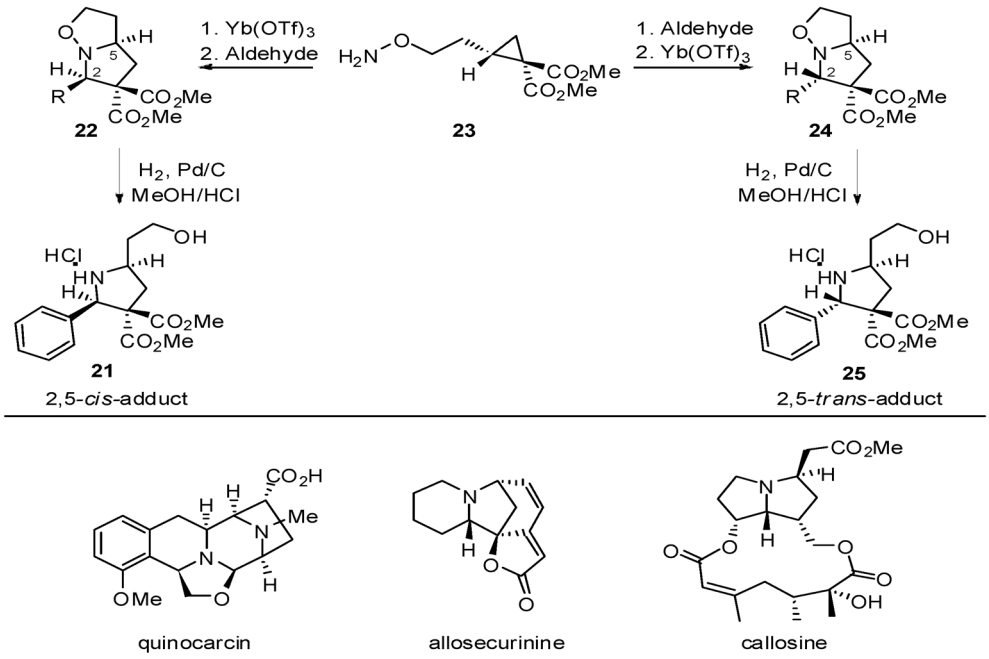
Table 3 Reductive cleavage of tetrahydro-1,2-oxazines to 1,4-*cis*-aminocyclohexanols.





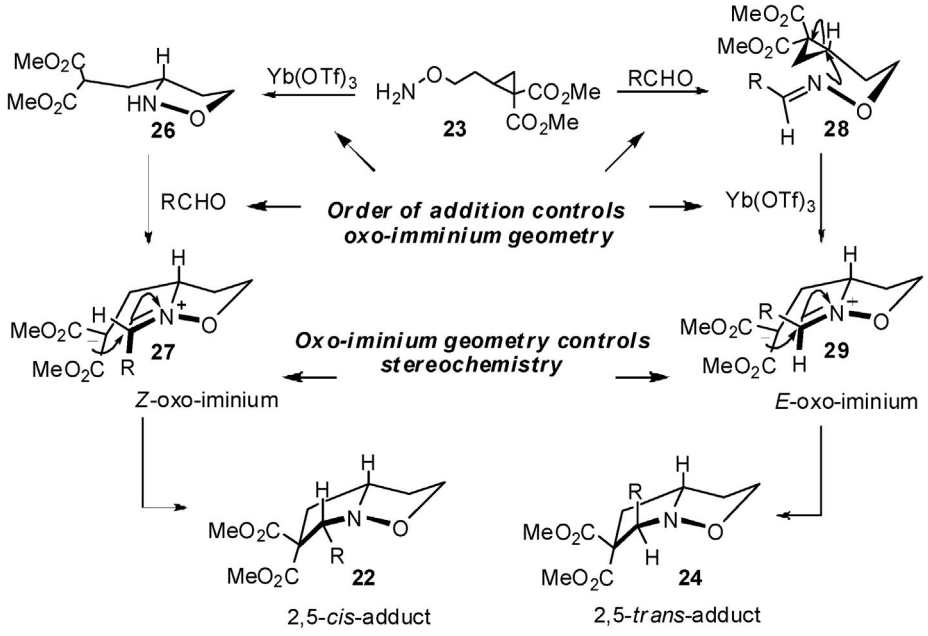
Reaction with oxime-ethers

The pyrrolidine motif is ubiquitous in both natural and unnatural products (*vide infra*). As such, stereodefined synthetic routes toward this heterocycle are of considerable interest to the synthetic community. Very recently, our group has reported a stereodivergent route to pyrrolidines via an intramolecular annulation of oxime-ether tethered cyclopropanes (Scheme 3) [17d].



Scheme 3 Intramolecular annulation of oxime-ethers and 1,1-cyclopropanediesters.

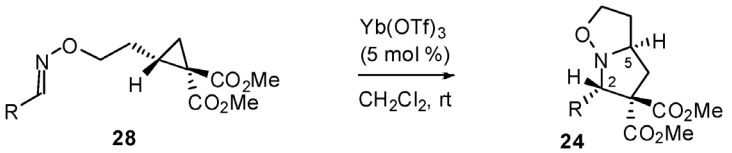
During our studies, it was found that by simply reversing the order of addition of the catalyst and aldehyde either 2,5-*cis*- or 2,5-*trans*-adducts could be obtained in a highly diastereoselective manner. Mechanistic rationale for this phenomenon can be seen in Scheme 4 where the geometry of the oxo-iminium dictates the stereochemical outcome of the resultant adduct.



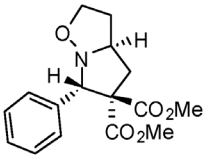
Scheme 4 Mechanistic rationale for the intramolecular oxime-ether/cyclopropane annulation.

If the aldehyde and alkoxyamino cyclopropane **23** are allowed to react before ring-opening of the cyclopropane the *E*-oxo-iminium **29** is formed as the dominant product and leads to 2,5-*trans*-adducts **24**. However, if the alkoxyamino cyclopropane is allowed to undergo ring-opening of the cyclopropane first and then treated with the aldehyde, the *Z*-oxo-iminium **27** becomes the favored geometry and the 2,5-*cis*-adduct **22** is formed. In practice, selectivity for the 2,5-*cis*-adducts is superior to that of the 2,5-*trans* with exclusive *Z*-oxo-iminium formation in all but one case. For both the *cis*- and *trans*-adducts the substrate scope was found to be exceptional, with a wide range of aldehydes undergoing the annulation reaction (Tables 4 and 5). Also, if homochiral alkoxyamino cyclopropane **23** is em-

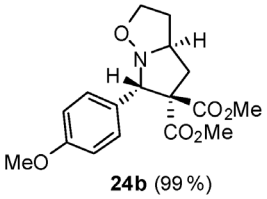
Table 4 Substrate scope for 2,5-*trans*-pyrrolo-isoxazolidines.



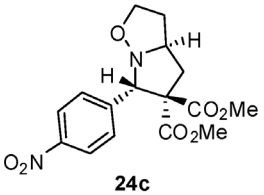
28 **24**



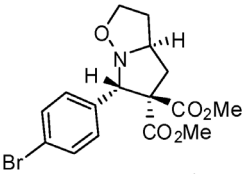
24a (98%)



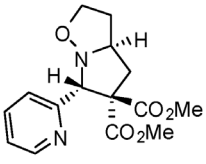
24b (99%)



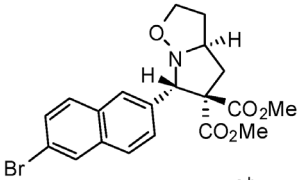
24c (99%)



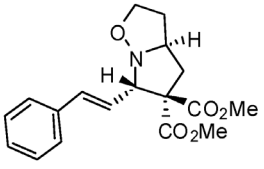
24d (99%)[a,b]



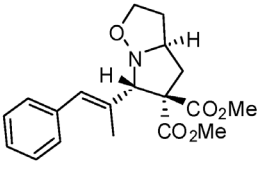
24e (97%)



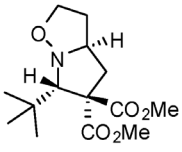
24f (99%)[a,b]



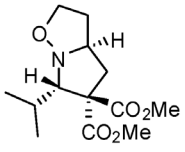
24g (81%) (*trans*:*cis* / 10:1)



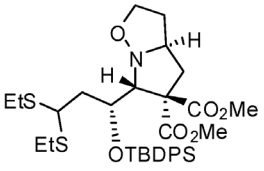
24h (85%)



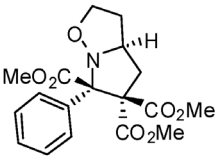
24i (75%)[a,b]



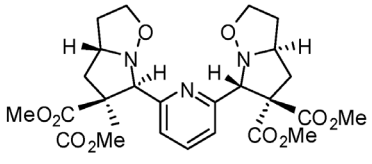
24j (82%)[c] (*trans*:*cis* / 8:1)



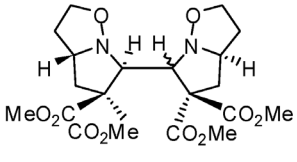
24k (94%)[a,b] (*trans*:*cis* / 20:1)



24l (98%)[a,b]



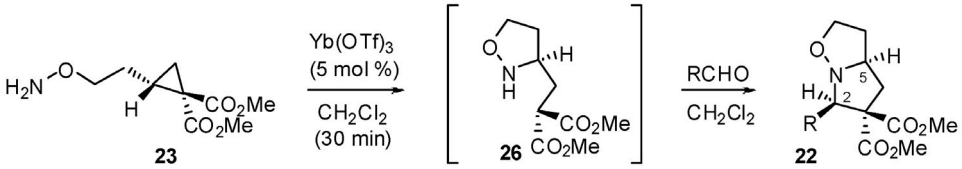
24m (70%)[a]



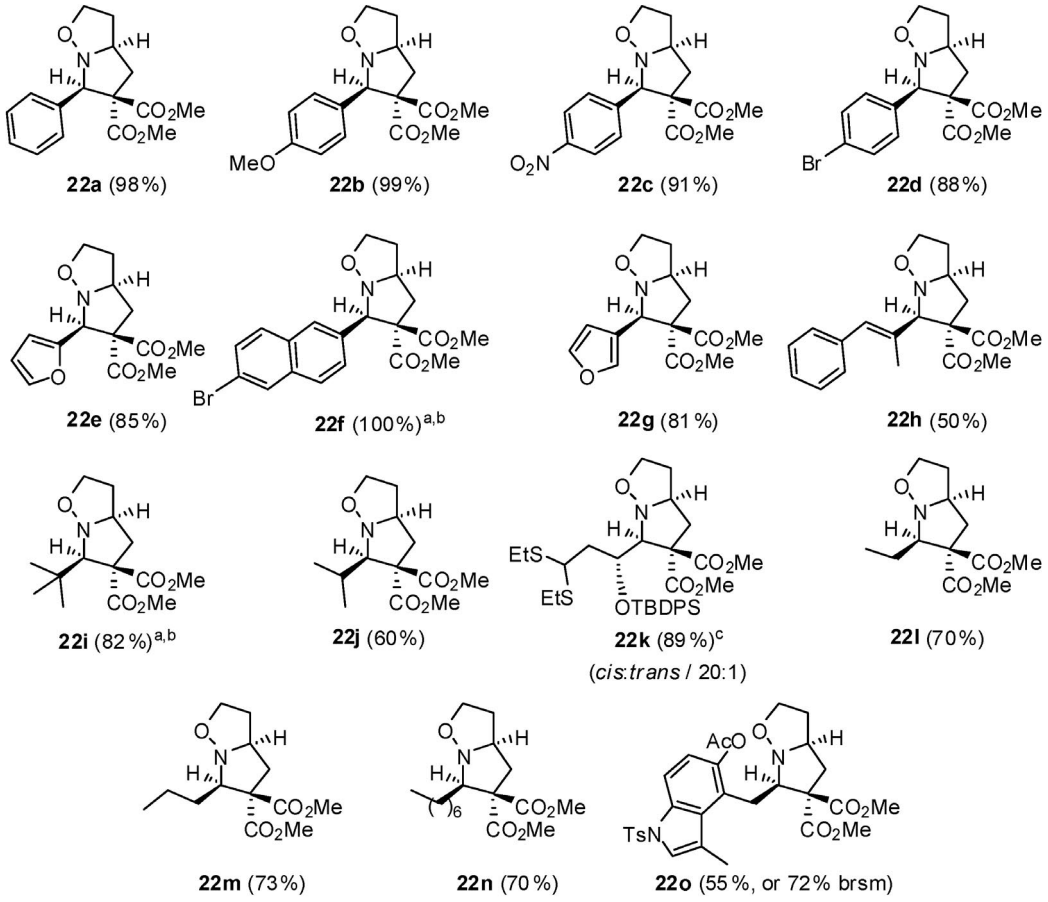
24n (H = 48%)[a,d]
24n' (H = 35%)

[a] Enantiopure (*S*)-cyclopropyl-alkoxylamine **23** was employed. [b] Product obtained in >99% *ee*. [c] 8:1 (*E*:*Z*) mixture of oxime ethers was employed. Product isomers were also inseparable. [d] 10:8:1 (*E*/*E*:*E*/*Z*:*Z*/*Z*) mixture of oxime ethers was employed.

Table 5 Substrate scope for 2,5-*cis*-pyrrolo-isoxazolidines.



23 26 22



22a (98%) **22b** (99%) **22c** (91%) **22d** (88%)

22e (85%) **22f** (100%)[a,b] **22g** (81%) **22h** (50%)

22i (82%)[a,b] **22j** (60%) **22k** (89%)[c] (*cis*:*trans* / 20:1) **22l** (70%)

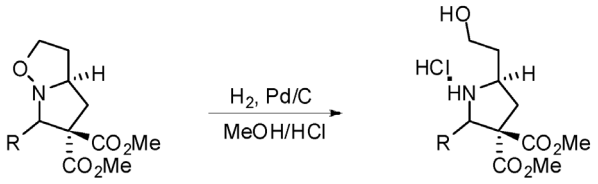
22m (73%) **22n** (70%) **22o** (55%, or 72% brsm)

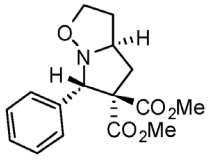
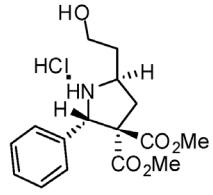
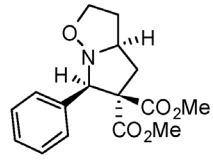
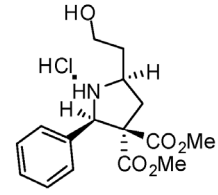
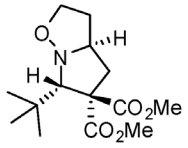
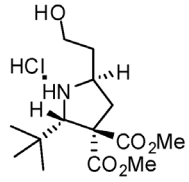
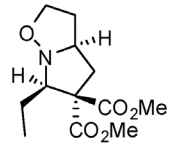
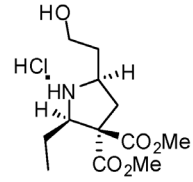
[a] Enantiopure (*S*)-cyclopropyl-alkoxylamine **23** was employed. [b] Product obtained in >99 % *ee*. [c] *cis*:*trans* of crude mixture.

ployed the level of optical purity is maintained in the resulting adducts through clean inversion of stereochemistry in the cyclopropane ring-opening step.

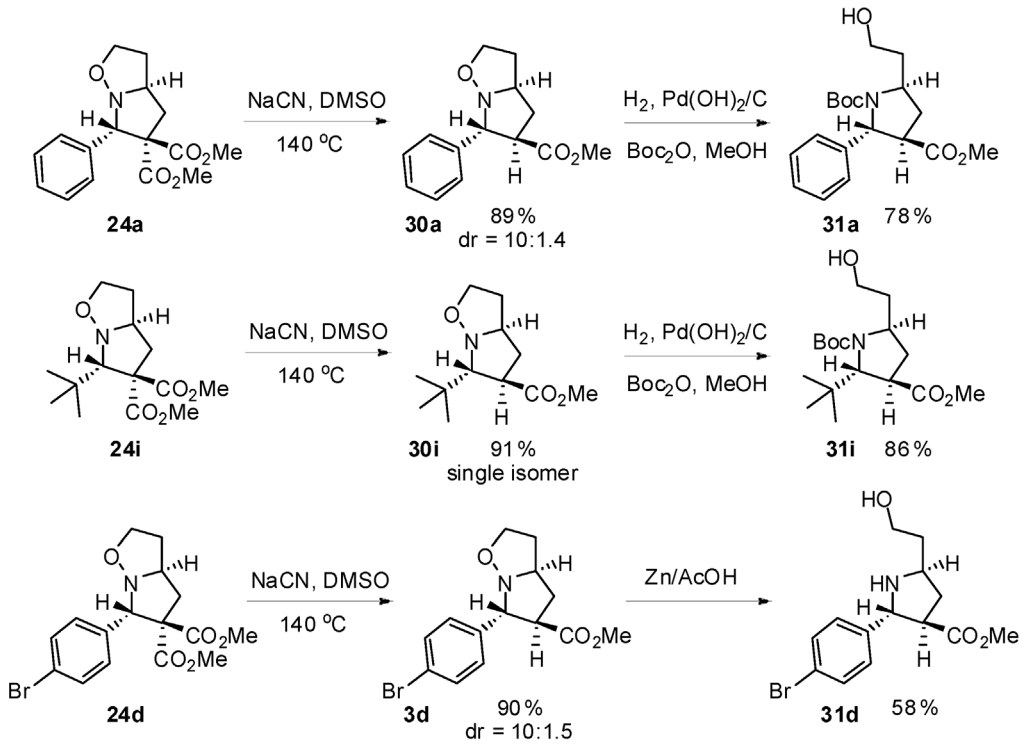
With a general route to pyrrolo-isoxazolidines, attention was then turned to N–O bond cleavage, allowing access to stereodefined pyrrolidines **21** and **22**. While initial attempts to cleave the N–O bond under neutral hydrogenation conditions led to epimerization of the C-2 center, presumably through a retro-Mannich pathway, acidic treatment allowed for facile cleavage without epimerization (Table 6).

Table 6 Access to pyrrolidines via reductive cleavage of the N–O bond of pyrrolo-isoxazolidines.



Substrate	Product	Substrate	Product
 **24a**	 **25a** (98 %)	 **22a**	 **21a** (99 %)
 **24i**	 **25i** (99 %)	 **22l**	 **21l** (99 %)

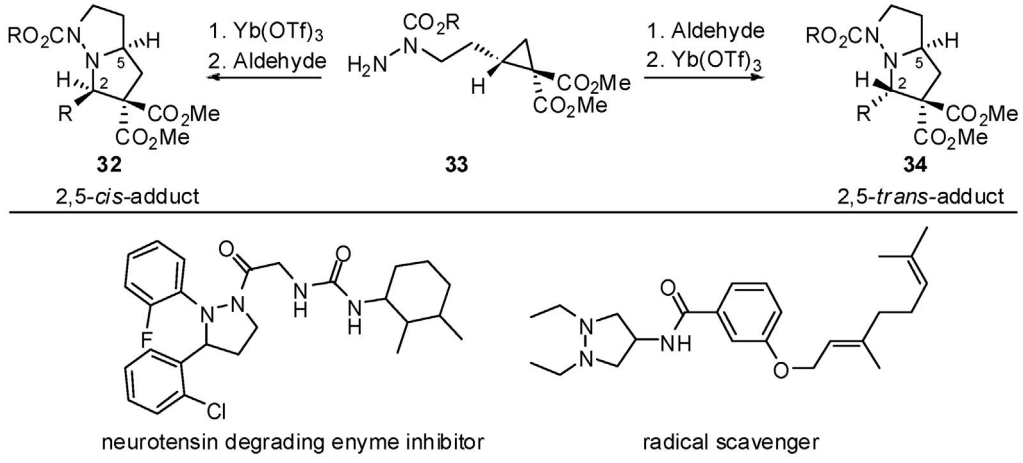
Alternatively, the *trans*-adducts, could also undergo diastereoselective Krapcho dealkoxycarbonylation [19] followed by reductive cleavage and nitrogen protection to allow access to *N*-protected 2,3,5-substituted diastereomerically pure pyrrolidines **31** (Scheme 5).



Scheme 5 Elaboration of 2,5-*trans*-pyrrolo-isoxazolidines to highly substituted pyrrolidines.

Reaction with hydrazones

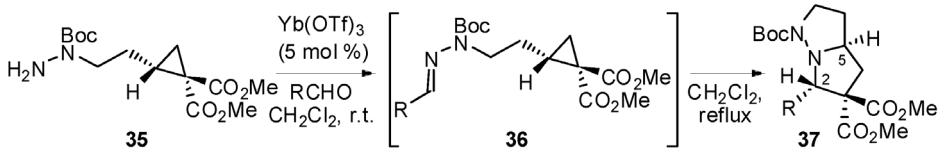
With the successful annulations of the oxime-ether tethered cyclopropanes, the use of other tethers was explored. Therefore, the use of a hydrazino tether was investigated, as it would allow access to substituted fused pyrazolidines, a heterocycle of considerable interest (Scheme 6) [17a].

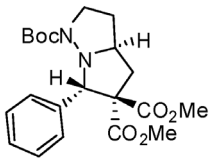


Scheme 6 Intramolecular annulation of hydrazones and 1,1-cyclopropanediesters.

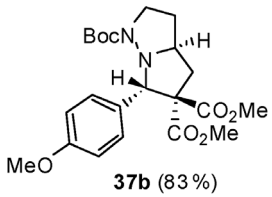
Again, the stereochemistry of the pyrazolidine adducts was found to be dictated by the geometry of the preceding aza-iminium, and similar mechanistic rationale to that found in Scheme 4 is presumed. In the case of the *trans*-adducts the increased steric bulk of the Boc group was found to improve the selectivity of the intermediate hydrazones with excellent yields obtained in almost all cases. The substrate scope was also found to be quite good, with a wide range of aldehydes undergoing the annulation reaction (Table 7).

Table 7 Reaction scope for 2,5-*trans*-pyrazolidines.

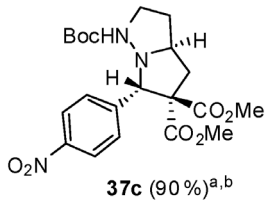




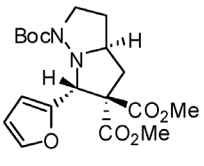
37a (85 %)



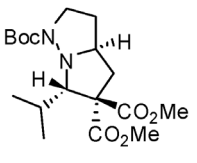
37b (83 %)



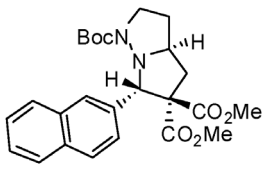
37c (90 %)[a,b]



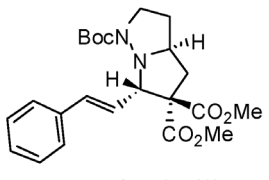
37d (89 %)[a,b]



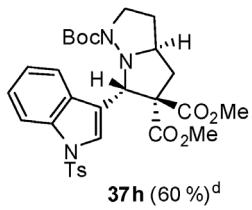
37e (85 %)



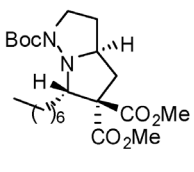
37f (80 %)[c]



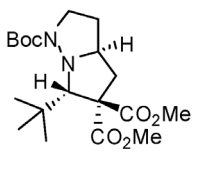
37g (83 %)



37h (60 %)[d]



37i (48 %)[e]

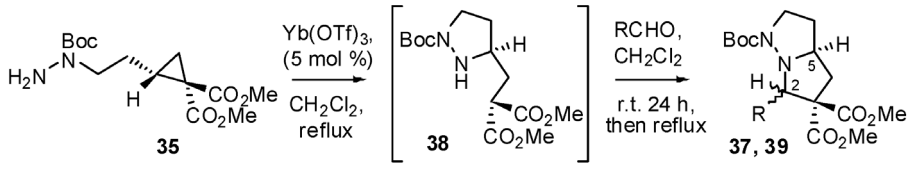


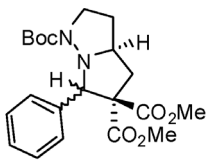
37j (70 %)[a,b]

[a] Enantiopure (*S*)-1,1-cyclopropanediester **35** was employed. [b] Product obtained in >99 % *ee*. [c] 17 % of *cis* isomer was also obtained. [d] 22 % of *cis* isomer was also obtained.[e] 14 % of *cis* isomer was also obtained.

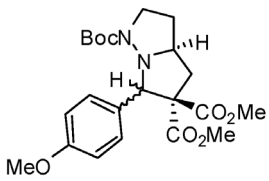
While the increased steric bulk of the Boc protecting group served to improve selectivity in the *trans*-adducts, it proved detrimental in the case of the *cis*-adducts, with significant amounts of the undesired *trans*-adduct also being formed (Table 8). In contrast to the facile ring-opening event observed with the oxime-ethers, the reaction was rather sluggish, requiring several hours at reflux instead of 30 min at room temperature. In regards to substrate scope, the use of sterically demanding aldehydes was not well tolerated for the *cis*-adducts. In order to improve the selectivity obtained for the *cis*-adducts, the use of the less sterically demanding methyl carbamate **40** could be employed (Table 9).

Table 8 Reaction scope for 2,5-*cis*-pyrazolidines.

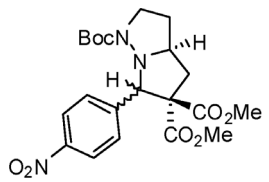




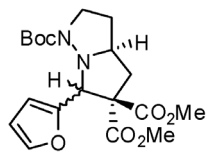
39a *cis* (61 %)[a,b]
37a *trans* (20 %)



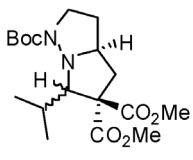
39b *cis* (48 %)
37b *trans* (24 %)



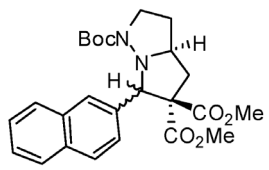
39c *cis* (66 %)[a,b]
37c *trans* (18 %)



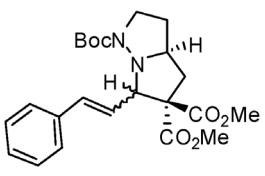
39d *cis* (75 %)
37d *trans* (22 %)



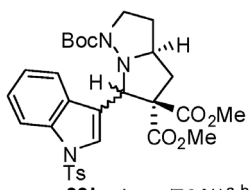
39e *cis* (16 %)
37e *trans* (49 %)



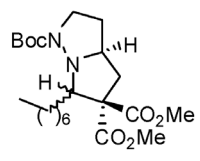
39f *cis* (58 %)
37f *trans* (17 %)



39g *cis* (56 %)
37g *trans* (27 %)



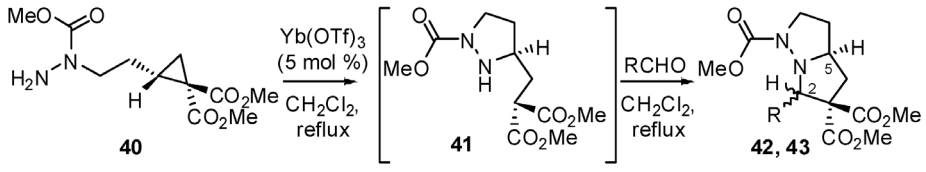
39h *cis* (72 %)[a,b]
37h *trans* (11 %)

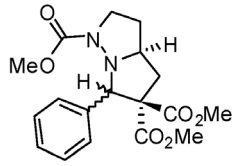


39i *cis* (53 %)
37i *trans* (16 %)

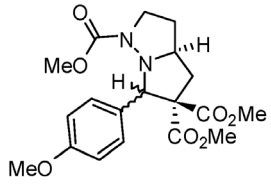
[a] Enantiopure (*S*)-1,1-cyclopropanediester **35** was employed.[b] Product obtained in >99 % *ee*.

Table 9 Improved selectivity for 2,5-*cis*-pyrazolidines.

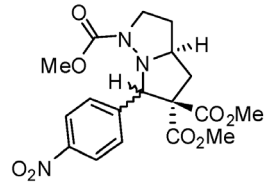




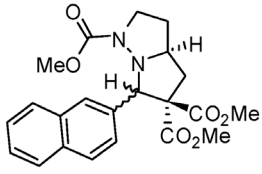
42a *cis* (72%)
43a *trans* (11%)



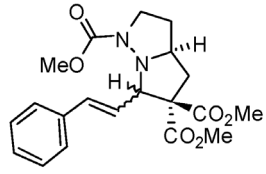
42b *cis* (83%)
43b trans (9%)



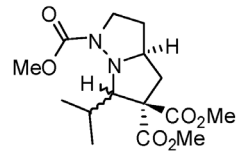
42c *cis* (70%)
43c *trans* (19%)



42d *cis* (75%)
43d *trans* (11%)



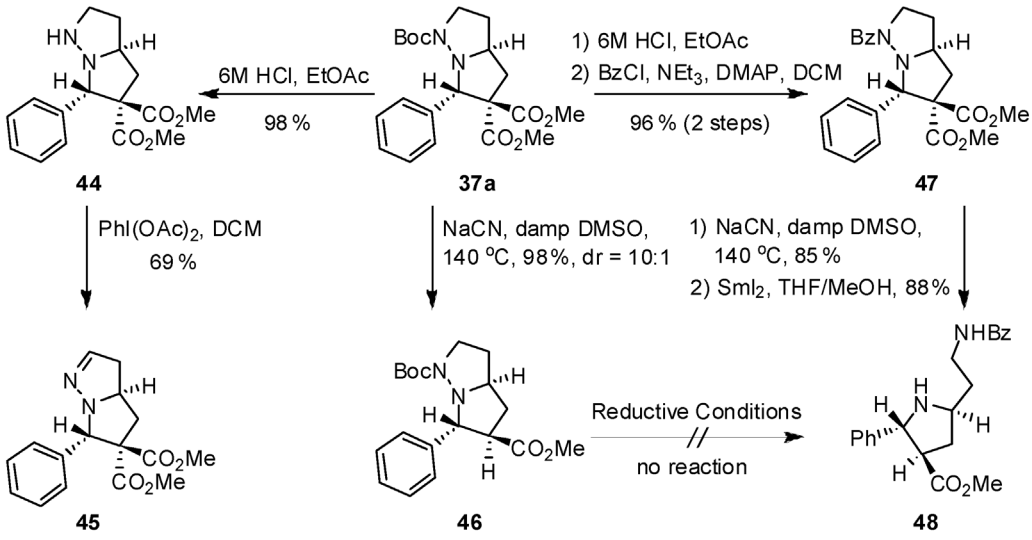
42e *cis* (65%)[a]
43e *trans* (20%)



42f *cis* (24%)
43f *trans* (40%)

[a] After aldehyde addition reaction was carried out at room temperature. When the reaction was carried out under reflux pyrazolidine **42e** and **43e** were isolated in a 24% and 72% yield respectively.

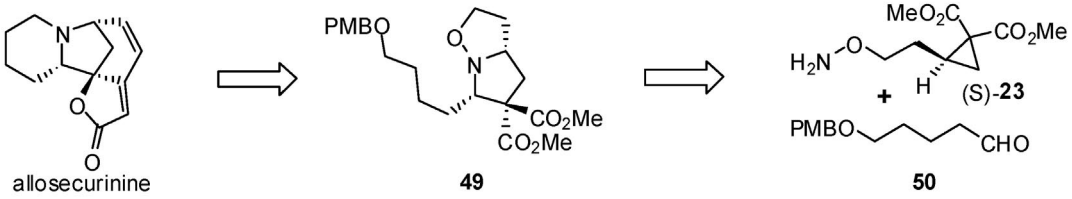
With easy access to either to 2,5-*cis*- or 2,5-*trans*-fused pyrazolidines, the conversion of these adducts to other useful heterocycles was also explored (Scheme 7). To this end, 2,5-*trans*-adduct **37a** could be deprotected under acidic conditions to give pyrazolidine **44**, which could then be oxidized to the corresponding pyrazoline **45**. Alternatively, Krapcho dealkoxycarbonylation of pyrazolidine **37a** led to monoester **46** and the generation of a new stereocenter with good diastereocontrol. While attempts to cleave the Boc-protected monoester **46** were unfruitful, simply swapping the Boc protecting group for the more electron-withdrawing benzoyl group **47** allowed for facile *N*–*N* bond cleavage and access to pyrrolidine **48**.



Scheme 7 Elaboration of pyrazolidine adducts to other heterocycles.

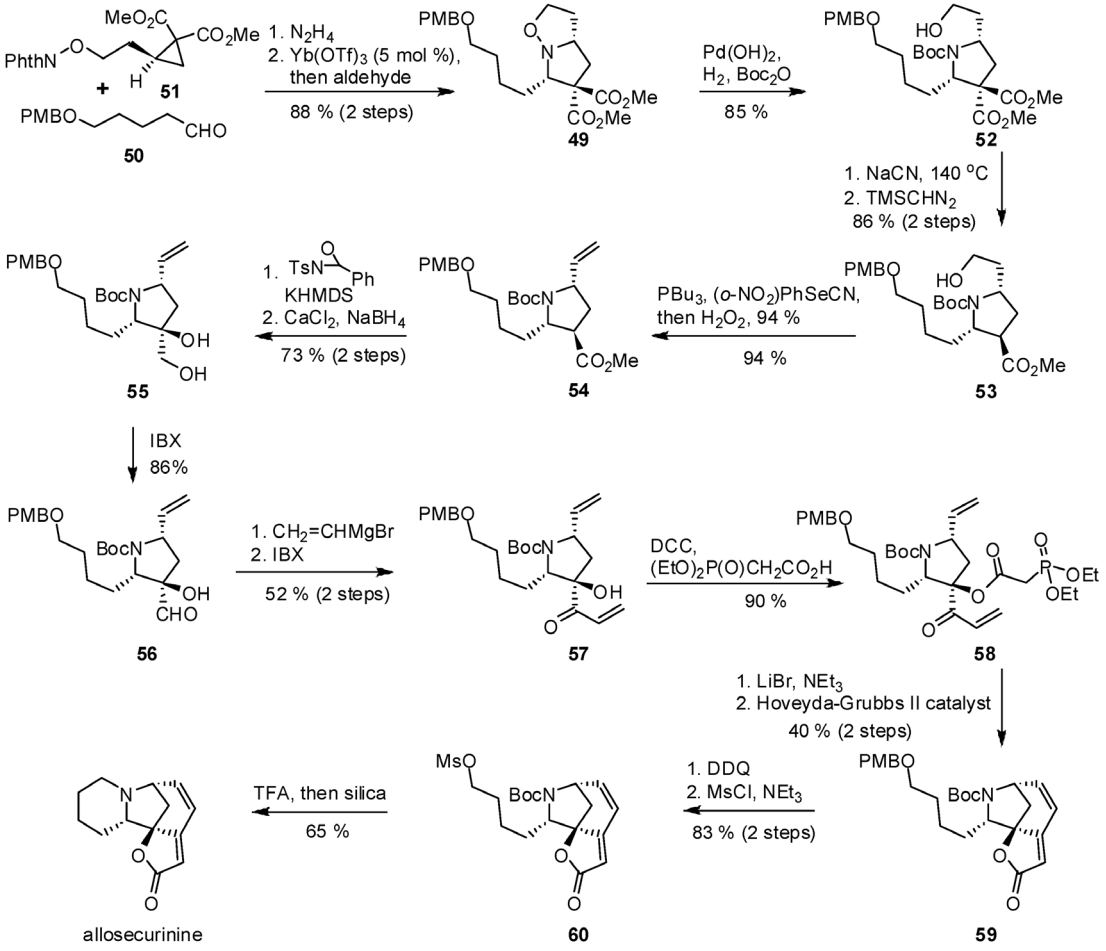
Application in total synthesis

Allosecurinine, a member of the *Securinega* family of alkaloids, was isolated in 1962 from the leaves of *Securinega suffruticosa* [20]. The first total synthesis of this alkaloid was recently reported, and it utilized an intramolecular annulation of an oxime-ether and 1,1-cyclopropanediester as a key step in the synthesis [17c]. A brief retrosynthesis is shown in Scheme 8, where it was envisioned that allosecurine could come from *cis*-pyrrolo-isoxazolidine **49**, which would in turn come from the annulation of cyclopropane (*S*)-**23** and aldehyde **50**.



Scheme 8 Retrosynthesis of allosecurinine.

The synthesis began with the deprotection of enantiopure cyclopropane **51** (Scheme 9) with ethanolic hydrazine to yield the free alkoxyamino cyclopropane (*S*)-**23**, which could then participate in the *cis*-selective annulation with aldehyde **50** to form pyrrolo-isoxazolidine **49** in excellent yield. Reduction of the N–O bond followed by Boc protection of the resulting amine then unveiled pyrrolidine **52**. Krapcho dealkoxycarbonylation, along with re-esterification of the carboxylic acid side product, resulted in the formation of mono-ester pyrrolidine **53** with excellent stereocontrol. Next, elimination of the primary alcohol using Grieco's procedure led to olefin **54** in an excellent yield [21]. Installation of the hydroxy group was carried out stereoselectively through enolate oxidation with Davis oxaziridine [22]. Reduction of the ester via a $CaCl_2/NaBH_4$ mediated reduction gave diol **55**. Oxidation of the primary alcohol with *o*-iodoxybenzoic acid (IBX) gave the corresponding aldehyde **56**, which was then treated with vinyl magnesium bromide to give a 1:1 mixture of diastereomeric alcohols which were immediately oxidized to enone **57**. Treatment of enone **57** with DCC and diethylphosphonoacetic



Scheme 9 Total synthesis of allosecurinine.

acid afforded phosphonate **58**, which could then undergo an intramolecular Horner–Emmons reaction installing the requisite butenolide. Treatment of the unstable butenolide with Hoveyda–Grubbs second-generation catalyst then allowed for ring closure and formation of pyrrolidine **59**. Removal of the *p*-methoxybenzyl (PMB) group with dichlorodicyano-*p*-benzoquinone (DDQ), followed by mesylation of the resulting alcohol furnished mesylate **60**, poised for an intramolecular displacement and formation of the final six-membered ring. This was achieved through removal of the Boc group with trifluoroacetic acid (TFA), neutralization, and treatment with silica to afford allosecurinine.

CONCLUSION

Annulations of donor–acceptor cyclopropanes offer convenient access to a variety of hetero- and carbocyclic products. We have shown that the intramolecular versions of these reactions impart an increased level of stereoselectivity and molecular complexity to the cycloadducts. These reactions promise to be useful tools for complex target-oriented synthesis.

ACKNOWLEDGMENTS

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