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Stereodivergent Synthesis of Fused Bicyclopyrazolidines: Access to Pyrazolines and Pyrrolidines

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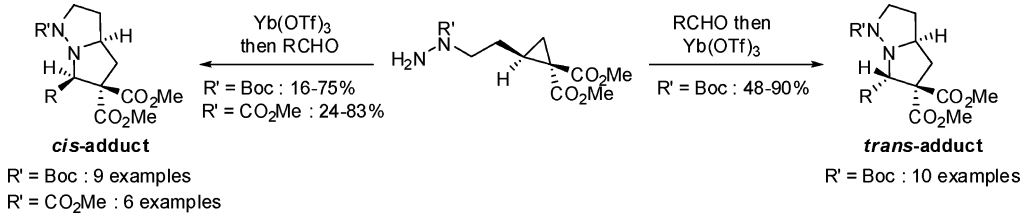
ABSTRACT



The reaction of hydrazinoethyl 1,1-cyclopropanediesters with aldehydes in the presence of catalytic $Yb(OTf)_3$ allows access to structurally complex fused bicyclo pyrazolidines. Either 2,5-*cis* or 2,5-*trans* adducts can be obtained in good to excellent yields in most cases by simply controlling the order of addition of the catalyst and aldehyde.

Nitrogen-containing heterocycles are of great importance to the pharmaceutical industry since they often possess interesting biological activity. As such, new and efficient approaches to rapid and easily modified libraries is of considerable interest to both medicinal and synthetic chemists.[1] Pyrazolidines have been shown to possess a variety of biological activities such as fungicidal, herbicidal, anti-inflammatory, local anesthetic, VLA-4 antagonist, anticonvulsant, dipeptidyl peptidase inhibitory activity, radical scavenger activity, and antibacterial.[2] Herein we wish to report an efficient diastereoselective (and diastereodivergent) synthesis of structurally complex fused bicyclopyrazolidines[3] using a novel intramolecular annulation of hydrazones and 1,1-cyclopropanediesters (Figure 1).

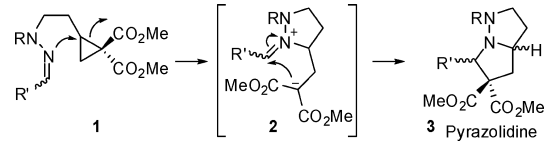


Figure 1. Intramolecular hydrazone/cyclopropane annulations.

Annulations of donor−acceptor cyclopropanes[4] have received considerable attention in recent years as they allow rapid access to a variety of hetero- and carbocyclic products.

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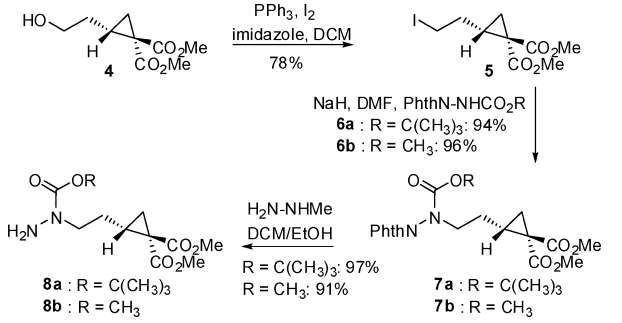
While there have been many intermolecular versions with a variety of dipoles such as nitrones,[5] imines,[6] aldehydes,[7] aromatic azomethine imines,[8] diazenes,[9] nitriles,[10] isocyanides,[11] isocyanates,[12] isothiocyanates,[13] α,β-unsaturated ketones,[14] allenes, acetylenes,[15] allylsilanes,[16] and indoles,[17] there have been limited reports on intramolecular versions.[18] Intramolecularity would in principle allow for increased reactivity as well as control of diastereoselectivity.[19] This idea was shown to have merit in our recently reported stereodivergent synthesis of pyrrolidines[18a] via an intramolecular annulation of oxime ether-tethered cyclopropanes, and the extension of this methodology was successfully employed in the total synthesis of allosecurinine.[20]

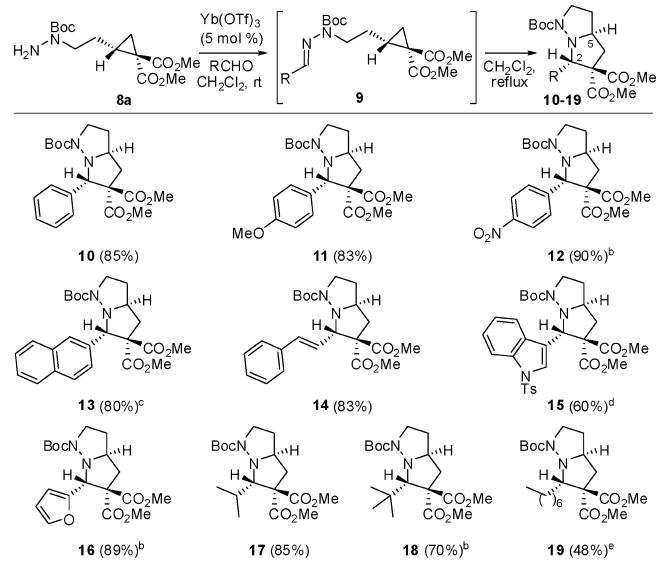
Synthesis of our desired cyclopropane began with readily available cyclopropane **4**[21] which was converted to its iodo derivative **5** by treatment with PPh_3, imidazole, and iodine in a 78% yield. Displacement of the iodo leaving group with unsymmetrically protected hydrazines **6a** and **6b** yielded cyclopropanes **7a** (94%) and **7b** (96%), respectively. Removal of the phthalimide protecting group was then achieved by treatment with methylhydrazine to afford the unprotected cyclopropanes **8a** (97%) and **8b** (91%) in excellent yields.

Scheme 1. Synthesis of Hydrazinoethylcyclopropane **8a** and **8b**



With our desired hydrazinoethyl 1,1-cyclopropanediester **8a** in hand, we next investigated the scope of the reaction. Our initial reaction involved stirring cyclopropane **8a** with benzaldehyde in the presence of 5 mol % $Yb(OTf)_3$. After complete conversion to the corresponding hydrazone, the reaction was brought to reflux to induce cyclization, providing 2,5-*trans*-pyrazolidine **10** in 85% yield. This sequence of events was then repeated with a variety of aldehydes, the results of which are shown in Scheme 2. The reaction is

Scheme 2. Synthesis of 2,5-*trans*-Pyrazolidines[a]



[a] Reagents employed: cyclopropane (1 equiv), aldehyde (1.2 equiv), $Yb(OTf)_3$ (0.05 equiv), and CH_2Cl_2 (4 mL). [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.

robust in its generality with respect to the aldehyde employed. The electronic nature of substituents on the aldehyde seems inconsequential and other aromatic and heteroaromatic aldehydes perform with equal aplomb. It is also of note that even sterically demanding aldehydes such as isobutyraldehyde and pivaldehyde work well. In each case, the adducts were formed as the 2,5-*trans* diastereomers (pyrrolidine numbering) with insignificant amounts of the 2,5-*cis* adducts present in most cases. Furthermore, when enantiomerically pure (*S*)-cyclopropane **4** was employed in the reaction the

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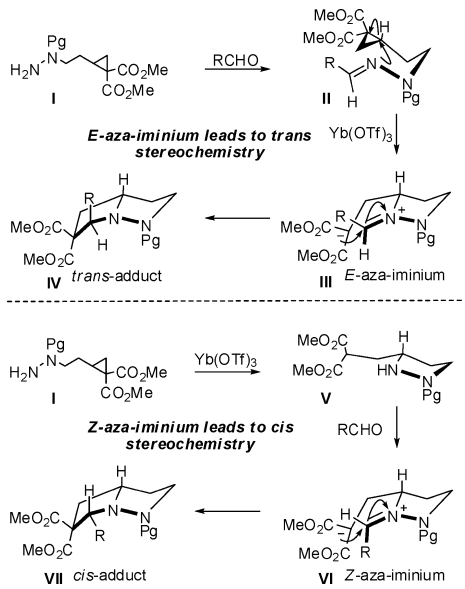
adducts where obtained with full enantiomeric integrity (pyrazolidine **12**, **16**, and **18**).

The diastereoselectivity of this reaction was not unexpected due to observations in our previous work with oxime ethers.[18a] The rationale for this selectivity is shown in Scheme 3. Generation of hydrazone **II** is expected to form

Scheme 3. Mechanistic Rationale

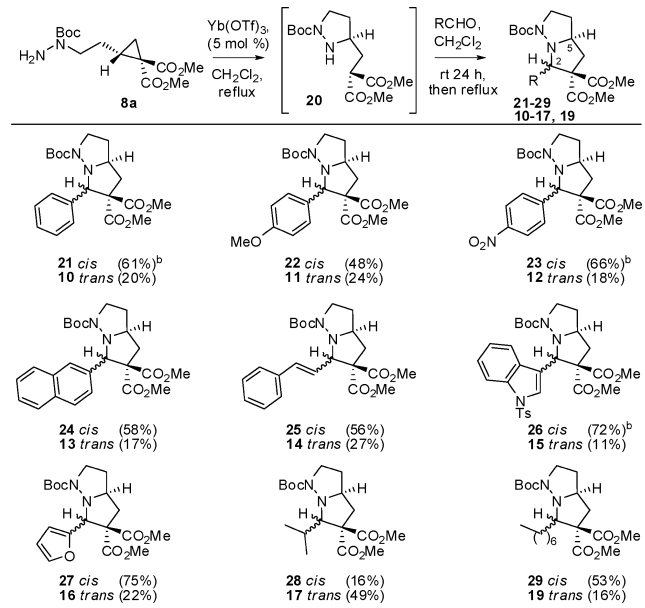


the *E*-product as the major (if not sole) isomer. Nucleophilic ring-opening by the imino nitrogen would generate aza-iminium ion **III** which, if holding its geometrical integrity, would give 2,5-*trans*-pyrazolidine **IV** upon Mannich ring closure.

We then reasoned that if we could generate the *Z*-azaiminium ion **VI**, Mannich closure would result in the formation of the complementary *cis*-pyrazolidine **VII**. The strategy for doing this is shown in Scheme 3 whereby pyrazolidine **V** would be condensed with an aldehyde to form *Z*-azaiminium ion **VI**, which would undergo cyclization to the 2,5-*cis*-pyrazolidine **VII**.

To this end, we treated cyclopropane **8a** with 5 mol % of $Yb(OTf)_3$ in refluxing CH_2Cl_2 to generate pyrazolidine **20**. The addition of benzaldehyde to the cooled (ambient temperature) reaction mixture for 24 h followed by reflux then led to the formation of the desired 2,5-*cis* adduct **21** in 61% yield along with 20% of the 2,5-*trans* cycloadduct **10**. This ratio is likely representative of the geometric ratio of the putative aza-iminium intermediates. The reaction scope with respect to the aldehyde partners was then investigated, the results of which are shown in Scheme 4.

Scheme 4. Synthesis of 2,5-*cis*-Pyrazolidines[a]



[a] Reagents employed: Cyclopropane (1 equiv), aldehyde (1.2 equiv), $Yb(OTf)_3$ (0.05 equiv), and CH_2Cl_2 (5 mL). [b] Product obtained in >99% ee.

It is evident from the results in Scheme 4 that the 2,5-*trans* cycloadducts are more than an insignificant impurity. This is likely due to the less than perfect geometrical selectivity in the formation of the requisite aza-iminium intermediate. In an attempt to improve the selectivity for the 2,5-*cis* adducts we switched from a Boc protecting group to the less sterically demanding methyl carbamate. Gratifyingly, this led to an increase in the desired 2,5-*cis* adducts in all cases (Scheme 5). Interestingly, however, when cinnamaldehyde was employed under the reaction conditions the 2,5-*trans* adduct was isolated as the major isomer. Furthermore, the *cis*/*trans* ratio varied depending on the reaction time. We suspected that the major adducts in a typical reaction are kinetically formed and that the products may be amenable to isomerization via a retro-Mannich/Mannich process. In order to investigate this phenomenon the 2,5-*cis* adduct **35** was heated in $CDCl_3$ in the presence of 5 mol % of $Sc(OTf)_3$ and the reaction monitored by ^1H NMR (Figure 2). It was found that the 2,5-*cis* adduct did indeed isomerize to the 2,5-*trans* adduct under the reaction conditions and after 27 h of heating the 2,5-*trans* adduct predominated in a 3.37:1 ratio.

To further demonstrate the synthetic utility of this methodology and the usefulness of the pyrazolidine adducts, conversion to other highly useful heterocycles such as pyrrolidines[22] and pyrazolines[23] was briefly examined (Scheme 6). Initial attempts to access the pyrrolidine motif involved dealkoxycarbonylation[24] of pyrazolidine **10** to give pyrazo-

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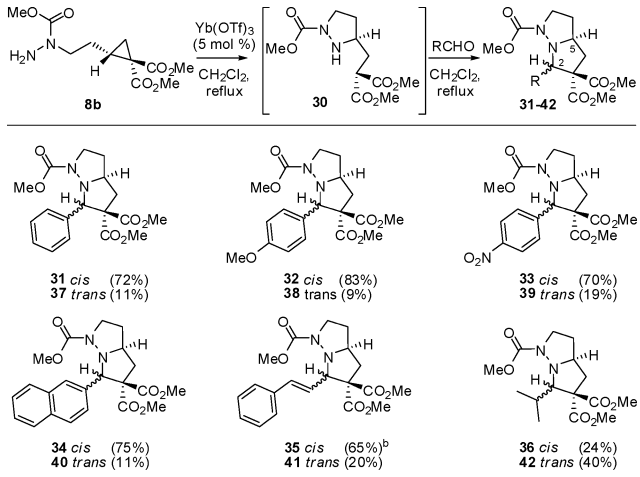
(21) Racemic **4** is easily prepared via hydroboration of (±)-2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester. Enantiomerically pure **4** can be prepared from commercially available (*R*)- or (*S*)-butane triol. For preparation of **4** see refs 18a and 20.

Scheme 5. Improved Selectivity for 2,5-*cis*-Pyrazolidines[a]



[a] Reagents employed: cyclopropane (1 equiv), aldehyde (1.2 equiv), $Yb(OTf)_3$ (0.05 equiv), and CH_2Cl_2 (5 mL). [b] After aldehyde addition, the reaction was carried out at room temperature. When the reaction was carried out under reflux, pyrazolidines **35** and **41** were isolated in 24% and 72% yield, respectively.

lidine **43** in a 98% yield and 10:1 diastereomeric ratio in favor of the 2,3-*trans* adduct. The N−N bond of this adduct, however, proved to be resilient as a variety of reductive conditions failed to give the desired cleaved product. This problem, however, was circumvented by simply swapping the Boc group for the more electron-withdrawing benzoyl group. Now, after dealkoxycarbonylation of pyrazolidine **44**

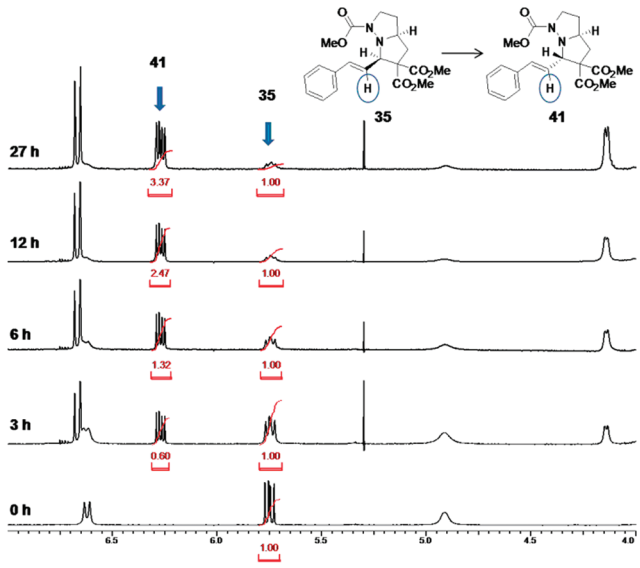
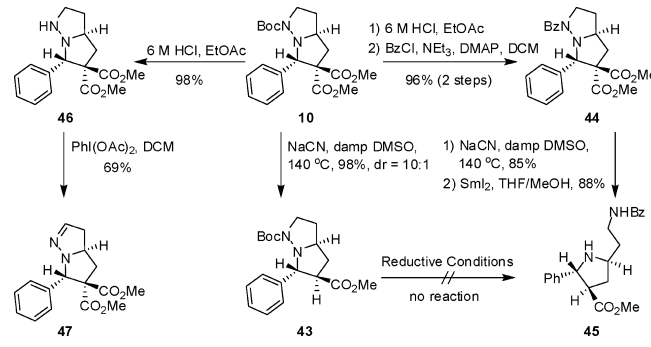


Figure 2. ^{1}H NMR observation of *cis*/*trans* isomerization.

Scheme 6. Modification of Pyrazolidine Adducts



treatment with SmI_2[25] allowed for facile N−N bond cleavage and access to pyrrolidine **45** in 88% yield. We next turned our attention to the access of pyrazolines. This was achieved through acidic treatment of pyrazolidine **10** to give the deprotected pyrazolidine **46**. Finally, oxidation of pyrazolidine **46** allowed access to pyrazoline **47** in 69% yield.

In conclusion, we have presented a general, diastereoselective synthesis of complex fused bicyclopyrazolidines. Either 2,5-*cis* or 2,5-*trans* adducts can be obtained in good to excellent yields by simply controlling the order of addition of the catalyst and aldehyde. If homochiral cyclopropanes are employed the chirality is maintained in the pyrazolidine adducts. Furthermore, the pyrazoldine adducts can also be converted to synthetically useful pyrrolidnes through N−N bond cleavage or oxidized to give pyrazolines.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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