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A New Entry to Enantiopure Polysubstituted Cyclopropanes: Stereoselective Denitrogenation of Sulfinylpyrazolines under $Yb(OTf)_3$ Catalysis

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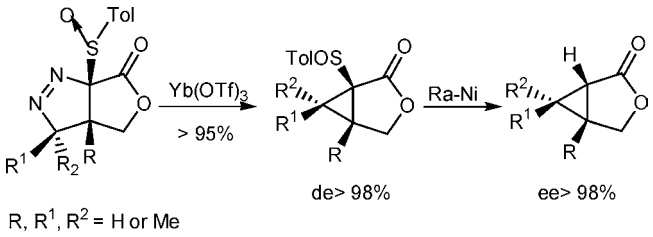
ABSTRACT



Chemoselective and completely stereoselective denitrogenation of optically pure pyrazolines, derived from 3-sulfinylfuran-2(5*H*)-ones, into cyclopropanes can be achieved under substoichiometric $Yb(OTf)_3$ catalysis. Reactions evolve in almost quantitative yields with complete retention of the configuration at both carbons flanking the nitrogen atoms. The resulting enantiomerically pure polysubstituted cyclopropanes, containing up to five substituens, can be desulfinylated with Ra–Ni providing polysubstituted cyclopropanecarboxylic acid derivatives.

Polysubstituted cyclopropanes are basic structural moieties in a wide range of natural and biologically active compounds, as well as important intermediates in organic synthesis.[1a,b] As a consequence, many strategies have been developed for their preparation in their optically pure form.[1c−e] In this context, reactions of ylides with electron-deficient alkenes,[2] halomethylmetals (modified Simmons−Smith reagents) with electron-rich alkenes,[3] and olefins with metal carbenes generated by metal-catalyzed decomposition of diazoalkanes[4] have been applied to build the polysubstituted cyclopropanic skeletons. However, very few of these methods are efficient for preparing enantiomerically pure cyclopropanes with three chiral carbons. Thus, Doyle's procedure has been used with only moderate success to prepare 1,2,3-trisubstituted rings,[5] and only some very recent articles describe the efficient synthesis of these systems. Those from Taylor[6] and Hoppe[7]

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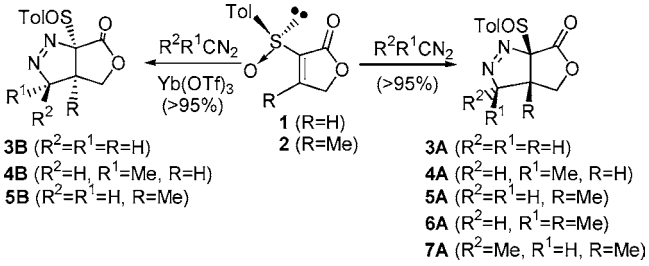
are based on the completely stereoselective cyclization of enantiomerically enriched homoaldol adducts, with the structure and optical purity of the precursors as the main limitation. Donaldson reported[8] the synthesis of optically active 2-(2′-carboxycyclopropyl)glycines in moderate yield by using an organoiron methodology. Organocatalysis also has been applied to the synthesis of cyclopropanes. Aggarwal provided the first example in this field when he described the catalytic asymmetric cyclopropanation of electron-deficient alkenes, which evolved in moderate yields and diastereoselectivities but with good enantioselectivity.[9] The results reported by Gaunt,[10] concerning the intramolecular cyclopropanation yielding synthetically versatile [3.1.0]-bicycloalkenes, describe only one example of optically active substrate, which is formed in moderate yield and with good ee. MacMillan[2b] has recently published a more general catalytic method for synthesizing enantiomerically pure polysubstituted cyclopropane carbaldehydes. Finally, one method has been published from the α,β-unsaturated Fischer carbene complex for the synthesis of tetrasubstituted cyclopropanes with three chiral centers, therefore containing a quaternary carbon.[11]

The synthesis of cyclopropanes by extrusion of nitrogen from pyrazolines[12] is a well-known reaction whose efficiency is restricted by the easy $\Delta^1 \rightarrow \Delta^2$ rearrangement of the substrates, as well as by the competitive formation of olefins, which are usually the major products under thermal conditions. The addition of Brönsted or Lewis acids significantly increases the proportion of cyclopropanes[13] and lowers the temperature required for denitrogenation. Very few papers have been reported on the use of pyrazolines as starting materials in the asymmetric synthesis of cyclopropanes. It could be due to the low configurational stability of the diradical or zwitterionic species usually postulated as intermediates for these reactions.[14] Photochemical extrusion of nitrogen has been efficiently used for synthesizing optically pure cyclopropanes[15] but, to our knowledge, only two reports concerning thermal denitrogenation in a totally stereoselective way have been so far published.[16,17] As they proceed at high temperatures, which are scarcely compatible with the configurational stability of zwitterionic intermediates, concerted mechanisms have been postulated to account for their stereoselective evolution.

We have recently reported a highly stereoselective and efficient method for synthesizing pyrazolines by reaction of diazoalkanes with optically pure (*S*)-3-*p*-tolylsulfinylfuran-2(5*H*)-ones, **1** and **2** (Scheme 1).[18]

Scheme 1. Synthesis of Pyrazolines



The formation of small amounts of cyclopropanes in a totally stereoselective way when some sulfinyl furopyrazolines were oxidized into their corresponding sulfones with *m*-CPBA[19] drew our attention onto the so far never reported role of acids in the stereochemical course of the denitrogenation processes. We report herein the conditions allowing totally stereoseletive denitrogenation of the pyrazolines depicted in Scheme 1, which provide a new access to optically pure cyclopropanes containing up to five substituents and their three chiral carbons.

Initially, we investigated the extrusion of nitrogen from pyrazolines **3** under different conditions (Table 1). When **3A** (R = H) was heated in refluxing toluene for 2 h, olefin **11** was obtained in almost quantitative yield[20] (entry 1). The addition of Lewis acids ($ZnBr_2$, $Eu(fod)_3$, $Eu(OTf)_3$, $BF_3.OEt_2$, $Yb(OTf)_3$) substantially lowered the reaction temperature and led to the formation of cyclopropane **8A**. Olefin **11** was quantitatively obtained in the presence of $Eu(fod)_3$ at room temperature (entry 2), whereas $Yb(OTf)_3$ provided the highest chemoselectivity favoring cyclopropane **8A**,[21] which was dependent on the amount of the catalyst. Olefins were exclusively obtained in the presence of 3 equiv of $Yb(OTf)_3$ (entry 3). Mixtures of cyclopropanes and olefins were formed by decreasing the amount of the catalyst (see entries 3 and 4), the highest proportion of cyclopropanes being observed when 0.5 equiv of $Yb(OTf)_3$ was used. Under these conditions, cyclopropane **8A** was obtained in 97% isolated yield after 5 h at room temperature (entry 5).

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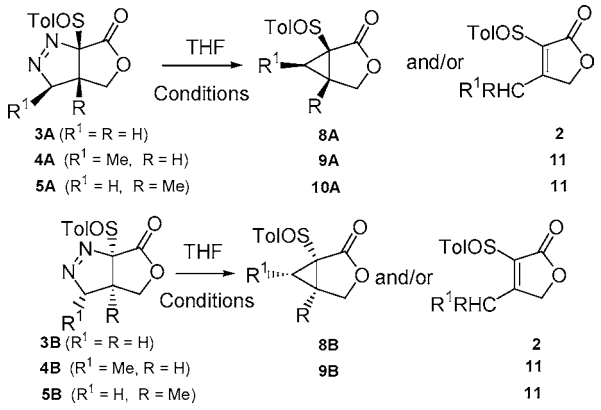
(20) A similar result had been obtained from other pyrazolines. See: García Ruano, J. L.; Fraile, A.; González, G.; Martín, M. R.; Clemente, F. R.; Gordillo, R. *J. Org. Chem.* **2003**, *68*, 6522.
(21) $ZnBr_2$, $Eu(OTf)_3$, and BF_3 also give cyclopropanes in substantial amounts, but the observed chemoselectivity is lower than with $Yb(OTf)_3$.

Table 1. Denitrogenation of Pyrazolines **3**, **4**, and **5** under Different Conditions



a	*b*	catal[c] (*d*)	*T*, °C	*t*, h	products (ratio)[e]	isolated yield, %[d]
1	**3A**		110[f]	2	**2**	98
2	**3A**	A (1)	25	3.5	**2**	97
3	**3A**	B (3)	25	3.5	**2**	91
4	**3A**	B (1.3)	25	4.5	**8A** (53)/**2** (47)	
5	**3A**	B (0.5)	25	5	**8A**	97
6	**3B**		110[f]	1	**2**	99
7	**3B**	A (1)	25	2	**2**	97
8	**3B**	B (3)	25	2	**2**	
9	**3B**	B (1.3)	25	2	**8B** (45)/**2** (55)	
10	**3B**	B (0.5)	25	3	**8B**	91
11	**4A**		110[f]	1	**11**	98
12	**4A**	A (1)	25	0.7	**11**	95
13	**4A**	B (0.5)	25	3	**9A** (65)/**11** (35)	
14	**4A**	B (0.5)	−40	19	**9A**	87
15	**4B**		110[f]	1	**11**	98
16	**4B**	A (1)	25	45	**11**	96
17	**4B**	B (0.5)	−40	10	**9B** (52)/**11** (48)	
18	**4B**	B (0.5)	−78	14	**9B** (70)/**11** (30)	68 (**9B**)
19	**5A**	A (1)	25	1	**11**	96
20	**5A**	B (0.5)	25	1	**10A**	95
21	**5B**	A (0.5)	25	0.6	**11**	97
22	**5B**	B (0.5)	0	1	**11**	91

[a] Entry. [b] Starting material. [c] A: Eu(fod)$_3$. B: Yb(OTf)$_3$). [d] Number of equivalents. [e] Determined by ^{1}H NMR. [f] Toluene.

A similar behavior was observed for diastereomeric pyrazoline **3B** but its denitrogenation was slightly easier than that of **3A** and hence required shorter reaction times (compare entries 1−5 with 6−10). Additionally **3B** exhibited a lower tendency than **3A** to evolve into their corresponding cyclopropane with Yb(OTf)$_3$ (compare entries 4 and 9). Nevertheless, **3B** can also be completely transformed into **8B** at room temperature by using 0.5 equiv of this catalyst (entry 10).

The behavior of **4A** and **4B** under different conditions was similar to that observed for **3A** and **3B**. They afforded olefin **11** by heating in refluxing toluene (entries 11 and 15) or treating with Eu(fod)$_3$ (entries 12 and 16) at room temperature. Much more interesting were the reactions of **4A** and **4B** with 0.5 equiv of Yb(OTf)$_3$ because they afforded trisubstituted cyclopropanes. To our delight, these reactions were completely stereoselective yielding compounds **9A** and **9B** only. These reactions required slightly shorter times than those from **3A** and **3B** and exhibited a lower tendency to form cyclopropanes. At room temperature **4A** yielded a 65:35 mixture of **11**:**9A** (entry 13). However, the chemoselectivity favoring cyclopropanes increased when the temperature was lower, and thus at −40 °C the reaction only yielded **9A** (87% isolated yield, >98% de, entry 14). **4B** also afforded olefin **11** under the conditions of entries 15 and 16, and exhibited an even smaller tendency than **4A** to evolve into cyclopropane **9B**, which could not be obtained in a completely chemoselective manner. Thus, at −40 °C it gave a 52:48 mixture of **9B**:**11** (entry 17), and under the best conditions (−78 °C), optically pure **9B** was isolated in 68% yield (entry 18).

It is noteworthy that the configuration of **9A** and **9B** at all their chiral centers is identical with that of their respective precursors **4A** and **4B**, which indicates that denitrogenation takes place with retention of configuration.

The cyclopropane formation under Yb(OTf)$_3$ catalysis can be explained as depicted in Figure 1. Initially, the metal forms

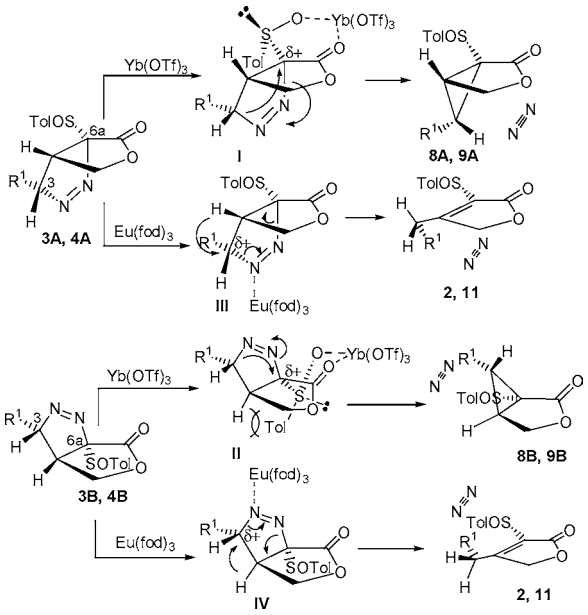


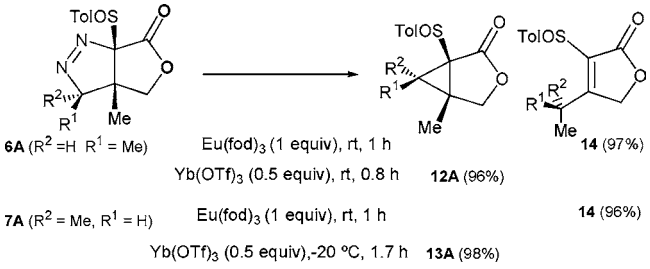
Figure 1. Stereochemical course of denitrogenation.

a chelated species with the sulfinyl and carbonyl oxygens (**I** and **II**). It increases the electronic deficiency at C-6a and provokes the concerted migration of C-3 (from nitrogen to C-6a) with extrusion of nitrogen. This process affords cyclopropanes with retention of the configuration at the migrating carbon. By contrast, the Eu(fod)$_3$ associates with the nitrogen (**III** and **IV** in Figure 1), which increases the electronic deficiency at C-3 provoking the migration of the hydrogen at C-3a and the extrusion of nitrogen, giving as the result the formation of the olefin. This latter migration must be easier than the former one affording cyclopropanes and therefore the olefins will be predominant when the association of the catalyst takes place at both nitrogenated

and oxygenated basic centers (as was the case when an excess of $Yb(OTf)_3$ was used). The selectivity of the catalysts could be attributed to their differential affinity to the oxygen but mainly to their different size. This would deal with the formation of cyclopropanes as the major reaction product when the catalyst was $Eu(OTf)_3$ instead of $Eu(fod)_3$. The model at Figure 1 explains that isomers **A** and compounds **3** evolve into cyclopropanes more readily than isomers **B** and compounds **4,** respectively. Chelates **I** derived from **A** are more stable than **II** resulting from **B** due to the $(Ph/H)_{1,3-diaxial}$ interaction, which decreases the stability of **II**. Moreover, steric effects suggest that the migration of C-3 onto C-6a must be easier when R^1 is hydrogen (pyrazolines **3**) than when R^1 = Me (pyrazolines **4**).

Finally we have studied the behavior of pyrazolines bearing a methyl group at C-3a. The results obtained from **5A** and **5B** are collected in Table 1. By refluxing in toluene or in the presence of $Eu(fod)_3$ they afforded **11** (entries 19 and 21). Under $Yb(OTf)_3$ catalysis, **5A** evolved into **10A** (entry 20), whereas **5B** was transformed into **11** (entry 22) even at low temperatures. This behavior is not unexpected due to the low stability of its chelated species, similar to species **II** in Figure 1, with the $(Tol/Me)_{1,3-diaxial}$ interaction instead of the $(Tol/H)_{1,3-diaxial}$ one. The behavior of pyrazolines **6A** and **7A** (Scheme 2) is similar to that observed for

Scheme 2

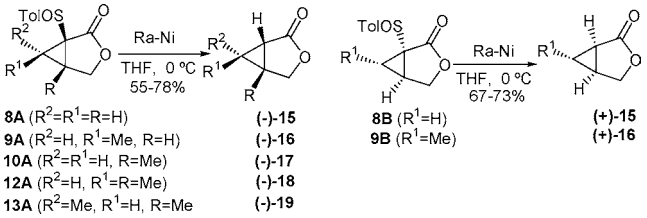


the other **A** stereoisomers that evolved into the olefin **14**[18] under thermal and $Eu(fod)_3$ catalyzed conditions, but afforded cyclopropanes **12A** and **13A** in the presence of $Yb(OTf)_3$.

Configurational assignment of the obtained cyclopropanes has been made by NMR studies and chemical correlations with known compounds (see the Supporting Information).

Raney-Ni desulfinylation of sulfinyl cyclopropanes yielded optically pure bicyclic lactones (Scheme 3), which are

Scheme 3. Desulfurization of Sulfinylcyclopropanes



immediate precursors of cyclopropanecarboxylic acids containing up to four substituents at the ring. Compounds obtained from **8A** and **9A** are enantiomers of those obtained from **8B** and **9B**, respectively.

Despite enantiomers (+)-**17**, (+)-**18**, and (+)-**19** not being obtained from (*S*)-4-methyl-3-*p*-tolylsulfinylfuran-2(5*H*)-one (**2**), it is noteworthy that all of them can be easily obtained starting from the enantiomer of compound **2**.

In summary, we have proven that optically pure sulfinyl pyrazolines can be easily transformed into cyclopropanes in the presence of substoichiometric amounts of $Yb(OTf)_3$ under very mild conditions in almost quantitative yields. The extrusion of nitrogen proved to be completely stereoselective, taking place with complete retention of configuration at the carbons flanking the nitrogen atoms. The combined use of this reaction with the cycloaddition of diazoalkanes to (*R*)- and (*S*)-3-*p*-tolylsulfinylfuran-2(5*H*)-ones[18] provides one of the most efficient procedures for synthesizing enantiomerically pure sulfinyl cyclopropanes bearing up to five substituens at the ring, which can be easily desulfinylated. We are currently extending the scope of this new method to obtain polysubstituted cyclopropanes to many other pyrazolines 3,3-disubstituted by electron-withdrawing groups.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **8**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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