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Synthesis of 3,4-Disubstituted Piperidines by Carbonyl Ene and Prins Cyclizations: A Switch in Diastereoselectivity between Lewis and Brønsted Acid Catalysts

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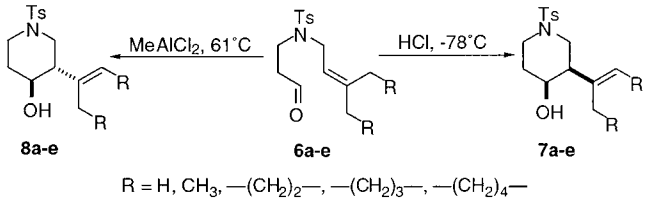
ABSTRACT



A novel diastereoselective approach to cis and trans 3,4-disubstituted piperidines is described. Carbonyl ene cyclization of aldehydes 6a–e catalyzed by the Lewis acid methyl aluminum dichloride in refluxing chloroform affords trans piperidines 8a–e with diastereomeric ratios of up to 93:7. By contrast, Prins cyclization of 6a–e catalyzed by hydrochloric acid at low temperatures affords cis products 7a–e with diastereomeric ratios of up to 98:2.

The piperidine ring system is ubiquitous in natural products and synthetic pharmaceuticals.[1] Many piperidine-containing alkaloids have interesting biological and pharmacological properties, and a variety of stereoselective approaches to these compounds have been developed.[2] Nevertheless, the variety of functionality and substitution patterns found in piperidine targets continues to drive the search for new methodologies.[3]

Intramolecular carbonyl ene reactions present an attractive method for ring closure, forming two contiguous stereocenters with an often high degree of stereocontrol.[4] One of the best studied carbonyl ene reactions is the cyclization of citronellal **1** to a mixture of isopulegol **2** and neoisopulegol **3**, Scheme 1. Cyclization can be effected under Lewis acidic conditions with a diastereomeric ratio of up to 95:5 in favor of the trans diastereoisomer isopulegol.[5] Cyclization in aqueous acid results in formation of the menthane diols **4** and **5**.

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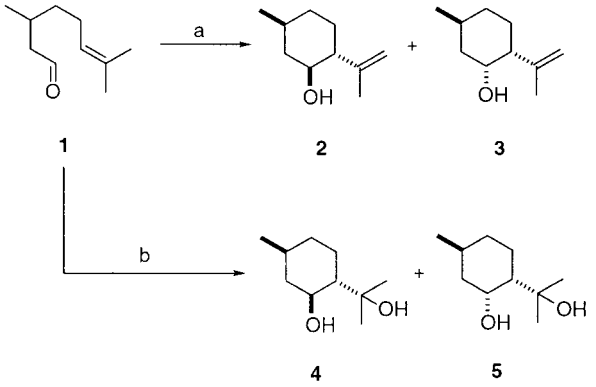
Scheme 1[a]

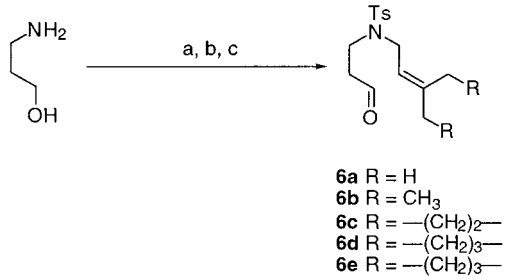


[a] Reagents and conditions: (a) Lewis acids; (b) aqueous acid.

Application of the carbonyl ene cyclization to piperidine synthesis has been little explored,[6] and we were interested to see whether the method could be used to synthesize 3,4-disubstituted piperidines.

The cyclization precursors were straightforwardly synthesized (Scheme 2) from 3-aminopropanol. N-Tosylation[7] followed by N-alkylation with the corresponding allylic bromide and subsequent oxidation with PCC or TPAP afforded aldehydes **6a**−**e**. We initially focused on cyclization of the unsubstituted system **6a** to diastereomeric piperidines **7a** and **8a** using a variety of Lewis acids in dry dichloromethane solution (Table 1).

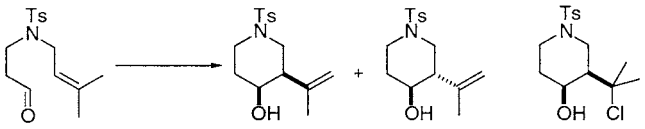
Scheme 2[a]



6a R = H
6b R = CH_3
6c R = —$(CH_2)_2$—
6d R = —$(CH_2)_3$—
6e R = —$(CH_2)_3$—

[a] Reagents and conditions: (a) *p*TsCl, Et_3N, CH_2Cl_2, 0 °C, 68%; (b) $BrCH_2CH{=}C(CH_2R)_2$, Cs_2CO_3, DMF, 25 °C, 59−86%; (c) PCC, celite, CH_2Cl_2, 25 °C, 57−70% or TPAP, NMO, 4 Å sieves, 25 °C, 83% **6c**.

Table 1. Cyclization of **6a** under Lewis and Brønsted Acid Conditions



6a **7a** **8a** **9**

entry	acid	equiv[a]	time (h)	**7a**:**8a**
1	CH_3AlCl_2	0.3	8	70:30
2	CH_3AlCl_2	0.5	8	67:33
3	CH_3AlCl_2	1.0	7	73:27
4	CH_3AlCl_2	0.3[c]	16	33:67
5	CH_3AlCl_2	1.0[d]	16	8:92[e]
6	$AlCl_3$	0.1	7	83:17
7	$Sc(OTf)_3$	0.5	7	50:50
8	$SnCl_4$	0.5	7	67:33
9	$FeCl_3$	0.5	7	trace[f]
10	CF_3SO_3H	0.5	8	78:22
11	HCl	3.0	16	95:5[g]
12	HCl	1.0	64[h]	93:7
13	HCl	3.0[d]	16	86:14
14	HCl[i]	n/a	6	94:6[j]

[a] All reactions were performed at −78 °C in dichloromethane unless otherwise stated. [b] Ratio was determined by integration of ^1H NMR spectra of a crude mixture of piperidines. Crude reaction yields were typically in excess of 90%. [c] Reaction was performed at 25 °C. [d] Reaction was performed at 61 °C in chloroform. [e] Isolated yields: **7a** (6%), **8a** (74%). [f] There was evidence of slight reaction (ca. 5%) after this time. [g] Isolated yields: **7a** (79%), **8a** (4%). [h] Reaction was only 80% complete after this time. [i] Reaction was performed using a solution of dry HCl gas in dichloromethane; the concentration was not determined. [j] Around 35% of chloride **9** was present in the crude product.

Conversion to the diastereomeric mixture of piperidines was essentially quantitative, with isolated yields of the crude piperidine mixtures typically in excess of 90%. Methyl aluminum dichloride proved to be a useful catalyst for the carbonyl ene reaction.[8] Surprisingly, even substoichiometric amounts of the Lewis acid were able to catalyze the cyclization at −78 °C (entries 1−3). At this temperature, the major product was cis diastereoisomer **7a**, and the diastereomeric ratio proved to be relatively insensitive to the amount of Lewis acid. Raising the temperature at which the reaction was performed to 25 °C resulted in preferential formation of piperidine **8a** (entry 4), suggesting that under these conditions the carbonyl ene reaction is reversible and that **7a** is the kinetic product, equilibrating to **8a** on warming. This was confirmed by raising the temperature to 61 °C (entry 5); under these conditions, piperidine **8a** predominated, with a ratio of **8a**:**7a** of 92:8. This product ratio was also reached by heating piperidine **7a** under the same conditions. The diastereoisomers were readily separated by column chromatography to afford the piperidines as crystalline solids. Single crystals of the major diastereoisomer **8a** were grown from petroleum ether and ethyl acetate, and X-ray analysis confirmed the trans relationship between the two substituents.

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(6) For examples, see: (a) Laschat, S.; Fox, T. *Synthesis* **1997**, 475−479. (b) Monsees, A.; Laschat, S.; Kotila, S.; Fox, T.; Wurthwein, E.-U. *Liebigs Ann.* **1997**, 533−540 and 1041. For a highly diastereoselective approach to indolizidines and quinolizidines via carbonyl ene reaction, see: (c) Laschat, S.; Grehl, M. *Chem. Ber.* **1994**, *127*, 2023−2034. Overman has reported piperidine synthesis via type II ene reactions: Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167−4170.

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(8) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4535−4545.

Other Lewis acids were examined in an effort to favor formation of the kinetic product **7a**. Aluminum chloride was found to be an effective catalyst, and favored formation of **7a** (entry 6). Scandium triflate and tin tetrachloride were both effective catalysts for the reaction (entries 7 and 8), but diastereoselectivities were poor. Ferric chloride afforded only trace amounts of products (entry 9), while zinc bromide, ytterbium triflate, and copper(II) triflate were completely ineffective.

Closely related to the carbonyl ene reaction is the Prins reaction, the addition of an aldehyde to an alkene catalyzed by a Brønsted acid. Reports of Prins cyclizations to form six-membered rings are less common than their carbonyl ene counterparts, but we were intrigued by a report from Holker and co-workers of a highly diastereoselective example catalyzed by HCl.[9] Thus, we undertook an investigation into the diastereocontrol exerted by a small number of Brønsted acids on the cyclization of **6a**.

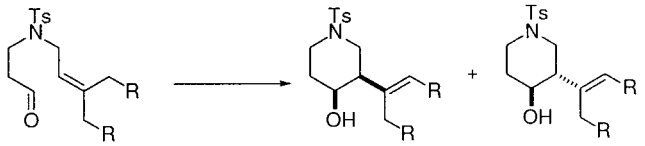
p-Toluenesulfonic acid did not catalyze the reaction at low temperature, while the stronger trifluoromethane sulfonic acid was effective but the diastereoselectivity was modest (entry 10). However, to our surprise we found that addition of 3.0 equiv of concentrated hydrochloric acid to the dichloromethane solution of **6a** at −78 °C effected quantitative cyclization to **7a** and **8a** with a diastereomeric ratio of better than 95:5 in favor of the kinetic isomer **7a** (entry 11). Frequently, a trace (<5%) of a side product, identified as the cis chloride **9**, was also produced under these conditions. Chloride **9** was difficult to separate from **7a** chromatographically, but simply stirring a solution of a mixture of **7a** and **9** with silica gel[10] or aqueous ammonia induced an elimination to afford pure **7a**.

Reducing the amount of acid led to an unacceptably slow reaction without improvement in diastereomeric ratio (entry 12). Although raising the temperature of the reaction lowered the diastereoselectivity, the cyclization still favored cis product **7a**. Thus, heating **6a** with 3.0 equiv of concentrated hydrochloric acid at reflux in chloroform (entry 13) afforded a 86:14 ratio of **7a**:**8a**. Diastereoselectivity using a solution of dry HCl gas in dichloromethane was essentially identical (entry 14), although the procedure was less convenient, and the presence of excess HCl led to an increase in the amount of chloride side product **9**.

Cyclization of the remaining aldehydes **6b**−**e** was studied under the optimized Lewis and Brønsted acid conditions; the results are shown in Table 2.

Analysis of products **7b** and **8b** from cyclization of **6b** was complicated by the presence of *E* and *Z* double-bond isomers, so the diastereomeric ratio was verified after hydrogenation to the saturated products. Lewis acid-catalyzed cyclization of **6b** afforded predominantly trans product **8b** as a mixture of double-bond stereoisomers (entry 1). Under Brønsted acid conditions, **6b** exhibited a remarkable diastereoselectivity of at least 98:2, with no trans product

Table 2. Cyclization Reactions of **6b**−**e**



6b-e **7b-e** **8b-e**

entry	aldehyde	acid[a]	time (h)	**7**:**8**	yield %[b]
1	**6b**	CH_3AlCl_2	35	22:78	55 (15)
2	**6b**	HCl	16	>98:2	86
3	**6c**	CH_3AlCl_2	27	30:70	53 (22)
4	**6c**	HCl	16	90:10	71 (7)
5	**6d**	CH_3AlCl_2	27	7:93	74 (4)
6	**6d**	HCl	16	89:11	72 (9)
7	**6e**	CH_3AlCl_2	27	25:75	61 (20)
8	**6e**	HCl	16	80:20	60 (14)

[a] CH_3AlCl_2 refers to 1 equiv at 61 °C in chloroform. HCl refers to 3 equiv of concentrated hydrochloric acid at −78 °C in dichloromethane. [b] Isolated yields of major (minor) isomers following chromatography.

detectable by NMR either before or after hydrogenation (entry 2). Paralleling our findings for **6a**, around 5% of the chloride resulting from addition of HCl to the double bond of **7b** was also obtained.

Further extending our study, we examined the cyclization of aldehydes **6c**−**e**, in which the alkene is exocyclic to a five-, six-, and seven-membered ring, respectively. Under acidic conditions, the preference for formation of cis diastereoisomers **7c**−**e** was again marked (entries 4, 6, and 8), although not as high as the acyclic examples. Under equilibrating Lewis acidic conditions, all three favored the trans diastereoisomer (entries 3, 5, and 7), a preference that was particularly marked in the case of the cyclohexyl system (entry 5).

As a reference point, we performed the cyclization of citronellal under our optimal hydrochloric acid conditions. The reaction was clearly a little more sluggish, since 25% of the citronellal remained unchanged after the usual period of 16 h at −78 °C. The principal products were isopulegol and neoisopulegol, although there was evidence from the NMR and GC-mass spectra that a number of side products were also present resulting from dimerization (and possibly higher oligomerization) of citronellal, presumably by aldol chemistry. Interestingly, the cyclization process favored cis product neoisopulegol **3**, but in marked contrast with our own system, the ratio of cis:trans products was only 75:25.

Both the acid- and the Lewis acid-catalyzed cyclizations of **6** appear to proceed initially through the formation of the kinetic product **7**, with conversion to the thermodynamic product **8** only proceeding at a significant rate under Lewis acidic conditions. In contrast, the cyclization of citronellal affords the thermodynamically more stable trans isomer isopulegol with a variety of Lewis acids. There is no evidence that cyclization proceeds through a kinetic intermediate that isomerizes. Indeed Nakatani demonstrated that under the

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(10) Iwamatsu, S. I.; Kondo, H.; Matsubara, K.; Nagashima, H. *Tetrahedron* **1999**, *55*, 1687−1706.

conditions of zinc bromide in benzene, the cyclization of citronellal to afford chiefly isopulegol is irreversible.[5a] More recently, however, Kocovsky has shown that several Lewis acids, including zinc chloride in dichloromethane, rapidly isomerize neoisopulegol to isopulegol.[11]

At present, it is not clear why our system should preferentially cyclize to the cis diastereoisomer. In the earlier work of Laschat,[6a−c] preference for the cis isomer was explained by the formation of a five-membered chelate between the Lewis acid, the aldehyde oxygen and the basic nitrogen. This explanation is less attractive in the case of our system and, in any event, cannot account for the Brønsted acid results. Coordination of a Lewis acid by the sulfonamide nitrogen would be expected to be weak, and results were poor with the strongly chelating $SnCl_4$, a Lewis acid that was very effective in Laschat's system. Attempts to prepare a cyclization substrate lacking the tosyl group were unsuccessful.

A reversal in the sense of diastereoselectivity of citronellal cyclization to favor the cis diastereoisomer neoisopulegol **3** (dr = 75:25) has been achieved with Wilkinson's catalyst, although this observation has not been satisfactorily explained.[12] Kocovsky has explored the cyclization with bulky molybdenum-based Lewis acids, observing a cis:trans ratio of up to 80:20. In this case, it is suggested that the bulky Lewis acid forces cyclization through a boatlike transition state, leading to the switch in diastereoselectivity.[11] This steric argument applied to our system is not compelling. Methyl aluminum dichloride is not a sterically demanding Lewis acid and with citronellal it affords predominantly the trans product.[13] A perhaps more plausible explanation is that citronellal and **6** cyclize via different mechanisms; both concerted and stepwise mechanisms have been proposed for ene reactions.[14]

The effect of Brønsted acid catalysis is remarkable. Here, citronellal parallels our findings in favoring the thermodynamically less stable diastereoisomer **3**, although the preference is much less marked and the reaction is not clean. When citronellal is cyclized using aqueous acid, the principal products are the menthane diols **4** and **5** (Scheme 1), which could be considered as coming from hydration of isopulegol and neoisopulegol, respectively.[15] Interestingly, there is again a preference for the cis diastereoisomer, with diol **5** predominating over the trans diol **4** in a ratio of 67:33. It is difficult to explain these results for citronellal on steric grounds, and the switch in diastereoselectivity observed when Lewis or Brønsted acids are used may indicate a change in cyclization mechanism.

In summary, we have discovered a highly diastereoselective synthesis of cis and trans 3,4-disubstituted piperidines from simple acyclic precursors, which should have application to the synthesis of more complex molecules. Experimental and theoretical studies are currently underway in an effort to elucidate the origins of the observed stereoselectivity.

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Supporting Information Available: Experimental procedures and full characterization for compounds up to and including **6a** and all piperidines **7a**−**e** and **8a**−**e**, as well as a general elimination procedure to remove **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See: (a) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947−6952. (b) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160−8164. (c) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126−8134.

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