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Article

# Intramolecular Ene Reactions Catalyzed by $NbCl_5$, $TaCl_5$ and $InCl_3$

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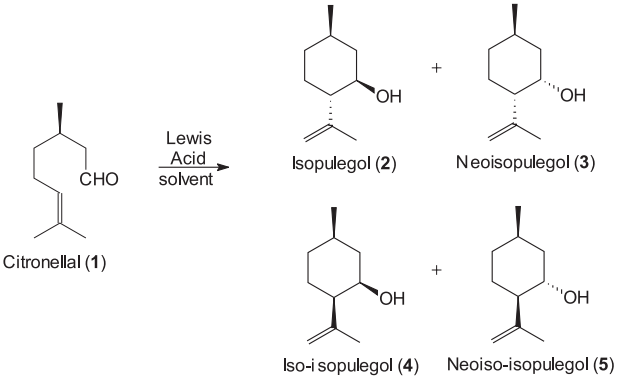
Pentacloreto de nióbio, pentacloreto de tântalo e tricloreto de índio catalisaram eficientemente a ciclização do (*R*)-citronelal a uma mistura de isopulegol e neoisopulegol, em bons rendimentos. Um estudo comparativo foi realizado demonstrando que $NbCl_5$ é o ácido de Lewis mais ativo enquanto que $InCl_3$ é o mais seletivo. A seletividade das reações variou de acordo com o ácido de Lewis utilizado e o solvente. $NbCl_5$ e $TaCl_5$ mostraram ausência de seletividade enquanto que o $InCl_3$ apresentou seletividade moderada em favor do isopulegol. A reação ene de um 1,7-dieno também foi investigada. Neste caso, todos os ácidos de Lewis testados apresentaram excelente seletividade.

Niobium pentachloride, tantalum pentachloride and indium trichloride efficiently catalysed the cyclization of (*R*)-citronellal to a mixture of isopulegol and neoisopulegol in good yields. A comparative study was carried out which demonstrated that $NbCl_5$ is the most active Lewis acid whereas $InCl_3$ is the most selective one. The selectivity of the reactions varied according to the Lewis acid used and to the solvent. The ene reaction of a 1,7-diene was also investigated. In this case, all Lewis acids tested showed excellent selectivity.

**Keywords:** citronellal, isopulegol, intramolecular ene reactions, Lewis acids, selectivity

## Introduction

The carbonyl-ene reaction is synthetically very useful since it enables the formation of a C–C bond with the construction of two vicinal chiral centers.[1] One of the most studied intramolecular versions of this reaction is the cyclization of citronellal (**1**) (Scheme 1).[2] The main isomers obtained in this reaction are isopulegol (**2**) and neoisopulegol (**3**). This is an important reaction since it is one of the steps in the industrial synthesis of menthol.[3] In addition, isopulegol (**2**) has also been applied to the synthesis of natural products such as pheromones.[4,5]




**Scheme 1.** Cyclization of citronellal.

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The selectivity of this reaction depends on the Lewis acid employed. In this respect, a great number of Lewis acids have been found to promote this cyclization. Good selectivities favoring isopulegol can be achieved with zinc salts ($ZnBr_2$ and $ZnI_2$),[4] although in stoichiometric amounts, and catalytic scandium triflate,[6] whereas neoisopulegol is slightly favored using $SbCl_5$[4] or molybdenum(II) and tungsten(II) catalysts.[7]

We wish to report that citronellal undergoes cyclization in the presence of catalytic amounts of $NbCl_5$, $TaCl_5$ and $InCl_3$.[8] $NbCl_5$ has been successfully used in our group as Lewis acid in a variety of reactions[9] and has gained increasing attention in recent years.[10] We decided to test $TaCl_5$ for comparison since niobium and tantalum belong to the same family in the periodic table. $InCl_3$ was chosen in view of its recent growing applications in organic chemistry as a Lewis acid.[11]

## Results and Discussion

The parameters we analyzed in this study were: solvents, Lewis acids, stereoselectivity, reaction time, reaction temperature and stoichiometric relationship of the reagents.

Using a catalytic amount of $NbCl_5$, the cyclized products were obtained in all solvents except for hexane

(Table 1). In ethanol the yield was low due to the formation of several other products. The yields were better in dichloromethane especially when 4Å molecular sieves were used. The selectivities were low and almost did not vary with the solvent. An interesting trend is the inversion of the isopulegol/noeisopulegol ratio when molecular sieves were employed as can be seen in entries 2, 6 and 7. No reaction was observed when citronellal was submitted to molecular sieves in $CH_2Cl_2$ in the absence of the Lewis acid. Up to this point the role of the molecular sieves is still unclear. Using a stoichiometric amount of $NbCl_5$, a complex mixture of products was obtained unless the reaction is run at –78 ºC. At this temperature the reaction was slower but the selectivity was the same. In view of the better results obtained with $CH_2Cl_2$ and $CH_3CN$, these solvents were chosen for further studies.

**Table 1.** Cyclization of citronellal catalyzed by $NbCl_5$ (10 mol%)

| Entry | Solvent | Time (h) | Yield (%)[c] | Ratio (iso:neo)[d] |
|---|---|---|---|---|
| 1 | $CH_3CN$ | 15 | 75 | 1.2 : 1 |
| 2[a] | $CH_3CN$ | 17 | 75 | 1 : 1.4 |
| 3 | EtOH | 15 | 30 | 1.7 : 1 |
| 4 | DMSO | 15 | 51 | 1.3 : 1 |
| 5 | $CH_2Cl_2$ | 15 | 75 | 1.9 : 1 |
| 6[a] | $CH_2Cl_2$ | 5 | 77 | 1 : 1.6 |
| 7[b] | $CH_2Cl_2$ | 5 | 90 | 1 : 1.2 |
| 8 | $CH_2Cl_2$ | 15 | 75 | 1.2 : 1 |
| 9 | Hexane | 15 | 0 | — |

[a] Powdered 4Å molecular sieves; [b] 4Å Molecular sieves; [c] Isolated yields of the chromatographically pure products; [d] Determined by GC analysis of the crude reaction products.

$InCl_3$ showed a greater selectivity as confirmed by the results shown in Table 2. The use of molecular sieves improved the yields, but lowered the selectivities (entry 3). The reaction did not work in ether. A different result was achieved using $TaCl_5$ (Table 3). In the presence of a catalytic amount of this Lewis acid, citonellal is slowly consumed (entry 1) whereas when 1.0 equivalent is used the yield of the products was high (entry 2). In both cases, neoisopulegol was the major isomer although in low selectivity.

**Table 2.** Cyclization of citronellal mediated by $InCl_3$

| Entry | Equiv. | Solvent | Time (h) | Yield (%)[b] | Ratio (iso:neo)[c] |
|---|---|---|---|---|---|
| 1 | 1.0 | $CH_3CN$ | 5 | 76 | 4.8 : 1 |
| 2 | 1.0 | $CH_2Cl_2$ | 5 | 82 | 4.9 : 1 |
| 3[a] | 1.0 | $CH_2Cl_2$ | 15 | 94 | 2.6 : 1 |
| 4 | 0.1 | $CH_2Cl_2$ | 22 | 52 | 3.1 : 1 |
| 5 | 0.1 | $Et_2O$ | 18 | 0 | — |

[a] 4Å molecular sieves; [b] Isolated yields of the chromatographically pure products; [c] Determined by GC analysis of the crude reaction products.

**Table 3.** Cyclization of citronellal mediated by $TaCl_5$

| Entry | Equiv. | Solvent | Time (h) | Conversion (%)[a] | Ratio (iso:neo)[a] |
|---|---|---|---|---|---|
| 1 | 0.1 | $CH_2Cl_2$ | 4 | 57 | 1 : 1.37 |
| 2 | 1.0 | $CH_2Cl_2$ | 6 | 100 | 1 : 1.44 |

[a] Determined by GC analysis of the crude reaction products.

The isomeric ratio was not improved at lower temperatures (Table 4). $NbCl_5$ showed almost complete conversion at –40 ºC, even when used in smaller amounts (1 mol% or 5 mol%). Surprisingly neoisopulegol was slightly favored (entry 1), whereas $InCl_3$ and $TaCl_5$ showed lower conversions under the same conditions (entries 2 and 3). This indicates that $NbCl_5$ is the more active Lewis acid.

**Table 4.** Comparison of the activity of the Lewis acids at lower temperatures[a]

| Entry | Lewis acid[b] | Temp. (ºC) | Time (h) | Conversion (%)[c] | Ratio (iso:neo)[c] |
|---|---|---|---|---|---|
| 1 | $NbCl_5$ | -40 | 6 | 98 | 1 : 1.2 |
| 2 | $InCl_3$ | -40 | 6 | 89 | 4.3 : 1 |
| 3 | $TaCl_5$ | -40 | 6 | 30 | 1 : 1.1 |

[a] Reactions run in $CH_2Cl_2$; [b] 10 mol%; [c] Determined by GC analysis of the crude reaction products.

In order to get a better insight into the influence of different Lewis acids on the cyclization, the reactions were monitored by gas chromatography and some interesting observations could be made.

Using a catalytic amount of $NbCl_5$, citronellal is consumed in 80 minutes (Figure 1). The relative ratio of isomers varied from 1.2:1 to 2.2:1 in 24h. Using an equimolar amount of this Lewis acid, several other products with higher retention times were detected after 10 minutes

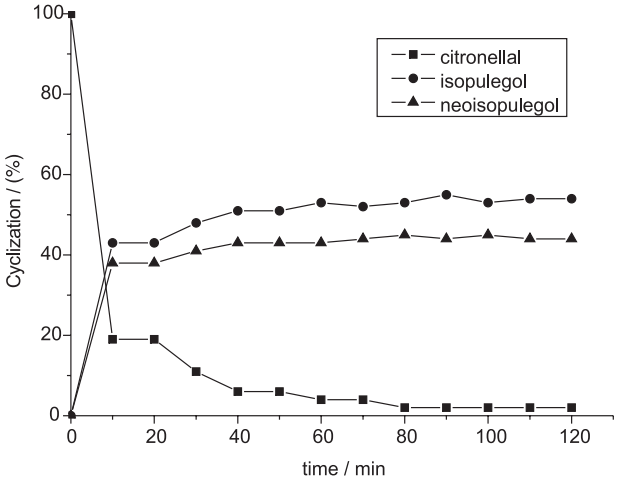



**Figure 1.** Cyclization of citronellal with $NbCl_5$ (10 mol%).

of reaction and almost complete decomposition of products was observed after 2h.

In the presence of $InCl_3$, citronellal is consumed in 60 min with 0.1 equivalent (Figure 2) and in less than 10 min with 1.0 equivalent (Figure 3). Small amounts (4-8%) of a third isomer could be detected. The isomeric ratio remains constant with a catalytic amount (3.3:1) whereas with a stoichiometric amount of the Lewis acid it raises from 3.3:1 in 1h to 6.75:1 in 7h and lowers back to 4.75:1 with prolonged reaction time (24h). This result may be due to decomposition of the isomers to products of higher retention times which are present in significant amounts after 3h (45%).

Using $TaCl_5$, the consumption of citronellal is not complete even after 22h with 0.1 equivalent (Figure 4) whereas with 1.0 equivalent the reaction takes 30 minutes to go to completion (Figure 5). The isomeric ratio remained constant (near 1.4:1 favoring neoisopulegol) in both cases even after 23h.

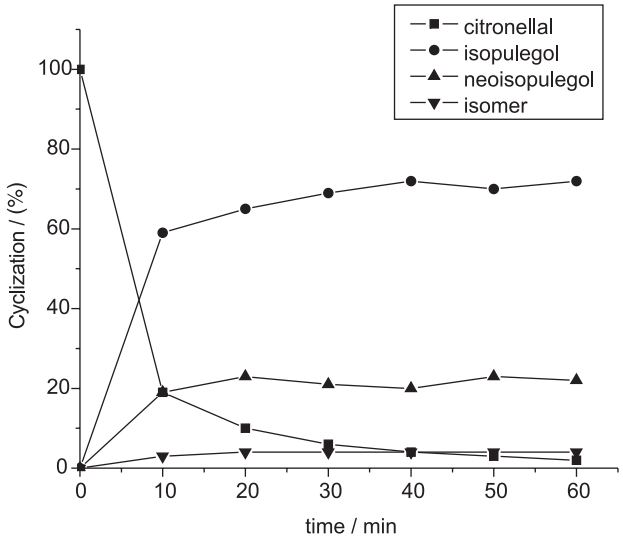



**Figure 2.** Cyclization of citronellal using $InCl_3$ (10 mol%).

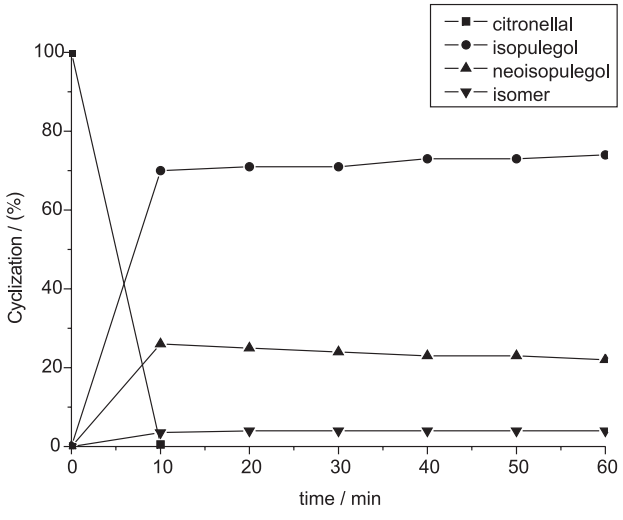



**Figure 3.** Cyclization of citronellal using $InCl_3$ (100 mol%).

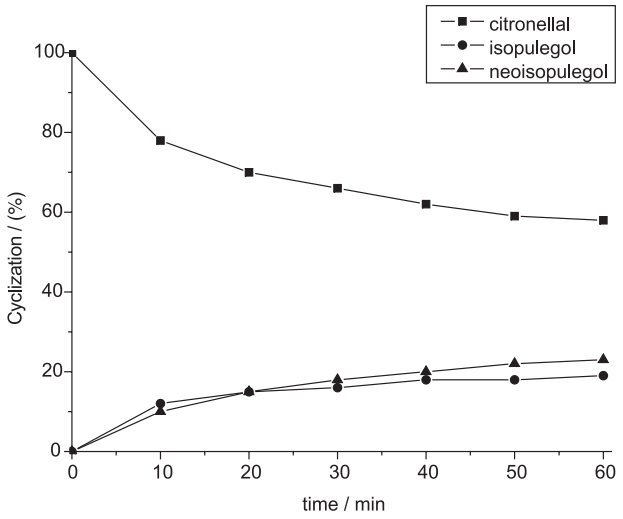



**Figure 4.** Cyclization of citronellal using $TaCl_5$ (10 mol%).

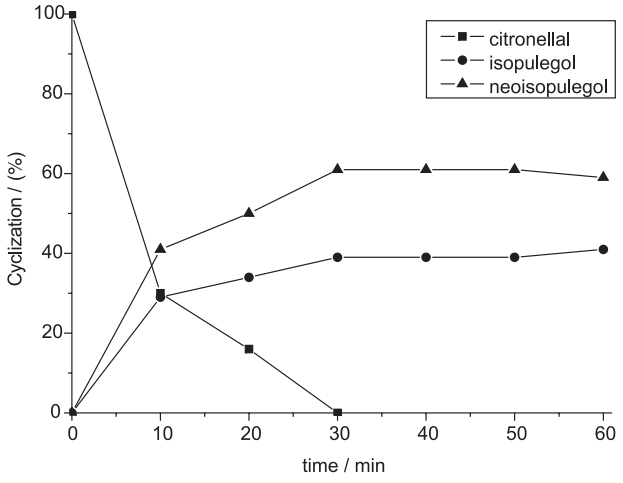
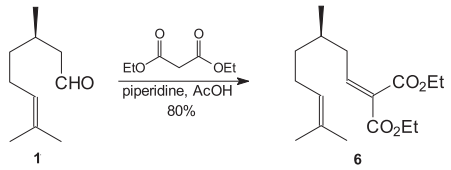



**Figure 5.** Cyclization of citronellal using $TaCl_5$ (100 mol%).

In order to be sure that no isomerization was taking place under the reaction conditions, isopulegol and neoisopulegol were separated by column chromatography and separately submitted to the Lewis acids (10 mol% and 100 mol%) in $CH_2Cl_2$. After 24h the crude reaction mixtures were analysed by GC using biphenyl as internal standard. In all cases no isomerization was observed, but by using 1 equivalent of $InCl_3$ two products of higher retention time were observed probably due to decomposition and/or dimerization of the isomers whereas when 1 equivalent of $NbCl_5$ was employed the isomers were almost completely destroyed and many peaks appeared in the chromatogram. In all other cases the isomers were recovered intact after the work-up.

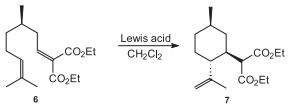
The second type of ene reaction we studied was the cyclization of compound **6** which was prepared by the Knoevenagel condensation of citronellal with diethylmalonate (Scheme 2) according to a known procedure.[12]




**Scheme 2.** Synthesis of the 1,7-diene **6**.

1,7-Dienes undergo the intramolecular ene reaction less readily than the corresponding 1,6-dienes. The temperatures required are higher and the reactions proceed in lower yields except for activated components. That is the case for compound **6**, which has two electron withdrawing groups. This reaction is usually very selective and the main product has all the substituents in equatorial positions. Indeed, for all Lewis acids studied the yields and selectivities were very good (Table 5). There was no need for molecular sieves in this reaction. These results are similar to those obtained with $ZnBr_2$.[12]

**Table 5.** Cyclization of the 1,7-diene **6**




| Entry | Lewis acid | Solvent | Time (min) | Yield (%)[a] | Ratio of isomers[b] |
|---|---|---|---|---|---|
| 1 | $NbCl_5$ | $CH_2Cl_2$ | 45 | 75 | 97:3 |
| 2 | $TaCl_5$ | $CH_2Cl_2$ | 180 | 82 | 95:5 |
| 3 | $InCl_3$ | $CH_2Cl_2$ | 60 | 75 | 96:4 |

[a] Isolated yields of the chromatographically pure products; [b] Determined by GC of the crude products.

## Conclusion

$NbCl_5$, $TaCl_5$ and $InCl_3$ efficiently catalyzed intramolecular ene reactions. Whereas $NbCl_5$ was the most active, $InCl_3$ was the most selective Lewis acid. $TaCl_5$ showed inverse selectivity slightly favoring neoisopulegol in the cyclization of citronellal. The best conditions for this reaction turned out to be the use of 0.1 equivalent of $InCl_3$ in $CH_2Cl_2$ at room temperature for 1h. The yields obtained in these reactions were invariably good but the selectivities were low except in the cyclization of compound **6** in which compound **7** could be obtained almost as the only isomer.

## Experimental

*General*

All reactions involving Lewis acids were performed under argon in a flame-dried flask. Ethereal solvents were distilled from sodium benzophenone ketyl. All other solvents were distilled from $CaH_2$ prior to use. $NbCl_5$ was supplied by Companhia Brasileira de Mineração e Metalurgia (CBMM). $TaCl_5$ and $InCl_3$ were purchased from Aldrich. (*R*)-Citronellal (Fluka) (GC *t* 20.48 min) was distilled prior to use. Compound **6** was prepared from (*R*)-citronellal according to a procedure described by Tietze *et al*.[12]

IR spectra were recorded on a BOMEM Hartman & Braun – Michelson MB series 100 LASER FT-IR. NMR spectra were recorded on a Varian Mercury Plus 300 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, etc), coupling constant and integration.

Column chromatography was performed on silica gel (70-230 mesh). GC analyses were carried out in a Shimadzu GC chromatograph, model GC-17A, employing a CBPI PONA-M50-042 column (50 m x 0.15 mm x 0.20 $\mu$m). The following parameters were used: initial temperature = 80 ºC; final temperature = 180 ºC; initial time = 1 min; final time = 30 min; detector temperature = 250 ºC; injector temperature = 250 ºC; temperature gradient = 10 ºC/min. Biphenyl was used as internal standard (GC *t* 25.00 min).

*General procedure for the cyclization of (R)-citronellal.* To a stirred suspension of the Lewis acid (0.13 mmol) in the specified solvent (4 mL) under an argon atmosphere, at 0 ºC, was added (*R*)-citronellal (1.3 mmol). The reaction was stirred at room temperature and the consumption of the reagent was monitored by GC and/or TLC. The reaction is generally finished within 1h. Then, sat. $NH_4Cl$ (4 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated at reduced pressure. The crude product was then purified by column chromatography (10% EtOAc in hexanes). The spectroscopic data are identical to those reported for compounds **2**[4,13,14] and **3**.[14]

*Isopulegol, (**2**).* IR (film) $\nu_{max}$/cm$^{-1}$: 3405, 3073, 2949, 2925, 2869, 1645, 1455, 1375, 1051, 1027; 887; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.95 (d, *J* 6.5 Hz, 3H), 1.10-2.10 (m, 9H), 1.71 (s br, 3H), 3.45 (td, *J* 10.1 and 4.4 Hz, 1H), 4.85 (br s, 1H), 4.90 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 19.1, 22.1, 29.6, 34.3, 42.6, 54.0, 70.3, 112.7, 146.6. GC *t* 20.79 min.

*Neoisopulegol, (**3**).* IR (film) $\nu_{max}$/cm$^{-1}$: 3465, 3085, 2943, 2925, 2861, 2845, 1643, 1455, 1375, 1024, 890; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.88 (d, *J* 6.4 Hz, 3H), 1.10-2.10 (m, 9H), 1.79 (s br, 3H), 3.99 (q, *J* 2.5 Hz, 1H), 4.79 (br s, 1H), 4.95 (br s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.8, 22.1, 31.3, 34.7, 40.9, 52.7, 66.3, 111.2, 147.2. GC *t* 21.04 min.

*General procedure for the cyclization of compound **6**.* To a stirred suspension of the Lewis acid (0.05 mmol) in $CH_2Cl_2$ (4 mL) under an argon atmosphere, at 0 ºC, was added compound **6** (0.52 mmol). The reaction was stirred at room temperature for 4h. Then, sat. $NH_4Cl$ (4 mL) was added and the reaction mixture was extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated at reduced pressure. The crude product **7** was then purified by column chromatography (10% EtOAc in hexanes). The spectroscopic data are identical to those reported for compound **7**.[12]

IR (film) $\nu_{max}$/cm$^{-1}$: 3060, 1750, 1735, 1645, 1155, 1035, 895; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.90 (d, *J* 6.5 Hz, 3H), 0.94-1.84 (m, 7H), 1.27 (t, *J* 7.0 Hz, 3H), 1.28 (t, *J* 7.0 Hz, 3H), 1.65 (s br, 3H), 2.03-2.17 (m, 2H), 3.51 (d, *J* 3.1 Hz, 1H), 4.17 (q, *J* 7.0 Hz, 2H), 4.18 (q, *J* 7.0 Hz, 2H), 4.73-4.76 (m, 1H), 4.78-4.80 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.0, 14.1, 18.9, 22.4, 32.3, 32.7, 34.6, 36.5, 39.7, 48.6, 53.2, 60.6, 61.0, 112.4, 147.5, 168.6, 169.7; GC *t* (major isomer) 35.10 min; *t* (minor isomer) 36.12 min.

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## References

1. Snider, B. B. In *Comprehensive Organic Synthesis*; I. Fleming, ed.; Pergamon: Oxford, 1991, vol. 2; p. 527; Mikami, K.; Shimizu, M.; *Chem. Rev*. **1992**, *92*, 1021; Snider, B. B.; *Acc. Chem. Res.* **1980**, *13*, 426; Oppolzer, W.; Snieckus, V.; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476; Hoffmann, H. M. R.; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556. For an excellent review on asymmetric ene reactions, see: Dias, L. C.; *Curr. Org. Chem.* **2000**, *4*, 305.
2. For representative examples of this reaction, see: Jacob, R. G.; Perin, G.; Loi, L. N.; Pinno, C. S.; Lenardão E. J.; *Tetrahedron Lett.* **2003**, *44*, 3605; Chuah, G. K.; Liu, S. H.; Jaenicke, S.; Harrison, L. J.; *J. Catal.* **2001**, *200*, 352; Yadav, G. D.; Nair, J. J.; *Langmuir* **2000**, *16*, 4072; Arata, K.; Matsuura, C.; *Chem. Lett*. **1989**, 1797. See also refs. 4, 5, 6 and 13.
3. Takeshi, I.; Yoshiki, O.; Yoji, H.; *European Patent EP1225163*, July 24, **2002**.
4. Nakatani, Y.; Kawashima, K.; *Synthesis* **1978**, 147.
5. Moreira, J.; Corrêa, A. G.; *J. Braz. Chem. Soc*. **2000**, *11*, 614.
6. Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, C.; *Tetrahedron Lett.* **1998**, *39*, 1997.
7. Koèovský, P.; Ahmed, G.; Šrogl, J.; Malkov, A. V.; Steele, J.; *J. Org. Chem.* **1999**, *64*, 2765.
8. Part of this work was presented at the *X Brazilian Meeting on Organic Synthesis* (BMOS), August 2003, São Pedro, SP, Brazil.
9. Andrade, C. K. Z.; Azevedo, N. R.; Oliveira, G. R.; *Synthesis* **2002**, 928; Andrade, C. K. Z.; Azevedo, N. R.; *Tetrahedron Lett*. **2001**, *42*, 6473; Andrade, C. K. Z.; Oliveira, G. R.; *Tetrahedron Lett*. **2002**, *43*, 1935; Andrade, C. K. Z.; Matos, R. A. F.; *Synlett* **2003**, 1189; Andrade, C. K. Z.; Kalil, P. P.; Rocha, R. O.; Alves, L. M.; Panisset, C. M. A.; *Lett. Org. Chem*. **2004**, *1*, 109.
10. Review on $NbCl_5$ applications in organic synthesis: Andrade, C. K. Z.; *Curr. Org. Synth*. **2004**, *4*, 333!
11. Ranu, B. C.; *Eur. J. Org. Chem.* **2000**, 2347.
12. Tietze, L. F.; Beifuss, U.; Ruther, M.; *J. Org. Chem*. **1989** *54*, 3120.
13. Jensen, B. L.; Malkawi, A.; McGowan V.; *J. Chem. Ed.* **2000**, *77*, 1474.
14. Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, Jr., W. F.; Jones, III, J. E. J.; Raleigh, J. S.; *J. Org. Chem.* **1995**, *60*, 4146.

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