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# Iron(III)-Catalyzed Consecutive Aza-Cope−Mannich Cyclization: Synthesis of *trans*-3,5-Dialkyl Pyrrolidines and 3,5-Dialkyl-2,5-dihydro-1*H*-pyrroles

**Rubén M. Carballo,[†,§] Martín Purino,[†] Miguel A. Ramírez,[†] Víctor S. Martín,[*,†] and Juan I. Padrón[*,†,‡]**

*Instituto Universitario de Bio-Orgánica "Antonio González", Departamento de Química Orgánica, Universidad de La Laguna, C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain, and Instituto de Productos Naturales y Agrobiología, CSIC, C/Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain*

*vmartin@ull.es; jipadron@ipna.csic.es*

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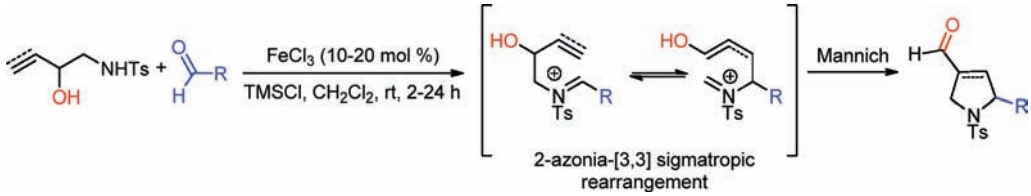
## ABSTRACT




**An efficient alkene aza-Cope−Mannich cyclization between 2-hydroxy homoallyl tosylamine and aldehydes in the presence of iron(III) salts to obtain 3-alkyl-1-tosyl pyrrolidines in good yields is described. The process is based on the consecutive generation of a $\gamma$-unsaturated iminium ion, 2-azonia-[3,3]-sigmatropic rearrangement, and further intramolecular Mannich reaction. Iron(III) salts are also shown to be excellent catalysts for the new aza-Cope−Mannich cyclization using 2-hydroxy homopropargyl tosylamine.**

Five-membered ring heterocycles containing nitrogen are structural motifs of particular interest in synthetic and medicinal chemistry, as they are present in a large number of bioactive compounds.[1] Considerable efforts have been devoted to the synthesis of this type of heterocycles.[2]

The aza-Cope−Mannich is a tandem chemical process between a cationic 2-aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement) and Mannich reaction.[3−5] It was discovered by Overman and co-workers in 1979,[6] and applied successfully in numerous alkaloid syntheses.[7]

They found that the direct reaction of aldehydes and tetrafluoroborate salts of homoallylic amine containing hydroxyl or alkoxyl substituents at the allylic site afforded, after heating under reflux, substituted 3-acylpyrrolidines. In addition, it was necessary to use sulfonic acid to promote this reaction when hydroxy or alkoxy homoallylic amine was used.[6]

The preparation of 3-formylpyrrolidines[4a,6f,8] was especially challenging for these authors. In this case the aza-Cope−Mannich afforded formylpyrrolidine dimethyl acetals in low yield together with material from the polymerization reaction.[6a,f]

[†] IUBO, Departamento de Química Orgánica, ULL.
[‡] Instituto de Productos Naturales y Agrobiología, CSIC.
[§] Current address: Laboratorio de Química Farmacéutica, Facultad de Química, Universidad Autónoma de Yucatán (UADY), Mérida, Yucatán, México.

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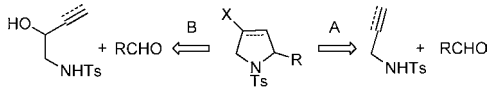
This polymerization was minimized when the reaction was carried out under acetalizing conditions or when employing a vinyloxazolidine was used as the starting material.

We have focused on a direct synthesis of five-membered azacycles considering two possibilities. The first is the direct reaction through a Prins cyclization between $\beta,\gamma$-unsaturated tosylamines and aldehydes (Scheme 1, A). Unfortunately, the

**Scheme 1.** Strategies to Five-Membered Azacycles Synthesis



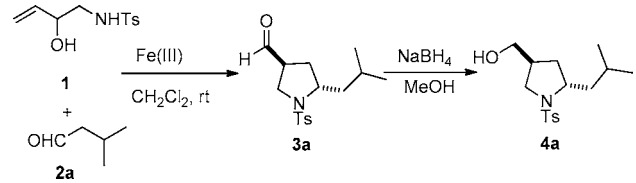

cyclizations of the allyl tosylamine and propargyl tosylamine with aldehydes (5-*endo-trig* cyclization) catalyzed by iron(III) salts were fruitless.[9] As an alternative, we focused our efforts on the aza-Cope−Mannich cyclization (Scheme 1, B).

Herein, we report that iron(III) catalyzes the direct aza-Cope−Mannich cyclization of 2-hydroxy homoallyl tosyl amine and aldehydes to afford 3-formylpyrrolidines. Iron(III) salts also catalyze a new alkyne aza-Cope−Mannich reaction between 2-hydroxy homopropargyl tosylamine and aldehydes to obtain 3-formyl-α,$\beta$-unsaturated pyrrolidines (**7**). To the best of our knowledge, this is the first report on the use of iron(III) salts catalyzing the aza-Cope−Mannich.

As a model study, we chose the reaction between 2-hydroxy homoallyl tosylamine (**1**)[10] and isovaleraldehyde (**2a**) with iron(III) chloride as catalyst in a sustainable chemical context. The hydroxy tosylamine **1** reacted with the aldehyde **2a** in dry methylene chloride at room temperature using one full equivalent of iron(III) chloride. It was observed that the desired reaction proceeded within 30 min under open atmosphere to give 5-isobutyl-1-tosylpyrrolidine-3-carbaldehyde (**3a**, a 40:60 *cis*:*trans* mixture of formyl epimers) in 30% yield. However, we had observed a unique *trans* pyrrolidine-carbaldehyde from the reaction crude.[11] We assumed that the low stability of the carbaldehyde under chromatographic conditions was responsible for the mixture of diastereomers and the low yield. For this reason, we decided to reduce the aldehyde before it was purified.[12] In this case the *trans*-5-isobutyl-1-tosylpyrrolidin-3-yl)methanol (**4a**) resulting from the aza-Cope−Mannich and further aldehyde reduction was obtained in 72% yield.

Table 1 summarizes the results obtained in this study using two iron(III) salts as catalysts.

**Table 1.** Iron-Catalyzed Alkene-Aza-Cope−Mannich of 2-Hydroxy Homoallyl Tosylamine (**1**) with Isovaleraldehyde (**2a**)[a]




| entry | $Fe(acac)_3$ (mol %)[b] | $FeCl_3$ (mol %) | TMSCl (equiv) | $t$ (h) | *trans*:*cis*[c] | yield (%) (**4a**)[d] |
|---|---|---|---|---|---|---|
| 1 | | 100 | | 0.5 | 99:1 | 72 |
| 2 | | 30 | | 24 | 99:1 | 70 |
| 3 | | 7.5 | | 72 | 99:1 | 65 |
| 4 | | 10 | 1.0 | 0.7 | 98:2 | 65 |
| 5 | | 5 | 1.0 | 2 | 98:2 | 60 |
| 6 | 10 | | 1.0 | 5 | 98:2 | 50 |
| 7 | 20 | | 1.0 | 5 | 98:2 | 45 |
| 8 | 50 | | | | | *e* |
| 9 | 100 | | | | | *e* |

[a] Reaction conditions: (i) **1** (1.0 equiv), **2a** (1.0 equiv), [Fe], $CH_2Cl_2$, rt, 2−12 h; (ii) $NaBH_4$ (2.1 equiv), MeOH, 0 °C to rt. [b] acac = acetylacetonate. [c] The ratio *trans*:*cis* was determined by $^1$H NMR [d] Yield of the pure product after silica gel chromatography. [e] The starting material was recovered.

The reaction works equally well using stoichiometric or catalytic amounts of $FeCl_3$ (Table 1, entries 1 and 3).[13] In both cases, we obtained a stereoselective reaction (>97% of *trans* stereoisomer) with similar yields but at different rates, being slower with the catalytic version. The addition of chlorotrimethylsilane (TMSCl) improved the reaction rate in the catalytic version, with similar or slightly lower yields (Table 1, entries 4 and 5). With respect to the catalyst loading, 10 mol % of the iron salt was found to be optimal (Table 1, entry 4). The use of 5 mol % of the iron salt furnished **4a** with lower yield and higher reaction time (60%, 2 h, Table 1, entry 5). Other iron(III) source, as $Fe(acac)_3$ only catalyzed the aza-Cope−Mannich in combination with TMSCl[13a] but with lower yields (Table 1, entries 6 and 7). When $Fe(acac)_3$ was used as the possible catalyst no reaction was observed and the starting material was recovered (Table 1, entries 8 and 9). In general, the process is higly stereoselective with respect to iron(III) salts (Table 1, entries 1−7).

Control experiments, using TMSCl as the promoter, confirmed that in the absence of the iron(III) salts no 5-isobutyl-1-tosylpyrrolidine-3-carbaldehyde (**3a**) was obtained. In this case, the corresponding isobutylvinyl oxazolidine (**5**) was the only product isolated (Scheme 2).[14,15] In the presence of $FeCl_3$

(6) (a) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310–1312. (b) Overman, L. E.; Kakimoto, M. *Tetrahedron Lett.* **1979**, *21*, 4041–4044. (c) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579–5581. (d) Overman, L. E.; Mendelson, L. T.; Flippin, L. A. *Tetrahedron Lett.* **1982**, *23*, 2733–2736. (e) Overman, L. E.; Jacobsen, J. *Tetrahedron Lett.* **1982**, *23*, 3733–2740. (f) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, P. *J. Am. Chem. Soc.* **1983**, *105*, 6622–6629.

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(8) Overman, L. E.; Ricca, D. J. *Comp. Org. Synth.* **1991**, *2*, 1007–1046.

(9) The unfavored 5-*endo-trig* cyclizations are based on the generation of a $\beta$-unsaturated iminium ion and subsequent nucleophilic attack by the unsaturated C−C bond.

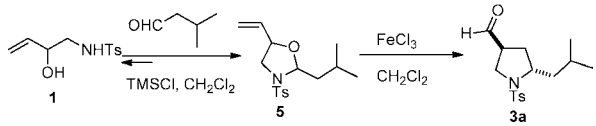
(10) This product was obtained in three steps. See Supporting Information.

(11) See $^1$H NMR of the reaction crude in Supporting Information.

(12) The best results were obtained using $NaBH_4$ as reducing agent. $LiAlH_4$ or DIBAL-H led to similar results but with lower yields.

(13) We have developed an iron catalyst system formed from $FeX_3$ or $Fe(acac)_3$ and trimethylsilyl halide to perform Prins cyclization processes: (a) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357–360. (b) Carballo, R. M.; Valdomir, G.; Purino, M.; Martín, V. S.; Padrón, J. I. *Eur. J. Org. Chem.* **2010**, 2304–2313.

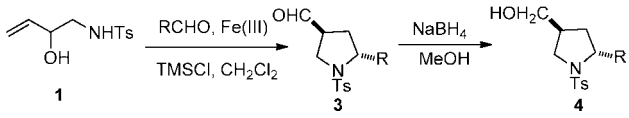
**Scheme 2.** Oxazolidine as Intermediate of the Aza-Cope−Mannich Reaction




this oxazolidine evolves to the corresponding 5-isobutyl-3-formyl pyrrolidine (**3a**), suggesting that it is an intermediate in the aza-Cope−Mannich (Scheme 2).

We next investigated the scope of the process regarding to the aldehyde. We tested aliphatic and aromatic aldehydes under the optimized reaction conditions, using 2-hydroxy homoallyl tosylamine (**1**) as the unsaturated compound. In general, the corresponding pyrrolidines (**4**) were obtained in good yields under the previously optimized conditions. This methodology works well with a wide range of aldehydes except when benzaldehyde was used (Table 2, entries 11 and 12). However, other aldehydes containing aromatic rings located in a distal position relative to the carbonyl group proceeded satisfactorily (Table 2, entry 10). The current iron-catalyst system efficiently promoted the aza-Cope−Mannich with slightly lower yields than the stoichiometric version. Interestingly, the iron catalyst also proved to be efficient in the cyclization process of aldehydes bearing functional groups such as a double bond (Table 2, entries 8 and 9).

**Table 2.** Cyclization of 2-Hydroxy Homoallyl Tosylamine (**3**) and Aldehydes Using Iron(III) Chlorides as Catalysts[a]

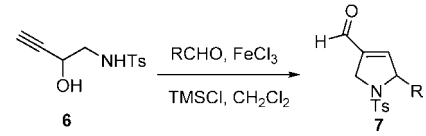



| entry | $FeCl_3$ (mol %) | TMSCl (equiv) | R | *trans:cis*[b] **4** | yield (%)[c] **4** |
|---|---|---|---|---|---|
| 1a | 100 | | *i*-Bu | 99:1 | 72 |
| 2 | 10 | 1.0 | *i*-Bu | 98:2 | 65 |
| 3 | 100 | | H | | 70 |
| 4 | 10 | 1.0 | H | | 62 |
| 5 | 100 | | *n*-Hep | 99:1 | 75 |
| 6 | 100 | | *c*-Hex | 99:1 | 60 |
| 7 | 100 | | *n*-Prop | 99:1 | 78 |
| 8 | 100 | | $CH_2$=$CH(CH_2)_2$− | 99:1 | 63 |
| 9 | 10 | 1.0 | $CH_2$=$CH(CH_2)_2$− | 98:2 | 55 |
| 10 | 100 | | Bn | 98:2 | 70 |
| 11 | 100 | | Ph | | *d* |
| 12 | 10 | 1.0 | Ph | | *d* |

[a] Reaction conditions: (i) **1** (1.0 equiv), aldehyde (1.0 equiv), [Fe], TMSCl (1.0 equiv), $CH_2Cl_2$, rt, 2−12 h; (ii) $NaBH_4$ (2.1 equiv), MeOH, 0 °C to rt. [b] The ratio *trans:cis* was determined by $^1$H NMR. [c] Yield of the pure product after silica gel chromatography. [d] The starting material was recovered.

With these results in hand, we extended our studies to the alkyne aza-Cope−Mannich, obtaining the corresponding 5-alkyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carbaldehyde (**7**) in good yields (Table 3).

**Table 3.** Iron-Catalyzed Alkyne Aza-Cope−Mannich Cyclization of 2-Hydroxy Homopropargyl Tosylamine (**6**) with Aldehydes[a]



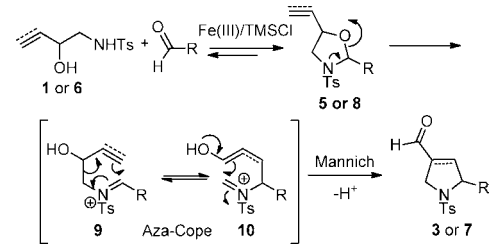

| entry | $FeCl_3$ (mol %) | TMSCl (equiv) | R | yield (%)[b] **7** |
|---|---|---|---|---|
| 1a | 120 | | *i*-Bu | 99 |
| 2 | 20 | 1.3 | *i*-Bu | 85 |
| 3b | 120 | | H | 99 |
| 4 | 20 | 1.3 | H | 87 |
| 5 | 120 | | *n*-Hex | 99 |
| 6 | 120 | | *c*-Hex | 95 |
| 7 | 120 | | *t*-Bu | 35 |
| 8 | 120 | | $CH_2$=$CH(CH_2)_2$− | |
| 9 | 20 | 1.3 | $CH_2$=$CH(CH_2)_2$− | |
| 10 | 120 | | Bn | 81 |
| 11 | 120 | | Ph | |
| 12 | 20 | 1.3 | Ph | |

[a] Reaction conditions: **6** (1.0 equiv), aldehyde (1.0−1.2 equiv), [Fe], TMSCl (1.3 equiv), $CH_2Cl_2$, rt, 2−12 h. [b] Yield of the pure product after silica gel chromatography.

We tested the aza-Cope−Mannich using a 2-hydroxy homopropargyl tosylamine (**6**)[16] as the unsaturated compound. In this case, it was necessary to slightly increase the amount of $FeCl_3$ and TMSCl (Table 3) with respect to the alkene aza-Cope−Mannich (Table 2). Again, the reaction works well with most aliphatic aldehydes. This alkyne aza-Cope−Mannich did not tolerate benzaldehyde and 4-pentenal (Table 3, entries 8, 9, 11, and 12). In general, the corresponding 3-formyl-α,β-unsaturated pyrrolidines (**7**) were obtained in high yields using either stoichiometric amounts of $FeCl_3$ or the catalytic system $FeCl_3$/TMSCl, although the yields in the stoichiometric version were slightly higher.

A plausible mechanism for this aza-Cope−Mannich is outlined in Scheme 3.[17] The reaction of the 2-hydroxy-

**Scheme 3.** Plausible Mechanism for the Iron-Catalyzed Alkene- and Alkyne-Aza-Cope−Mannich Reaction




unsaturated (alkyne and alkene) tosylamine and aldehyde catalyzed by ferric halide generates the corresponding unsaturated oxazolidine (**5** or **8**),[18] which evolves to the iminium ion

(14) The oxazolidines and the aldehyde are in an equilibrium that depends on the aldehyde nature. In the case of isovaleraldehyde this equilibrium was displaced almost completely toward the oxazolidine species, but with 2-phenylacetaldehyde it was displaced toward the aldehyde.

(15) This oxazolidine was obtained as a single isomer that epimerized (60:40) under chromatographic conditions. See Supporting Information.

(16) This product was obtained in two steps. See Supporting Information.

**9**. This iminium ion undergoes a 2-azonia-[3,3]-sigmatropic rearrangement to give iminium ion **10**, which reacts through an irreversible intramolecular Mannich reaction to give the corresponding pyrrolidine derivatives (**3** or **7**).

To provide further evidence of the proposed mechanism, DFT theoretical calculations at the B3LYP/6-31+G(d) level were performed. The results of these calculations are summarized in the energy diagrams shown in Figure 1.[19]

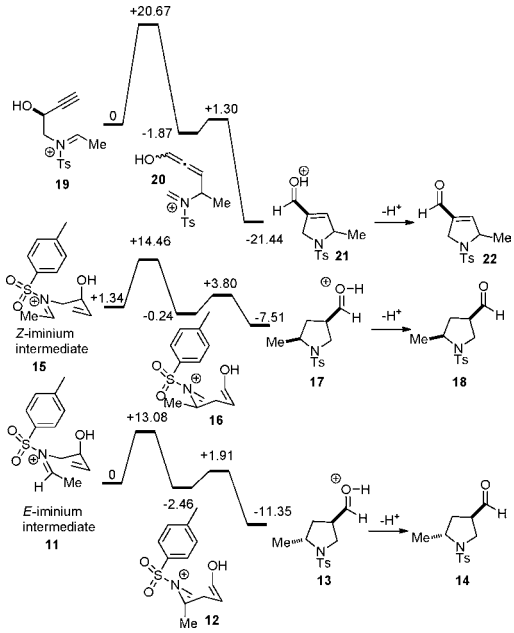


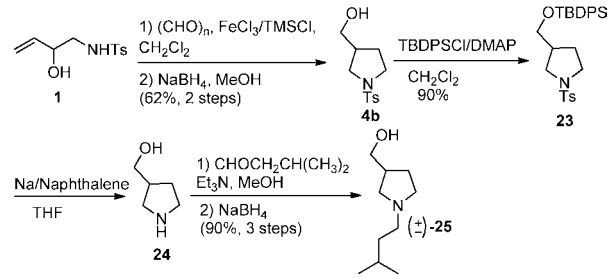

**Figure 1.** Energy (kcal/mol) profile of 2-azonia-[3,3]-sigmatropic rearrangements and Mannich reaction.

The calculations showed that the *E*-iminium ion (**11**), precursor of *trans*-stereoisomer **14**, is slightly more stable than the corresponding *Z*-iminium ion (**15**), precursor of the *cis*-isomer **18**. The main difference between these processes could be found in the Mannich intramolecular cyclization that was more exothermic for the *trans*-isomer than for the *cis*-isomer. In both cases, the aza-cope rearrangement was slightly favored.

In the alkyne aza-Cope−Mannich, the 2-azonia-[3,3]-sigmatropic rearrangement is also favored but with a higher activation energy. However, the strongly exothermic final alenol-intramolecular Mannich cyclization is responsible to drive all the tandem process. This energy profile correlates very well with our proposed mechanism.[20]

Finally, to explore the synthetic scope of this methodology, we synthesized the racemic 1-(3-methylbutyl)pyrrolidin-3-methanol **25**, one of the pyrrolidine alkaloids isolated from the poison gland of ants *Leptothoracini* (Myrmicinae).[21] Thus, the *N*-tosyl pyrrolidine **4b** was obtained in 62% yield from an aza-Cope−Mannich and further reduction of the resulting aldehyde. At this point, it was necessary to protect the hydroxymethyl as TBDPS to carry out the *N*-detosylation. Deprotection of the *N*-tosyl group with sodium/naphthalene led to pyrrolidine **24**. The last step was a reductive amination with 3-methylbutanal and $NaBH_4$ in methanol that leads to the pyrrolidine alkaloid **25** in good yield (Scheme 4).

**Scheme 4.** Synthesis of 1-(3-Methylbutyl)pyrrolidin-3-methanol Pyrrolidine Alkaloid from Poison Glands of *Leptothoracini* Ants




In summary, we have developed a novel iron-catalyzed aza-Cope−Mannich of 2-hydroxy-$\gamma,\delta$-unsaturated (alkyne and alkene) tosylamines with different aldehydes. The coupling between 2-hydroxy homopropargyl tosylamine and aldehydes provides 5-alkyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carbaldehydes in good yields. The process catalyzed by iron(III) salts is direct, avoiding the preformation of the oxazolidine as the starting material. It is based on the consecutive generation of $\gamma$-unsaturated-iminium ion, 2-azonia-[3,3]-sigmatropic rearrangement, and further intramolecular Mannich reaction. DFT theoretical calculations support the proposed mechanism.

Overall, this process builds up two carbon−carbon bonds, one nitrogen−carbon bond, and a ring in a regioselective and efficient manner.

**Acknowledgment.** This research was supported by the Ministerio de Educación y Ciencia of Spain, co-financed by the European Regional Development Fund (CTQ2008-06806-C02-01/BQU), the Spanish MSC (RTICC RD06/0020/1046 and RD06/0020/0041), the Canary Islands Government (ACIISI) (PI 2007/022), FUNCIS (REDESFAC PI 01/06), Consejo Superior de Investigaciones Científicas (CSIC) (PIE 200880I032) and FICIC (Grant-G.I. 08/2007). M.P. is supported by the Programme Alban, the European Union Programme of High Level Scholarships for Latin America, scholarship E07D402567AR.

**Supporting Information Available:** $^1$H NMR and $^{13}$C NMR spectra for all new compounds and computational calculating data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Based on Overman's proposal. (a) Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329–4336. (b) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250.

(18) TMSCl also promoted the corresponding alkyne oxazolidine formation as intermediate in the alkyne aza-Cope−Mannich.

(19) The absolute configuration of the hydroxyl group was fixed to simplify the calculations.

(20) The DFT studies confirm the alkyne aza-Cope−Mannich mechanism vs alkyne Prins−pinacol alternative.

(21) Reder, E.; Veith, H. J.; Buschinger, A. *Helv. Chim. Acta* **1995**, *78*, 73–79.