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Yttrium Triflate-Catalyzed Addition of Lithium Enolates to 1,2-Epoxides. Efficient Synthesis of γ-Hydroxy Ketones

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Dedicated to Prof. G.Berti on the occasion of his 70th birthday

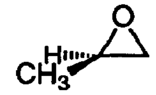
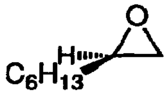
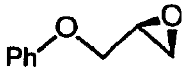
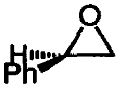
Abstract: A simple, efficient method is described for the synthesis of γ-hydroxy ketones by the direct opening of 1,2-epoxides with lithium enolates derived from simple ketones in anhydrous toluene, in the presence of $Y(OTf)_3$.

1,2-Epoxides constitute one of the most valuable functional groups in organic chemistry, because of their easy synthesis and availability, and the large potentiality of their reactivity in nucleophilic addition reactions.[1] However, compared with many well-documented and easily obtained opening reactions of 1,2-epoxides, the direct opening of this system with simple enolates derived from ketones is much less common in literature and, as a consequence, in practical organic synthesis.

Recently,[2] we found that $LiClO_4$ successfully promotes the addition of enolates **3** [derived from pinacolone (**1**)] and **4** [derived from acetophenone (**2**)] to some representative epoxides (**5**,**7**, and **8**), to give the corresponding γ-hydroxy ketones in very nice yields. This result is undoubtedly interesting, not only in view of the above considerations, but also because, to our knowledge, nothing new on this subject has appeared in literature in recent years, while interest in this field is growing.[3,4] However, this method, even if of value, is not completely satisfactory, and, in our opinion, suffers from certain limitations: a) the operating reaction temperatures were somewhat elevated (50°C) in some cases, b) a large amount of the promoting salt ($LiClO_4$) had to be used (1.5:1 ratio to the epoxide), and c) long reaction times, in some cases.

In a program whose aim is to search for new metal salts, more efficient than $LiClO_4$, able to promote the addition of enolates to 1,2-epoxides under operating conditions as mild as possible, several metal salts, particularly lanthanide salts, have been tried in this period.[5] We now wish to report some preliminary results indicating that a new, unprecedently prepared, yttrium salt, the yttrium triflate, [$Y(OTf)_3$],[6] promotes in an extraordinarily efficient way the addition of enolates **3** and **4** to epoxides **5-8**, to give the corresponding γ-hydroxy ketones in almost quantitative yield (Table). The yttrium-catalyzed reactions occur under particularly mild conditions compared with the corresponding ones promoted by $LiClO_4$: lower temperature and shorter reaction times (see reaction conditions A and C in the Table). The addition reactions occur at 0°C, or ar r.t. in the case of the less reactive epoxides. In these conditions it is possible to have the addition reaction also with epoxide **6** which was completely unreactive under the $LiClO_4$-promoted protocol (entry 9, Table).[7]

Table. Reaction of Epoxides 5-8 with Lithium Enolates 3 and 4, Derived from Pinacolone (1) and Acetophenone (2), in Toluene in the Presence of $Y(OTf)_3$.

entry	epoxide[a]		enolate	reaction conditions,[b] time (h) and temperature		α attack[c]	β attack[d]	yield %[e]
1	**5**		3	A	18 h (0°C)	<1	>99[f]	99
2			3	B	18 h (0°C)	<1	>99[f]	47
3			3	C	72 h (r.t.)	<1	>99[f]	98
4			4	A	18 h (0°C)	<1	>99[g]	99
5			4	C	72 h (r.t.)	<1	>99[g]	86
6	**6**		3	A	18 h (r.t.)	*h*		90
7			3	B	18 h (r.t.)	*h*		35
8			4	A	18 h (r.t.)	*i*		83
9			3 or 4	C	48 h (r.t.)	no reaction[j]		-
10	**7**		3	A	18 h (0°C)	<1	>99[k]	99
11			3	C	24 h (r.t.)	<1	>99[k]	90
12			4	A	18 h (0°C)	<1	>99[l]	99
13			4	C	24 h (50°C)	<1	>99[l]	76
14	**8**		3	A	18 h (r.t.)	40[m]	60[n]	95
15			3	C	24 h (50°C)	9[m]	91[n]	95
16			4	A	18 h (r.t.)	85[o]	15[p]	80
17			4	C	24 h (50°C)	12[o]	88[p]	80

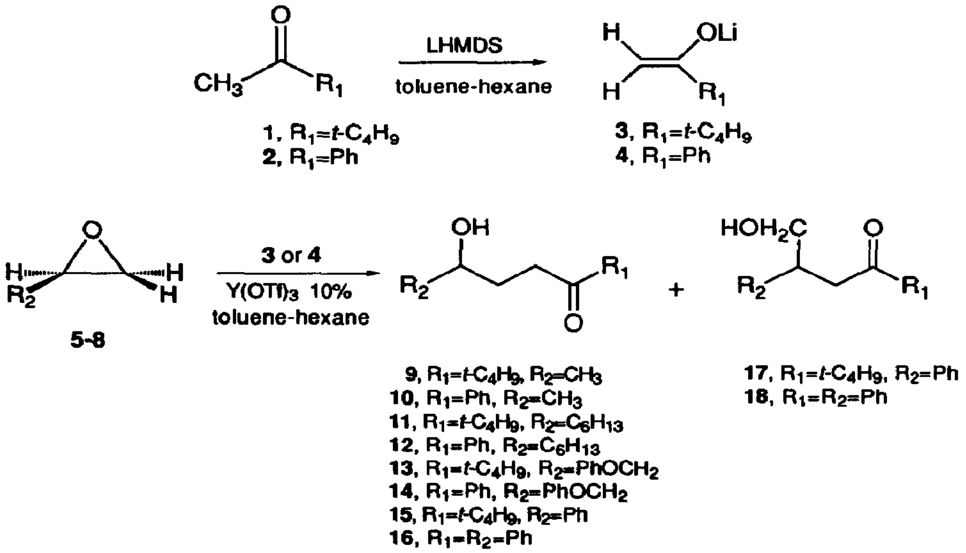
[a] Racemic material. [b] A: see General Procedure; B as in A, the enolate being prepared in THF. C: $LiClO_4$ protocol, ref. 2. [c] Attack of the nucleophile on the more substituted oxirane carbon. [d] Attack of the nucleophile on the less substituted oxirane carbon. [e] Yields calculated by weight and ^1H NMR analysis of the crude reaction product. [f] Hydroxy ketone (HK) **9**. [g] HK **10**. [h] HK **11**. [i] HK **12**. [j] See ref.7. [k] HK **13**. [l] HK **14**. [m] HK **15**. [n] HK **16**. [o] HK **17**. [p] HK **18**.

Furthermore, only 10% mol amount of the new catalyst is required in order for the addition reaction to uccur. In the case of the $LiClO_4$-promoted addition, THF was the solvent chosen.[2] In the present case, the simultaneos use of toluene as the solvent and 1.0 M lithium bis(trimethylsilyl)amide (LHMDS) in hexane (Aldrich), totally excluding the use of THF, dramatically raised the yields and the quality of the crude reaction product (compare reaction conditions A and B in the Table). The reactions are completely regioselective, with the attack of the nucleophile (lithium enolate) on the less substituted oxirane carbon to give the *contra*-Markovnikov type product (compounds **9-16**).[2] The only exception is given by epoxide **8**, in which substantial amount of the Markovnikov-type addition product (compounds **17** and **18**) have interestingly been obtained (entries 14 and 16, Table). As a consequence, with epoxide **8**, the alternate use of the $LiClO_4$-[2] and the $Y(OTf)_3$-catalyzed procedures for the lithium enolate nucleophilic addition makes it possible to obtain a nice regioalternating process (entries 14-17, Table).[8]

The method appears to give the best results with terminal 1,2-epoxides, structurally related to the epoxides **5-8**, whereas bicyclic epoxides, such as cyclohexene oxide (not shown in the Table), have so far proved to afford the corresponding addition products only in lower overall yields (55% and 70% in the reaction with enolates **3** and **4**, respectively).

The catalytic effect of $Y(OTf)_3$ in this reaction appears to be ascribable to the strong ability of Y^{+3} to coordinate tightly to the oxirane oxygen,[5] thus favoring the nucleophilic ring opening process. In the case of epoxide **8**, the oxophilicity of Y^{+3} is decidedly able to allow the attack of the enolate on the benzylic oxirane carbon, reasonably through a slightly carbocationic transition state.[8]

On the basis of these and other results,[5,9] we also tried to perform the enolate addition to 1,2-epoxides, preparing and testing a chiral Lewis acid catalysts such as the Yb[(+)10-camphorsulfonate)]$_3$.[6] In a preliminary examination, the Yb[(+)10-camphorsulfonate)]$_3$ turned out to be sufficiently effective in promoting the addition of enolate 3 to epoxide (±) 5,[10] its ability being only somewhat less than Y(OTf)$_3$.[9] However, unfortunately, the kinetic resolution induced was low (ee 16% calculated on the Mosher's ester of the reaction product 9), even if encouraging, considering that the attacking carbon of the enolate 3 and the chiral center of the epoxide 5 are in a 1,3-relationship. Work is in progress in order to make this procedure more general and in order to achieve decidedly satisfactory degree of kinetic resolution.



General Procedure and Identification of γ-Hydroxy Ketones

A 1.0 M LHMDS solution in hexane (6.0 ml) (Aldrich) was treated under stirring at 0°C with a solution of the ketone (5.0 mmol)[11] in anhydrous toluene (1 ml), added over a period of about 10 min. After 30 min at the same temperature, a solution of the epoxide (2.0 mmol)[11] in anhydrous toluene (2 ml) was added in 5 min, and the resulting reaction mixture was treated at 0°C with Y(OTf)$_3$ (0.107 g, 0.2 mmol).[6] The reaction mixture was stirred at 0°C for the time shown in the Table (in the case of the reaction carried out at r.t., the reaction temperature was allowed to warm slowly to r.t., then kept at this temperature for the time shown in the Table). Dilution with ether, treatment with saturated aqueous NH_4Cl, and evaporation of the washed (water) organic solution afforded a crude reaction product which was analyzed by ^1H NMR. Preparative TLC afforded pure γ-hydroxy ketones which were identified by comparison with authentic sample prepared in accordance with literature procedures.[2] In the case of new compounds (compounds **11**, **12**, and **17**) their structure was determined on the basis of their ^{1}H and ^{13}C NMR spectra and confirmed by satisfactory microanalysis results (C,H ± 0.3% of the calculated value).

Compound 11: a liquid; ^{1}H NMR δ 3.37-3.46 (m,1H), 2.56 (t, 2H, *J*=6.9 Hz), 1.63-1.79 (m,1H), 1.43-1.62 (m,1H), 1.32-1.41 (m,2H), 1.09-1.17 (m,8H), 1.05 (s,9H), 0.64-0.80 (m, 3H). ^{13}C NMR δ 217.69, 72.15, 38.51, 33.60, 31.72, 32.41, 29.94, 27.08, 26.24, 23.20, 14.49.

Compound 12: a solid, m.p. 61°C; ^{1}H NMR δ 7.96-8.02 (m,2H), 7.41-7.61 (m,3H), 3.61-3.73 (m,1H), 3.16 (dt,2H, *J*=1.9 and 6.1 Hz), 1.91-2.07 (m,1H), 1.70-1.89 (m,3H), 1.28-1.49 (2m. 8H), 0.84-0.91 (m, 3H). ^{13}C NMR δ 201.59, 137.59, 133.75, 129.24, 128.78, 72.15, 38.54, 35.65, 32.48, 32.04, 29.99, 26.32, 23.26, 14.74.

Compound 17: a liquid; ^{1}H NMR δ 7.15-7.42 (m,5H), 3.65-3.73 (m,2H), 3.33-3.46 (m,1H), 2.84 (dd,2H, *J*=3.5 and 6.8 Hz), 1.15 (s,9H). ^{13}C NMR δ 220.35, 144.72, 129.39, 129.23, 128.52, 67.71, 44.22, 30.39, 27.19, 26.93.

References and Notes

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4. Hoye, T.H.; Crawford, K.B. *J.Org.Chem.* **1994**, *59*, 520-522.
5. Unpublished results from this laboratory. The tentative use of Ln(III) salts, such as $Ln(OTf)_3$, in this lithium enolate addition to 1,2-epoxides, was justified by the previously observed strong catalytic effect of these salts in the aminolysis of 1,2-epoxides: Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433-436.
6. The previously unreported $Y(OTf)_3$ was prepared in the following way: a suspension of Y_2O_3 (5.73 g, 25.4 mmol) in water was treated with CF_3SO_3H (10 g, 66.6 mmol) and the reaction mixture was refluxed under stirring until the aqueous solution became neutral. Evaporation of the filtered aqueous solution afforded pure $Y(OTf)_3$ which was carefully dried at 140°C under vacuum for two days. The anhydrous $Y(OTf)_3$ thus obtained was stored in a dessiccator. In order for the efficiency of $Y(OTf)_3$ to be maintained, the drying procedure should be repeated in the case of a long period (more than two weeks) of storage. Also the previously unreported Yb[(+)10-camphorsulfonate)]$_3$ was prepared following a closely related procedure starting from Yb_2O_3 and (+)10-camphorsulfonic acid.
7. Unpublished results from this laboratory.
8. Chini, M.; Crotti, P.; Macchia, F. *J.Org.Chem.* **1991**, *56*, 5939-5942.
9. Also $Yb(OTf)_3$ is effective in promoting the addition reaction of enolate **3** to epoxides **5** and **6**. However, in this case the yields are lower and decidedly more complex reaction mixtures are obtained than in the $Y(OTf)_3$-catalyzed reactions. Y[(+)10-(camphosulfonate)]$_3$ was not tested.
10. The reaction of enolate **3** with epoxide (±)**5** in the presence of Yb[(+)10-camphorsulfonate]$_3$ was performed at 0°C, following the General Procedure, with an enolate:epoxide ratio= 1:4.
11. The commercially available ketones **1** and **2** and epoxides **5**-**8** must be accurately distilled and stored on molecular sieves prior to use. In this reaction, as in the previously described $LiClO_4$-catalyzed addition of lithium enolate to 1,2-epoxides,[2] the accurate purification of the starting materials is a very important point in order to obtain high yields of the addition products (see note 3, ref.3.).

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