VIP Enantioselective Protonation

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Catalytic Enantioselective Tautomerization of Isolated Enols

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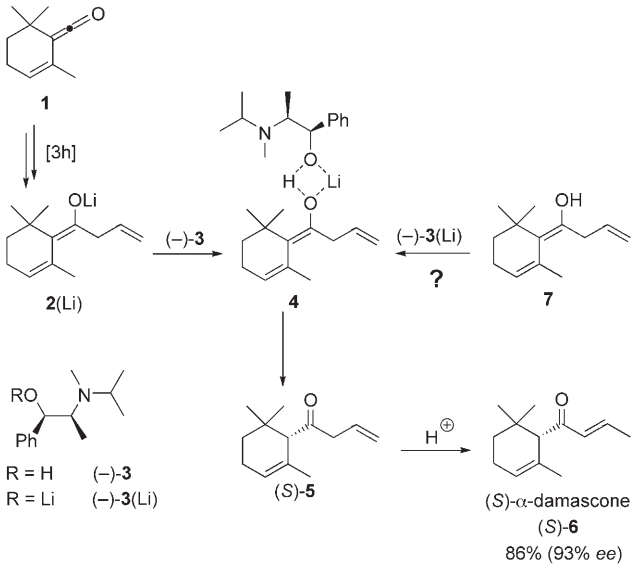
In recent years, the enantioselective protonation of enolates (or enol equivalents) has emerged as a powerful method for the synthesis of chiral ketones and esters.[1,2] We have successfully applied it to the synthesis of several important fragrance compounds[3] and were the first to extend this reaction to catalytic enantioselective protonation.[3g,h]

As exemplified in Scheme 1 for the synthesis of the rose-smelling fragrance compound (*S*)-α-damascone ((*S*)-**6**) by protonation of lithium enolate **2**(Li) by using (−)-*N*-isopropylephedrine ((−)-**3**), we postulated that prior to the irreversible stereocontrolled C-protonation, a tight transition-state-like complex **4** would be formed, which may be further aggregated with chiral or achiral ligands. If this mechanistic hypothesis is correct, the "inverse" process, the tautomerization of the unknown enol **7** by using the deprotonated chiral reagent (−)-**3**(Li), should also lead to the same hypothetical species **4** and thus to (*S*)-α-damascone.



Scheme 1. The postulated enol/enolate complex **4**, which is formed prior to irreversible stereocontrolled C-protonation.

Recently, Vedejs et al.[4] designed an ingenious experiment that demonstrated, contrary to expectations, that the enantioselective protonation of an amide enolate with a chiral aniline does not occur by direct C-protonation, but takes place via en enol intermediate and/or an aggregate with the generated lithiated chiral aniline. This result supports our proposal of an indirect enantioselective protonation via a mixed chiral enol/enolate aggregate; however, the best confirmation of this reaction course would be the aforementioned (−)-**3**(Li)-catalyzed tautomerization of enol **7**.[5]

In general, enols tautomerize very rapidly into ketones and cannot be isolated. Notable exceptions are highly sterically hindered enols.[6] We felt that it might be possible to isolate **7** because we had obtained some indirect evidence for its presence in the reaction medium. Indeed, although the enantioselective protonation of **2**(Li) with (−)-**3** is rapid, protonation of **2**(MgCl) is very slow and inefficient.[3a] Successive treatment of **2**(MgCl) with (−)-**3** and aqueous HCl immediately afforded a 1:1 mixture of **5** and its isomer resulting from γ-protonation, whereas prolonged treatment with aqueous acetic acid (AcOH) or aqueous LiOH afforded **5** exclusively.

First attempts to generate enol **7** by protonation of **2**(MgCl) by using AcOH, MeOH, or water (1 or 2 equiv) either gave rise to mixtures of **5** and **7** or incomplete protonation (loss of material in the filter cake). In addition, failure to rigorously exclude oxygen resulted in rapid formation of autoxidation products. After some experimentation, we found that addition of allyl-MgCl to ketene **1** in toluene/THF (2:1) at −78 °C, followed by slow addition (15 min) of H_2O (7.5 equiv) in THF to the resultant enolate **2**(MgCl) (−70 °C then −50 °C) and filtration through Celite afforded pure enol **7** containing trace amounts of water (Scheme 2).[7] This solution was used directly for tautomerization experiments but could also be stored in the freezer without noticeable ketonization (< 5 % in 24 h). All analytical data are consistent with the postulated enol structure.

For the enantioselective tautomerization of enol **7**, we added the solution of **7** to (−)-**3**(Li) at such a rate that **7** would ketonize continually, thus keeping the risk of a noncatalytic pathway as low as possible. Under our optimized conditions, the toluene/THF solution of **7** (1 equiv, ≈0.2 M) was added slowly to a cooled (−78 °C) solution of (−)-**3**(Li) (0.33 equiv) in THF. After addition of one third of the solution (stoichiometric conditions), the formed (*S*)-**5** showed an *ee* value of 92 %, after addition of two thirds of the solution there was 83 % *ee*, and after complete addition there was 76 % *ee* (Scheme 2).The reduction in *ee* values when adding excess enol may be due to the presence of residual water in **7**, leading to less-efficient aggregates or to a competing LiOH-catalyzed tautomerization.

Interestingly, by using (−)-**3**(Li) of 50 % *ee*, a distinct nonlinear effect was observed. Continual introduction of **7** (0.25, 0.5, 1.0, 1.5 equiv) to (−)-**3**(Li) (50 % *ee*) afforded (*S*)-**5** with 69, 65, 57, and 50 % *ee* respectively. This experiment

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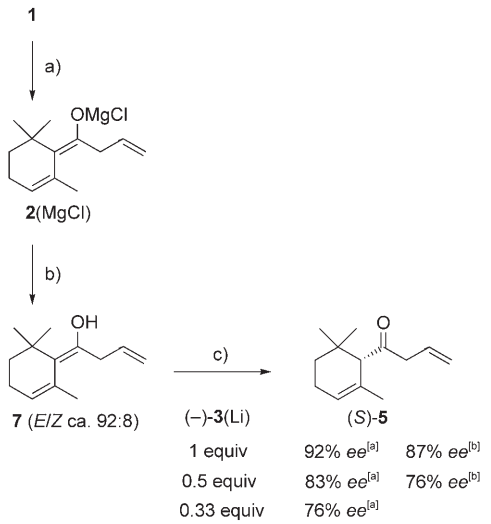
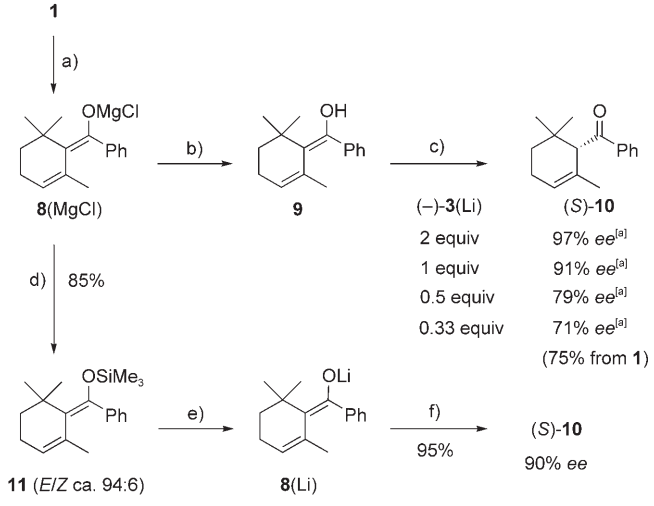


Scheme 2. Preparation and reactivity of enol **7**. a) Allyl magnesium chloride (1.04 equiv), THF, toluene, −70 °C→RT; b) H_2O (7.5 equiv), THF, toluene, −70→−50 °C, 15 min, ca. 95 % crude yield; c) addition of **7**, THF, toluene to (−)-**3**(Li), THF, toluene, −78 °C; [a] 12-mmol scale, total addition time: 45 min; [b] 24-mmol scale, total addition time: 2 h.

demonstrates that higher-order mixed aggregates are involved in the enantioselective transformation of enols into ketones.

In the context of taiwaniaquinoids[8] and to demonstrate the broader applicability of enantioselective enol tautomerization, we prepared the phenyl ketone (*S*)-**10** by tautomerization of enol **9**, which is readily isolated as a solution in THF (95 % crude yield, purity > 90 %; Scheme 3). To ensure rapid tautomerization, a reaction temperature of −30 °C was chosen. As shown in the first example, the enantioselectivity is very high at the beginning of the addition of **9** to (−)-**3**(Li) and decreases upon further addition of **9** (97 % *ee* with 2 equivalents of (−)-**3**(Li); 71 % *ee* with 0.33 equivalents of (−)-**3**(Li)).



Scheme 3. Preparation and reactivity of enol **9**. a) PhMgCl (1.07 equiv + 0.16 equiv (after 5 h)), THF, 55 °C, 7 h; b) H_2O (7.5 equiv), THF, −70→−35 °C, 15 min, ca. 95 % crude yield; c) addition of **9**, THF to (−)-**3**(Li), THF, −30 °C; [a] 3-mmol scale, THF, total addition time: 70 min; d) Me_3SiCl (1.6 equiv), −50 °C→RT, 1 h; e) MeLi (1.15 equiv), THF (Et_2O), 40 °C, 15 min; f) addition of **8**(Li), THF to (−)-**3**(Li) (1.2 equiv)/(−)-**3** (1.2 equiv), THF, 2 °C in 1 h.

Alternatively, enantioselective protonation of the *E*-rich lithium enolate **8**(Li) (E/Z ≈ 94:6), which was obtained indirectly via enol silyl ether **11**[9] by its addition to a 1:1 mixture of (−)-**3** (1.2 equiv) and (−)-**3**(Li) (1.2 equiv)[10] in THF at 2 °C, afforded (*S*)-**10** with 90 % *ee* in 95 % yield.[11]

In conclusion, we have developed a procedure for the stereoselective generation and isolation of (*E*)-enols. Employing these enols, we have achieved their catalytic enantioselective ketonization and validated the postulate of indirect enolate protonation, which occurs via enols and higher-order mixed aggregates.

Experimental Section

7: A solution of allyl magnesium chloride in THF (1.80 M, 13.9 mL, 25.0 mmol) was added at −70 °C over 10 min to a stirred solution of **1** (3.60 g, 24.0 mmol) in THF/toluene (1:1, 60 mL). The pale-colored reaction mixture was allowed to warm to 25 °C (over 30 min) and was then cooled at −78 °C. By means of a syringe pump, a solution of H_2O (3.24 mL; 180.0 mmol) in THF (15 mL) was added over 15 min to the cooled reaction mixture. The suspension was allowed to reach −50 °C and a clear liquid phase was formed, which could be easily separated from the heavy material sticking to the walls of the flask by filtration over Celite (under N_2). $MgSO_4 \cdot H_2O$ (approximately 4 g) was added and the mixture was swirled under N_2. After 2 min, the suspension was filtered and rinsed with THF/toluene (1:2, 60 mL) to obtain a volume of 115 mL (containing a maximum of 24.0 mmol of **7**).

For the preparation of **7** in deuterated solvents (for NMR spectroscopic measurements), the above solution of allyl magnesium chloride was concentrated to dryness and treated at −78 °C with a solution of **1** in [D_8]THF/[D_8]toluene. The addition of water was performed as described above. The solution obtained after filtration over Celite was used as such.

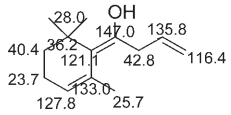
Analytical data of **7** (*E*/*Z* ≈ 9:1) (prepared in [D_8]toluene/[D_8]THF (2:1)): IR (THF): 1620, 3000–3700 cm^{-1} (br). ^1H NMR ((*E*)-**7**; [D_8]THF/[D_8]toluene (1:2)): $\delta = 1.46$ (*s*, 6H), 1.47 (dd, $J = 6$, 6 Hz, 2H), 1.96 (split *s*, 3H), 2.00 (m, 2H), 3.06 (br d, $J = 5$ Hz, 2H), 5.05 (m, 1H), 5.15 (m, 1H), 5.59 (m, 1H), 5.82 (m, 1H), 6.24 (*s*, 1H; disappears with D_2O); characteristic signals of (*Z*)-**7**: 1.20 (s, 6H), 3.15 ppm (br d, $J = 5$ Hz, 2H). ^{13}C NMR ([D_8]THF/[D_8]toluene (1:2)): $\delta = 23.7$ (t), 25.7 (q), 28.0 (2q), 36.2 (s), 40.4 (t), 42.8 (t), 116.4 (t), 121.1 (s), 127.8 (d), 133.0 (s), 135.8 (d), 147.0 ppm (s).

(*S*)-**5**: The solution of **7** in toluene/THF (≈1:1, 115 mL) was added by means of a syringe pump (over 2 h) to a cooled (−78 °C) solution of (−)-**3**(Li) (12.0 mmol; prepared form (−)-**3** (2.49 g; 12.0 mmol), BuLi (1.45 M in hexane, 8.28 mL, 12.0 mmol), and THF (15 mL) in the presence of a trace of *o*-phenanthroline (indicator). After complete addition, the reaction mixture was allowed to reach −40 °C and was then poured into 5 % HCl (250 mL) and extracted with Et_2O (2x). The organic phases were washed successively with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and then dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation (oven temperature 75–100 °C/10 mbar, then 2 mbar) afforded a head fraction of volatile materials (mainly 1,5-hexadiene) and a second fraction of (*S*)-**5** (3.71 g, 96 % pure, 77 % from **1**; 76 % *ee* (chiral GC: CP-Chirasil-DEX CB, 25 m × 0.25 mm)).

(*E*)-**9**: ^1H NMR([D_8]THF): $\delta = 1.12$ (split s, 3H), 1.39 (s, 6H), 1.48 (dd, $J = 6$, 6 Hz, 2H), 2.03 (m, 2H), 5.43 (m, 1H), 7.17 (s, 1H), 7.20–7.33 ppm (m, 5H). ^{13}C NMR ([D_8]THF): $\delta = 24.0$ (t), 25.6 (q),

27.8 (2q), 36.2 (s), 42.4 (t), 121.7 (s), 127.3 (d), 128.5 (2d), 128.5 (d), 130.3 (2d), 133.7 (s), 143.2 (s), 150.2 ppm (s).

^{13}C NMR signals for **7** and **9** are assigned as shown.



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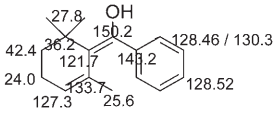

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(*S*)-**10**: $[\alpha][\alpha]_D^{20}$ ($CHCl_3$; $c = 2.3$) −256 (63 % *ee* by chiral GC (CP-Chirasil-DEX CB, 25 m × 0.25 mm; major enantiomer: first peak)).

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[7] The different qualities of enol **7** were shown to contain 0.1–0.2 equivalents of H_2O ("Karl Fischer" method). It was not possible to rigorously dry **7** in toluene/THF in the presence of 4A molecular sieves as these conditions resulted in rapid ketonization. For determination of the enol content, air was bubbled through a sample of enol solution (room temperature for 5 min), thus affording γ-oxygenated products (primarily the hydroperoxide). These represent 97–98 % by GC and ketone **4** amounts to 2–3 %. Nonvolatile by-products: approximately 5 %.

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[9] The addition of PhLi in Bu_2O to **1** in THF at −70 °C affords a 3:1 mixture of (*E*/*Z*)-**8**(Li) which is unsuitable for enantioselective protonation (74 % *ee*!).

[10] Under these conditions, accumulation of transient **9** is avoided; see reference [3e].

[11] The absolute configuration of (*S*)-**10** was determined by independent synthesis (PhLi + *p*-chlorothiophenylester of (*S*)-α-cyclogeranic acid (Ref. [3g]).

