Reverse Chemoselectivity in the Competitive Addition of Thallium Ate Complexes to Enones and Ketones†

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The chemistry of triorganothallium (TOT) compounds has received little attention.[1] As part of a general program aimed at developing the synthetic potential of the somewhat neglected group IIIb elements In, Ga, and Tl, we have prepared a selection of TOT derivatives and their ate complexes and studied their reactions with a variety of substrates.[2] We have found that TOT compounds react smoothly with acid chlorides to afford ketones in high yields.[3] This method probably represents one of the most versatile routes to ketones. TOT reagents also add to activated tertiary halides to give quaternary carbon centers.[4] The first catalytic process using organothallium derivatives for the formation of C–C bonds has also been reported.[5] Finally, *tetraorganothallium ate complexes were found to behave toward enones in a manner totally opposite their aluminium counterparts*, forming 1,2-addition products with acyclic enones and 1,4-addition products with cyclic enones.[6]

In this Communication, we report on yet another unique property of tetraorganothallium ate complexes: *their ability to react preferentially with enones in the presence of ketones, providing a unique, previously unavailable, synthetic transformation.*[7-10] Thus, when an equimolar mixture of an enone **1** and a ketone **2** is treated with 1 equiv of a thallium(III) ate complex in ether at −50 °C[11] (inverse addition of the ate complex[12]), a rapid reaction takes place,[13] giving rise to the preferential formation of the allylic alcohol **3** over the saturated tertiary alcohol **4** (Figure 1).

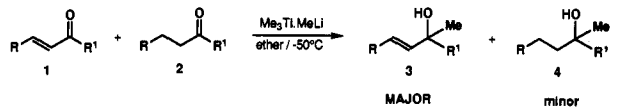
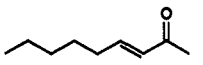
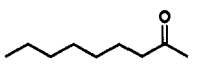
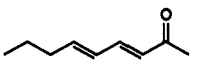
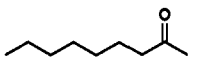
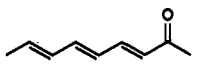
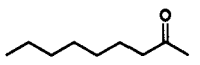
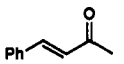
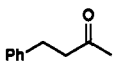
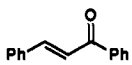
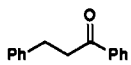
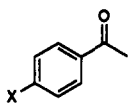
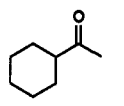
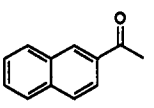
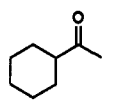


Figure 1.

Table I. Chemoselective Addition of Me_3Tl·MeLi to Enones/Ketones

entry	enone	ketone	UA/SA[a,b]	yield[c]
1			5 : 1	78%
2			10 : 1	89%
3			20 : 1	79%
4			40 : 1	84%
5			>75 : 1	98%
6				
	a : X = H		15 : 1	84%
	b : X = OMe		1 : 1	86%
	c : X = CN		>75 : 1	95%
7			45 : 1	95%

[a] UA, unsaturated alcohol; SA, saturated alcohol. [b] The ratios were measured by ^1H NMR at 300 and 500 MHz. [c] All reactions were performed in ether at −50 °C unless stated otherwise. The yields are based on the complete consumption of both starting ketones. Authentic samples of each tertiary alcohol were prepared from the corresponding ketone by reaction with either MeMgI or MeLi.

Some representative examples of this chemoselective transformation are displayed in Table I. Several important features emerge from this collection of data. *One of the most striking observations is that the selectivity of the process increases as the substrate becomes more conjugated and the intrinsic reactivity of the carbonyl function decreases.* Thus, 2-nonenone reacts 5 times faster than 2-nonanone. Whereas the trienone is attacked almost exclusively, the dienone is of intermediate reactivity (entries 1–3). Such an observation is also supported by entries 4 and 5.

The chemoselectivity displayed by the thallium ate complexes is opposite that shown by various other reagents, most of which

† Dedicated fondly and with due respect to Professor A. McKillop for his constant encouragement and friendship.

(1) Thallium reagents are used only sparingly by organic chemists. This is perhaps due to the overexaggerated toxicity of these compounds. Indeed, it is important to realize that thallium, in contrast to lead and mercury, is not a cumulative poison, thallium being gradually excreted from the body by soft-tissue turnover: (a) Browning, E. C. *Toxicity of Industrial Metals*; Butterworths: London, 1961. (b) Grunfeld, O.; Hinostroza, G. *Arch. Int. Med.* **1964**, *114*, 132. (c) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338. The TOT derivatives we use are prepared *in situ*, from diorganothallium (DOT) halides[3] by the addition of 1 equiv (TOT)[3] or 2 equiv (TOT ate complex)[16] of an organolithium salt. The starting DOT halides, which are typically high-melting solids insoluble in organic solvents and in water, are precipitated at the end of the reaction by a mild acidic workup, filtered, washed, and recycled (recovery 90–95%). Therefore, handling of the more volatile, and hence more dangerous, TOT compounds is completely avoided.

(2) For some interesting developments in organoindium and organogallium chemistry, see: (a) Gilbert, K. B.; Boocock, S. K.; Shore, S. G. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 6, p 879. (b) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 824.

(3) Markó, I. E.; Southern, J. M. *J. Org. Chem.* **1990**, *55*, 3368.

(4) Markó, I. E.; Southern, J. M.; Kantam, L. M. *Synlett* **1991**, 235.

(5) Markó, I. E.; Kantam, L. M. *Tetrahedron Lett.* **1991**, *32*, 2255.

(6) Markó, I. E.; Rebière, F. *Tetrahedron Lett.* **1992**, *33*, 1763.

(7) To the best of our knowledge, the only chemoselective attack on an enone carbonyl in preference to a ketone was reported by Reetz, but the selectivity was rather poor: (a) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 90. Organomanganese reagents also display preference for addition to enones. We are very grateful to Professor Cahiez for providing us with this unpublished information.

(8) In contrast to the Luche's $CeCl_3$–$NaBH_4$ chemoselective reduction of enones *vs* ketones in MeOH[9] or the titanium-based system of Reetz,[10] the thallium-mediated reaction does not appear to proceed *via* selective protection of the most reactive carbonyl.

(9) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 628.

(10) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259.

(11) We have previously shown that thallium ate complexes were generated under these conditions (−40 °C).[6] They were reacted with cyclohexenone and found to give smoothly the 1,4-addition product. At higher temperature, equilibration between the ate complex and its components (Me_3Tl and MeLi) took place, resulting in the formation of some 1,2-addition product. The amount of 1,2-addition product increases with temperature, eventually reaching a value similar to that obtained using MeLi itself. That MeLi is responsible for the formation of the 1,2-addition product is inferred by the lack of reactivity of Me_3Tl toward enones. Some thallium ate complexes containing acetylene ligands have been prepared previously: Nast, R.; Kab, K. *J. Organomet. Chem.* **1966**, *6*, 456.

(12) Inverse addition proved to be a key observation in the optimization of this reaction. By adding an equimolar mixture of benzalacetone and 1-phenyl-3-butanone to the preformed ate complex, a 5:1 ratio was observed instead of the 40:1 ratio obtained using an inverse addition technique.

(13) A transient yellow coloration is noticed in almost all these reactions. This color disappears when the ate complex is completely consumed.

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are unselective (e.g., MeLi and MeMgI, ratio ~ 1:1). Titanium-based reagents somewhat parallel the thallium preference for enones *versus* ketones but are poorly selective, providing, for example, a ratio of 78:22 in the case of benzalacetone/1-phenyl-3-butanone (as compared to 40:1 using $LiMe_4Tl$, entry 4).

The fact that electronic rather than steric factors are playing a key role is clearly illustrated by the examples involving substituted aromatics, displayed in Table I, entry 6. Indeed, whereas a 15:1 ratio is obtained in the competition reaction between acetophenone and cyclohexyl methyl ketone (entry 6a), no selectivity is observed when a *p*-methoxy group is present on the aromatic nucleus (entry 6b). *In sharp contrast, when the aromatic ring is substituted by an electron-withdrawing group, the selectivity is almost exclusively in favor of the conjugated ketone* (entry 6c).

Although the origin of the reverse chemoselectivity displayed by the thallium reagents is not clearly understood at present, several mechanistic features are worth noting. The results depicted in entries 6a, 6b, and 6c argue against a reaction mechanism involving the preferential coordination of the thallium reagent to the more electron-rich carbonyl of the aromatic ketones or that of the enones. Indeed, if coordination is responsible for the preferential attack at the conjugated carbonyl, the expected chemoselectivity of the reaction with substituted aromatics should be reversed, with the highest ratio being obtained with the *p*-methoxy derivative and the lowest with the *p*-cyano system.[14]

The reactivity of tetraorganothallium ate complexes is also fundamentally different from that of the analogous cuprate reagents (for example, acetylenic ligands are transferred selectively over any other group when bound to Tl but act as "dummy" ligands when attached to Cu), and an initial π-complex is unlikely.

From the data collected in Table I, it appears that the chemoselectivity of the reaction increases as the reduction potential of the enone substrate decreases.[15] As a rationale, we would like to propose that a single-electron-transfer (SET) mechanism might operate, as shown in Figure 2.

Thus, the tetraorganothallium ate complex **5** could transfer an electron to the enone **1**, forming the radical anion **7** and the unusual thallium(IV) complex **6**.[16] A rapid recombination of these two species, probably in a solvent cage, will then take place, leading to trimethylthallium **8**[17] and the lithium alkoxide **9**, which

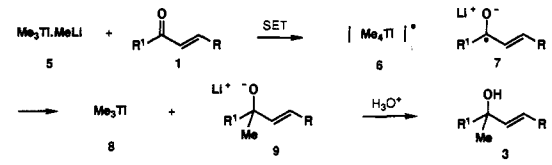

Figure 2.

is hydrolyzed to **3** during workup. Further experiments are currently underway to investigate the validity of this mechanistic hypothesis.

In conclusion, we have shown that TOT ate complexes add with high preference to the carbonyl function of enones in the presence of the corresponding saturated ketones.[18] This unusual chemoselectivity should find interesting synthetic applications. Further studies aimed at improving the selectivity and delineating the scope of this reaction are currently under active investigation in our laboratory and will be reported in due course.

CAUTION: Thallium and its derivatives are toxic. Appropriate care should be taken during their handling and in their disposal.[1]

Acknowledgment. Financial support by the Science and Engineering Research Council (SERC) is gratefully acknowledged.

(14) Indeed, a *p*-methoxy group increases the electron density on the carbonyl oxygen and should enhance binding to the metal complex. The exact opposite should result with the powerful electron-withdrawing *p*-cyano group.

(15) House, H. O.; Huber, L. E.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 8471. It is interesting to compare the measured reduction potential of the respective enone substrates with the selectivity ratio observed in the competition reaction using the TOT ate complex: $CH_3CH{=}CHCOCH_3$ ($E_{1/2}$ = −2.08 V; UA/SA = 5:1), $PhCH{=}CHCOCH_3$ ($E_{1/2}$ = −1.64 V; UA/SA = 40: 1), and PhCH=CHCOPh ($E_{1/2}$ = −1.41 V; UA/SA = 75:1).

(16) We have not yet been able to detect the intermediate Tl(IV) species. EPR studies and radical trapping experiments are currently underway in our laboratory in an attempt to establish its existence.

(17) This compound may actually exist as the alkoxy ate complex: $Me_3Tl{\cdot}ROLi$. Indeed, we have found that such species were obtained when lithium alkoxides were added to TOT derivatives. They also react slowly with aldehydes and ketones. Such a side reaction may result in a lower allylic alcohol/saturated alcohol ratio under uncontrolled conditions.

(18) Typical experimental procedure (entry 4): In a flamed-dried (100 mL) three-necked round-bottomed flask, maintained under a positive pressure of argon, were placed 500 mg of Me_2TlCl (1.86 mmol) and 30 mL of anhydrous ether. To the stirred white suspension was added MeLi (1.2 mL, 1.6 M solution in ether, 1.86 mmol) dropwise at room temperature. The white solid disappeared gradually upon addition, giving a slightly turbid solution which was cooled to −40 °C. After the mixture was stirred at −40 °C for 10 min, a further equivalent of MeLi (1.2 mL, 1.6 M solution in ether, 1.86 mmol) was added, and the resulting "ate" complex was maintained at −40 °C for 1 h. After being cooled to −50 °C, the "ate" complex solution was transferred *via* a cooled (crushed dry ice) double-ended needle to a cold (−50 °C) ether solution (20 mL) of benzalacetone **1** (R = Ph, R^1 = Me, 272 mg, 1.86 mmol) and 1-phenyl-3-butanone **2** (R = Ph, R^1 = Me, 275 mg, 1.86 mmol). The reaction mixture was stirred at −50 °C for 1 h and then hydrolyzed by the addition of 20 mL of a 2 M aqueous HCl solution. Me_2TlCl precipitated immediately. The mixture was filtered, the organic layer separated and dried ($MgSO_4$), and the solvent removed *in vacuo*, giving 490 mg (84%) of a colorless oil containing the two alcohols and the starting ketone (1-phenyl-3-butanone). ^1H NMR analysis revealed a 40:1 ratio of unsaturated alcohol:saturated alcohol. Allylic alcohol **3** (R = Ph, R^1 = Me): IR (neat) 3376, 3027, 2973, 1494, 1448, 1375, 1361, 1150, 969 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (6H, s), 1.97 (1H, s), 6.34 (2H, d, J = 16.1 Hz), 6.58 (2H, d, J = 16.1 Hz), 7.15–7.40 (5H, m); ^{13}C NMR ($CDCl_3$) δ 29.75, 70.93, 126.27, 126.34, 127.32, 128.49, 136.89, 137.51; MS m/z (EI) 162 (M^+), 147, 129, 91. Tertiary alcohol **4** (R = Ph, R^1 = Me): IR (neat) 3379, 3027, 2970, 1495, 1455, 1378, 1365, 1212, 1152, 927 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (6H, s), 1.57 (1H, s), 1.74–1.82 (2H, m), 2.65–2.74 (2H, m), 7.12–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ 29.21, 30.67, 45.65, 70.79, 125.68, 128.27, 128.35, 142.51; MS m/z (EI) 164 (M^+), 149, 146, 131, 91.