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UNPRECEDENTED *GAMMA*-SELECTIVE MICHAEL ADDITION OF TIN(II) DIENOLATES TO ACYCLIC α,β-UNSATURATED KETONES

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Tin(II) dienolates were found to react exclusively at the *gamma* carbon with acyclic α,β-unsaturated ketones in the Michael sense. Either acyclic 1,7-diketones or 2-cyclohexenol derivatives could be obtained in moderate to excellent yields by appropriate choice of reaction parameters. Moreover, in the latter case, only a *single* cyclohexenol adduct was afforded.

It has been well established that enolate anions, notably lithium enolates, of α,β-unsaturated carbonyl compounds react predominantly at the *alpha* carbon.[1,2] Because, in certain cases, *gamma*-substituted products would be of synthetic value, several methods have been devised to direct *gamma* addition. Notably, since it was first reported from this laboratory that 1-trimethylsilyoxybutadiene reacts with acetal exclusively from the *gamma* position in the presence of Lewis acid catalyst,[3] a series of silicon-directing *gamma*-substitution reactions with a variety of electrophiles has been reported.[4]

Surprisingly, the *gamma*-selective addition of dienolates to Michael acceptors[5] has virtually been unexplored even though such a reaction may be of important synthetic, as well as theoretical, value. Maruyama and coworkers[6] in their synthetic efforts directed toward the synthesis of pyranonaphthoquinones employed an α-silyl β,γ-unsaturated ester as a dienolate anion equivalent of crotonic acid for directing *gamma*-selective Michael addition. Kraus[7] has also reported that treatment of 1-trimethylsilyloxybutadiene with butyllithium followed by treatment with α,β-unsaturated carbonyl compound gave an annulation product, albeit in poor yield. This intriguing reaction was speculated to arise from reversible Michael addition in which the observed product represents the most stable one. However, a metal-assisted Diels-Alder reaction cannot be disregarded.

During the course of our studies on the scope and limitation of tin(II) enolate chemistry,[8] we deemed it worthy to investigate the reactivity and regiochemistry of tin(II) dienolates.[9] And, in this communication we wish to disclose our preliminary findings on the reaction of tin(II) dienolates with α,β-unsaturated ketones.

In the first place, to the tin(II) dienolate of 2,2-dimethyl-5-hexen-3-one, generated by standard procedure at -45 °C in dichloromethane, was added 1-phenyl-

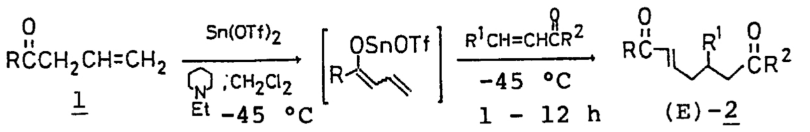

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Table 1. Selective preparation of trans-olefinic 1,7-diketones[a)]

Entry	R	α,β-Unsaturated ketone	Yield of 2/%[b)]
1	^{t}Bu	(E)-PhC(O)CH=CHCH$_3$ (3)	83
2		MVK[c)]	75[d)]
3		(E)-PhC(O)CH=CHPh	81
4		(E,E)-PhC(O)CH=CHCH=CHPh	71
5		cyclohexenone	-
6	^{i}Pr	3	72
7		MVK[c)]	55[d,e)]
8	Et	3	60[e)]
9		MVK[c)]	38[d,e)]

Molar ratio of Sn(OTf)$_2$: N-ethylpiperidine : 1 : α,β-unsaturated ketone = 1.1 : 1.2 : 1.0 : 0.9.
a) Only the trans-isomer (J = 16 Hz) was obtained. b) Isolated yield. All products gave satisfactory spectral data. c) Methyl vinyl ketone. d) Reaction was conducted at -78 °C. e) Enolization was performed at -78 °C.

2-buten-1-one (3). Aqueous work-up of the reaction mixture revealed that the trans-olefinic 1,7-diketone 2 (J = 16 Hz) had been afforded as the only isolable product in 83% yield (Table 1, entry 1). This result represents unprecedented Michael addition of the tin(II) dienolate exclusively from the *gamma* carbon; no *alpha* Michael addition product or 1,2-addition products were detected. Next, the reaction of a number of readily available α,β-unsaturated ketones with a series of tin(II) dienolates, derived from the corresponding β,γ-unsaturated ketones,[10)] was examined and the results are summarized in Table 1.

As can be seen from the results recorded in Table 1, with the exception of cyclohexenone (entry 5), in all examples examined a smooth reaction proceeds to give exclusively the 1,7-diketone 2 in moderate to excellent yields via *gamma*-selective 1,4-conjugate addition of the tin(II) dienolate to the α,β-unsaturated ketone. Although not entirely clear at this stage, preliminary investigations support that product formation is purely kinetic and not a result of Michael addition reversibility.

Scrutinization of the present reaction pathway suggests that *gamma*-selective addition of the tin(II) dienolate to the α,β-unsaturated ketone should regenerate an intermediate tin(II) enolate. Hence, subsequent intramolecular aldol cyclization would provide a simple step-wise route to the corresponding cyclohexenol derivatives, Diels-Alder type adducts. As a test of this postulate, examination of the reaction of the tin(II) dienolate generated from 2,2-dimethyl-5-hexen-3-one with 1-phenyl-2-buten-1-one (3) under a variety of reaction conditions

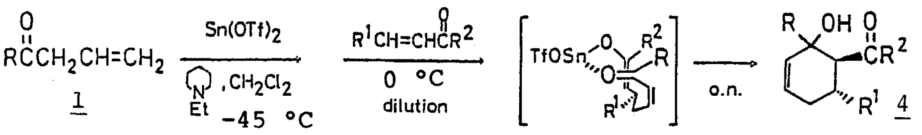

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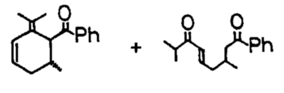
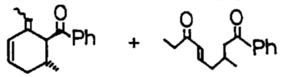
Table 2. Stereoselective preparation of cyclohexenols

Entry	Method$^{a)}$	R	α,β-Unsaturated ketone	Yield of 4$^{c)}$
1	A	^{t}Bu	3	73%
2	A	^{t}Bu	(E)-PhC(O)CH=CHPh	70%
3	A	^{t}Bu	(E,E)-PhC(O)CH=CHCH=CHPh	72%
4	A	^{i}Pr	3	 5 (25%) 6 (25%)
5	B	^{i}Pr	3$^{d)}$	5 (66%) + 6 (trace)
6	B$^{b)}$	^{i}Pr	3	5 (62%) + 6 (≈5%)
7	B	Et	3	 7$^{e)}$ (52%) 8 (trace)
8	B$^{b)}$	Et	3	7 (53%) + 8 (≈8%)

Molar ratio of $Sn(OTf)_2$: N-ethylpiperidine : 1 : α,β-unsaturated ketone = 1.1 : 1.2 : 1.0 : 0.9. Reaction was carried out at ≈0.03 mmol/ml.
a) Method A: α,β-unsaturated ketone was added at 0 °C after dilution. Method B: After addition of α,β-unsaturated ketone and stirring for ≈5 min , the reaction mixture was diluted and the temperature raised to 0 °C for 12-16 h. b) Reaction mixture was left standing for 3 d at 0 °C. c) Isolated yield. All products gave satisfactory spectral data. ^{1}H NMR and ^{13}C NMR analysis implied that 4 is a *single* isomer. d) Enolization was performed at -78 °C. e) Approximately a 57:43 isomeric mixture.

was undertaken. And, it was established that by conducting the reaction at 0 °C and at high dilution (≈ 0.03 mmol/ml), the desired cyclic adduct 4 (Eq. 2) was readily afforded in excellent yield (Table 2, entry 1).[11] Furthermore, careful analysis of the procured cyclohexenol adduct revealed that only a *single* isomer had been afforded, indicating that the reaction proceeds in a highly stereoselective manner. Other examples are listed in Table 2.

Several striking features of the abovementioned reaction are apparent on evaluation of the results in the Table. Namely, isolation of a *single* cyclohexenol adduct 4 demonstrates the remarkable stereocontrol achievable in the present reaction (entries 1,2,3,5, and 7). Concerning the relative stereochemical relationship between the three contiguous asymmetric carbons, a vicinal coupling constant of ≈12 Hz between the C-5 and C-6 protons implies a trans-pseudoaxial orientation of these two hydrogen atoms. Unfortunately the relative configuration at tertiary carbinol center could not be unambiguously determined, though preferential pseudoequatorial orientation of the alkyl substituent seems most likely. Furthermore, prolonged reaction time led to the formation of diene products (entries 6 and 8), necessarily derived from the corresponding cyclohexenols 4, in which elimination to the exo-cyclic double bond product was exclusive. This result can be explained by considering that elimination to the alternate cyclohexadiene adduct is restricted by the severe gauche interactions that would arise between the ring substituents.

Although this reaction could well be the Diels-Alder type reaction, accumulated experimental data suggests otherwise. We tentatively speculate that a step-wise mechanism is operative by which *gamma*-selective 1,4-conjugate addition to α,β-unsaturated ketone is followed by successive intramoleculare aldol-type cyclization in a highly stereoselective manner.

In summary, tin(II) dienolates were found to undergo unprecedented *gamma*-selective 1,4-conjugate addition to α,β-unsaturated ketones. Appropriate choice of reaction parameters led to the formation of either trans-olefinic 1,7-diketones or cyclohexenol derivatives at will. Furthermore, it was speculated that the *single* cyclohexenol adduct yielded arose via a step-wise mechanism with remarkable stereocontrol.

References

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6) Y. Naruta, H. Uno, and K. Maruyama, Chem. Lett., 1982, 609.

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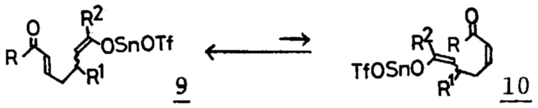
8) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984) and references cited therein.

9) Tin(II) dienolates were found to react exclusively at the *alpha* carbon with aldehydes and saturated ketones (unpublished results).

10) Initial attempts to generate the tin(II) dienolate directly from the corresponding α,β-unsaturated ketone (for example, 3) were always complicated by self-coupling reactions.

11) 1,7-Diketone (2) was isolated with trans geometry, however, the formation of the cyclic adduct (4) implies that (E)-isomer (9) and (Z)-isomer (10) are in equilibrium in the reaction mixture and that the cyclization takes place via (Z)-isomer (10).



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