

Carbanion Stabilization by Distal Silyloxy Groups. Origin of the High Diastereoselectivity in the Formation of Quaternary Centers with Aryllead(IV) Triacetate Reagents

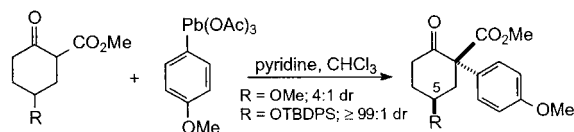
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ABSTRACT



Derivatives of methyl 5-hydroxy-2-oxo-1-cyclohexanecarboxylate react with aryllead(IV) reagents in high yield and with wide variation in diastereoselectivity. *Ab initio* calculations are consistent with a heretofore unrecognized attraction between the carbanionic center of the β -ketoester intermediate and the distal OSiR₃ group. This attractive interaction stabilizes the silyl group in the axial conformation and leads to the excellent *trans* diastereoselection in the formation of quaternary centers.

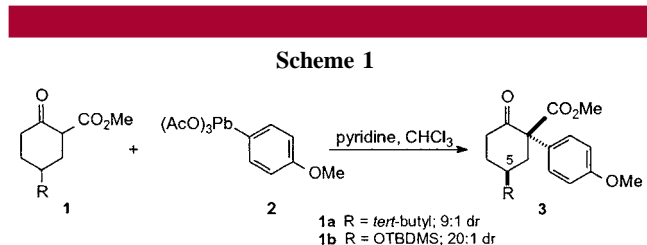
Steric effects dominate the conformational analysis and reactivity of substituted neutral six-membered ring systems. However, studies by Nagao et al.¹ and Woerpel and co-workers² have established dominant stereoelectronic effects in the conformational preferences of 4-silyloxycyclohexanones and 4-alkoxy-1-oxocarbenium ions, respectively, resulting in a pseudoaxial orientation of the C-4 substituent, which greatly affects reaction stereochemistry. Herein we present synthetic and computational evidence to suggest that a conceptually similar and heretofore unrecognized interaction between a β -ketoester anion and a distal OSiR₃ group in arylation reactions mediated by aryllead(IV) triacetate reagents³ accounts for the exceptional stereoselectivity in the formation of quaternary centers⁴ under very mild conditions.

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(2) Romero, J. A. O.; Tabacco, S. A.; Woerpel, K. A. J. *Am. Chem. Soc.* **2000**, *122*, 168–169.

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The diastereoselectivity difference between compounds **1a** and **1b** in reactions with **2** (Scheme 1⁵) were of particular



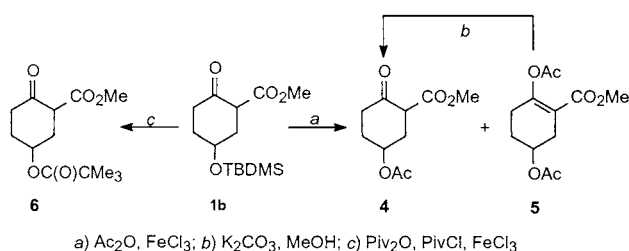
interest, since conventional conformational energies (“A values”)^{6,7} and mechanistic analysis⁷ suggest that the “larger” *tert*-butyl substituent should have afforded higher selectivity

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in the C–C bond formation reaction. Since our previous work suggested that C-5 alkyl substituents behaved in the predicted manner, we focused our attention on the preparation and reaction of a series of methyl 5-hydroxy-2-oxo-1-cyclohexanecarboxylate derivatives.

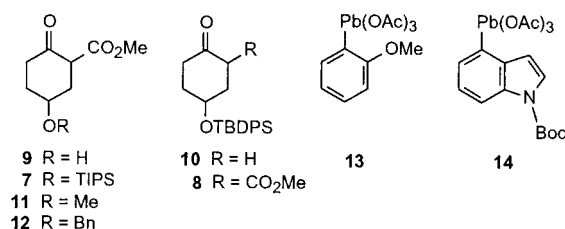
The production of these compounds, while not difficult, was surprisingly diverse. Acetate **4** was obtained by treatment of **1b** with Ac₂O in the presence of a catalytic amount of FeCl₃·6H₂O⁸ to produce a mixture of the desired β-ketoester and the corresponding enol carboxylate product **5**. The latter could be converted easily to desired product by mild base treatment, affording an overall yield of 89%. Pivalate **6** was prepared in an analogous procedure in 96% yield from **1b**; in this case, the corresponding enol carboxylate was not formed (Scheme 2).

Scheme 2



Silyl protected compounds **7** and **8** were prepared by slightly different routes (Scheme 3). Compound **1b** was

Scheme 3



treated with 1% HCl in EtOH to afford the corresponding 5-hydroxyl compound **9** in 88% yield, which was subjected to TIPSCl/imidazole to give **7** in 95% yield. Conversely, the synthesis of **8** evolved from the reaction of known ketone **10**⁹ with NaH/dimethyl carbonate. Ethers **11** and **12** were prepared from 4-hydroxycyclohexanone. Ketal formation preceded alkylation of the free hydroxyl group.⁹ Ketal removal and carbomethoxy group installation completed the synthesis.

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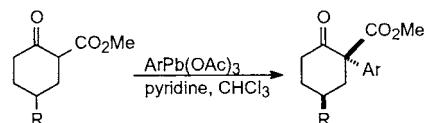
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Table 1. Arylation Results for 5-Substituted β-Ketoesters



β-ketoester (R)	ArPb(OAc) ₃	product, % yield	dr ^e	–ΔG ^f (kcal/mol)
1a (<i>tert</i> -butyl) ^{a,b}	2	3a , 96	9:1	4.7
1b (OTBDMS) ^{a,b}	2	3b , 97	20:1	1.06
1b (OTBDMS) ^a	13	15 , 98	30:1	1.06
1b (OTBDMS) ^c	14	16 , 98	30:1	1.06
4 (OAc) ^d	2	17 , 64	4:1	0.68
6 (OPiv) ^d	2	18 , 68	6:1	
7 (OTIPS) ^d	2	19 , 92	15:1	0.94
8 (OTBDPS) ^d	2	20 , 95	>99:1	0.56
11 (OMe) ^d	2	21 , 96	4:1	0.55–0.75
12 (OBn) ^d	2	22 , 85	6:1	

^a Reactions consisted of 1 mmol of β-ketoester, 1.4 mmol of aryllead(IV) reagent, and 3.3 mmol of pyridine at RT. ^b Taken from ref 5. ^c Taken from ref 12. ^d Reactions consisted of 1 mmol of β-ketoester, 1.4 mmol of aryllead(IV) reagent, and 4.5 mmol of pyridine at 40 °C. ^e dr = diastereomer ratio. ^f Taken from refs 6 and 7.

Table 1 gives the results of reactions between the series of β-ketoesters and aryllead(IV) reagents **2**,¹⁰ **13**,¹¹ and **14**.¹² The presence of acetate, pivalate, carbon ethers, or the *tert*-butyl group at the C-5 position produces modest selectivities. Compound **1a** is the most selective of this group, as would be expected due to its large A value. Conversely, a 5-OSiR₃ group affords very high stereoselectivity and the results do not correlate with the published A values. Variations in selectivity can be seen with changes in aryllead(IV) reagent (**13** and **14** are more selective than **2** in reaction with **1b**) and in the identity of the silyloxy substituent (**8** > **1b** > **7**). In all cases, the major product was determined to have a *trans* relationship between the aryl group and the C5 proton, both of which are axial substituents.⁵

A computational study was undertaken to understand the interaction, if any, between the 5-OSiR₃ group and the β-ketoester anion that could account for these results. We selected the 5-OSiH₃ group (i.e., **23**) as a model for the silyloxy-substituted anions employed in our synthetic work and performed a complementary series of calculations on the anion formed from **11** (5-OCH₃) for comparison. Three conformations of each anion were considered: a C-5 group as an axial substituent with rotation toward the carbanion (axial-endo conformer), a C-5 group as an axial substituent with rotation away from the carbanion (axial-exo conformer), and a C-5 group as an equatorial substituent on the carbanion (equatorial). Selected results are shown in Table 2; full results are available in Supporting Information.

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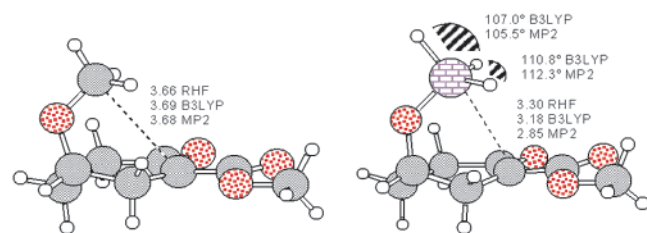
Table 2. Computed Conformational Energies for Anions **11** and **23**^{a,b}

carbanion	calculation	axial-endo	axial-exo	equatorial
11	6-31+G(d,p)	0.00	-0.9	-5.1
	B3LYP	0.00	-0.2	-5.0
	MP2 ^c	0.00	+1.64	-3.3
	MP3//MP2 ^d	0.00	+1.12	-4.0
23	6-31+G(d,p)	0.00	+1.3 (+4.4)	-1.6 (+1.2)
	B3LYP	0.00	+1.5 (+5.0)	-0.94 (+2.4)
	MP2 ^c	0.00	+5.8	+2.4
	MP3//MP2 ^d	0.00	+4.7	+2.2

^a Values are in kcal/mol. ^b Values in parentheses are for the MP2 wave function computed at the optimized geometry for that row; i.e., MP2//RHF or MP2//B3LYP. ^c Insufficient disk space to compute the MP2 frequencies; the B3LYP values were used. ^d MP3 wave function calculated at the MP2/6-31+G(d,p) geometry.

Our basic calculations¹³ (first two rows for each compound) are consistent with positive A values⁷ for the silyloxy and methoxy groups. The equatorial conformer in anion **23** is lower in energy by 1.6 kcal/mol (RHF) to 0.94 kcal/mol (B3LYP); the observed value for a neutral system is 0.74 kcal/mol for -OSiMe₃. These computed values are enthalpy differences: $\Delta H = \Delta E_{\text{elec}} + \Delta zpe + \Delta C_{\text{vib}}T$ with both the zero-point energy (zpe) and vibrational heat capacity appropriately scaled.¹⁴ However, the axial-endo conformation in **23**, with the silyloxy oriented toward the carbanion, is the lowest in energy when the effects of polarization are fully developed in the Moller-Plesset method for electron correlation. These effects are clearly evident at both the MP2 and MP3 levels of calculation. By contrast, the calculations on the carbanion of **11** at this level show no change in the dominant conformation.

Figure 1 depicts the computed axial-endo conformation for both anions. For **11**, the distance between the anionic

**Figure 1.** Calculated structures of the carbanions formed from **11** (left) and **23** (right) showing distances (Å) between the carbanionic carbon and the methyl or silyl group. For **23**, geometries around the silicon atom are also given. (Carbon, gray; oxygen, red; silicon, blue; hydrogen, white.)

center and the carbon of the C-5 substituent is invariant with computational method. Anion **23**, on the other hand, shows significant variation in distance for the silicon atom to the anionic center. In addition, the angles around the silicon atom suggest partial rehybridization toward pentacoordinate geometry.

The atomic and group charges do not change from one computational method to another. We conclude that the polarization of the silyl group allows for favorable intramolecular stabilization of the carbanionic charge. Thus, 5-OSiR₃ compounds react through a unique ring conformation in which the axial C-5 substituent effectively blocks the cis face of the β -ketoester anion, directing the electrophilic lead(IV) reagent more dramatically toward trans product formation than would be expected through the normal mechanism. Larger alkyl groups on the silicon atom afford increasing blockage and selectivity (**8** vs **1b**) until the size of the alkyl groups precludes close contact with the anionic center. We believe that this is the origin of the lower selectivity of **7**, which bears the very large OTIPS group.¹⁵

The delocalized nature of a β -ketoester anion is well-known. However, charge must be localized on carbon at the transition state for the reaction to proceed. Bernasconi and Wenzel¹⁶ have shown that this localization of charge raises the TS energy above that of the delocalized anion. We interpret the MP3//MP2 results as a favorable interaction between the diffuse silicon atom and the carbanion, providing stabilization via orbital interactions that compensate for the destabilization of the transition state due to charge localization.

In conclusion, aryllead(IV) tricarboxylates have been shown to be effective arylation agents for the formation of sp²-sp³ bonds with a variety of carbon acids. The present study indicates that extremely high and predictable diastereoselectivity (>99:1) in the formation of highly functionalized quaternary centers can be achieved under mild conditions, providing new opportunities for stereoselective synthesis. Computational data suggest that the origin of this selectivity is a stabilizing effect between the carbanionic center of the β -ketoesters and a distal OSiR₃ group. Further studies with aryllead(IV) reagents are ongoing in our laboratory and will be reported in due course.

Acknowledgment. We wish to thank NSF (CDA-9724237) for funding the purchase of computer facilities.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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