The synthetic approach described herein, which provides a practical route to **2**, also appears well suited to the synthesis of key metabolites of thromboxane $A_2$, with the inclusion of a Baeyer–Villiger oxidation in the multistep process.[15,16]

**Supplementary Material Available:** Listing of IR, NMR, and mass spectral data for the intermediates in this synthesis (7 pages). Ordering information is given on any current masthead page.

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(15) We are indebted to Dr. Robert A. Lewis of the Harvard Medical School for drawing our attention to this problem and for collaboration on the immunoassay study.

(16) This work was supported in part by grants from the National Institutes of Health and the National Science Foundation.

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## Synthetic Applications of Titanocene Methylene Complexes: Selective Formation of Ketone Enolates and Their Reactions

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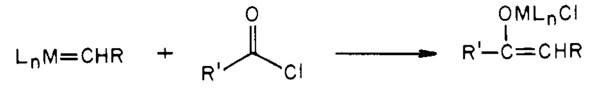
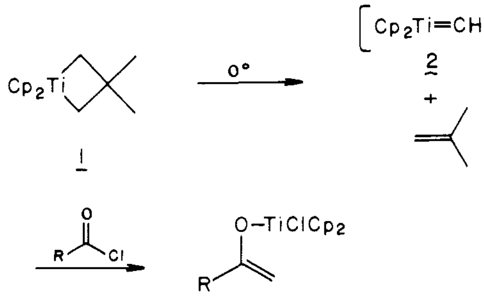
Over the past few years, the development of organo–transition-metal chemistry has provided new methods to solve classic problems in organic synthesis. One important development has been the use of group 4 enolates to control aldol stereochemistry;[1] however, their use is limited by the inability in many cases to form the enolate desired selectively. We report here a solution of the problem of regioselective enolate formation.

Early-transition-metal alkylidene complexes react with acid chlorides[2] to yield the corresponding enolate complex (eq 1). The enolate is formed instead of the vinyl chloride expected as the product of Wittig-type chemistry.[3] The easily generated titanocene methylidene complex (**2**, eq 2) gives an excellent entry into the most useful enolates, those of methyl ketones, which we have found to be of utility in synthetic reactions. This regiospecific synthesis of stable enolates avoids many of the problems of standard approaches.[4]



(1)



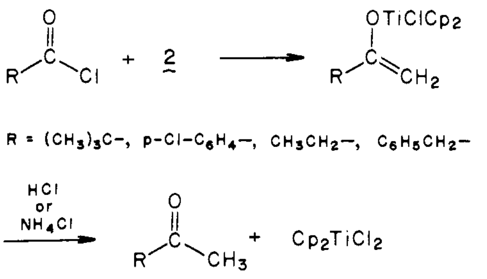
(2)

Table I.

| RC(O)Cl | reaction conditions[a] 0 °C | 3 °C | 15 °C | 20 °C | $RC(O)CH_3$ yield, %[b] |
|---|---|---|---|---|---|
| benzoyl chloride | 2 | | 5 | | 92[c] |
| pivaloyl chloride | 5 | | | 75 | 96[c] |
| ethyl chloroformate | 5 | | | 15 | 48[c] |
| ethylsuccinyl chloride | 5 | 6 | | | 89[c] |
| phenylacetyl chloride | 5 | 45 | | | 97[c] |
| 3-phenylpropionyl chloride | 5 | 45 | | | 87[d] |
| 1-naphthoyl chloride | 3 | | 5 | | 92[d] |
| 5 | 10 | 45 | | | 76[e] |

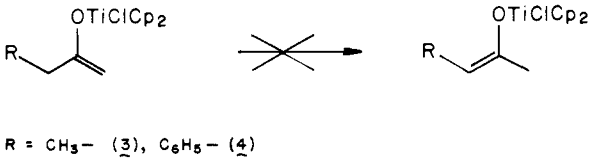
[a] The numbers reported for each acid chloride are the times, in minutes, that the reaction was allowed to stir first at 0 °C and then at a second, higher temperature. [b] Based on the amount of acid chloride added.[9] [c] Yield was determined by quantitative VPC analysis. Product was characterized by VPC and $^1$H NMR comparison with an authentic sample. [d] Yield of isolated product from 1 mmol of acid chloride. Product was characterized by $^1$H and $^{13}$C NMR comparison with an authentic sample. [e] Yield of isolated product from 1 mmol of acid chloride. The reaction was quenched with saturated aqueous $NH_4Cl$. Product was characterized by $^1$H NMR, $^{13}$C NMR, and IR spectroscopy in addition to comparison with an independently synthesized sample. The product produced satisfactory C,H analysis.

The titanium methylidene complex is generated in situ from its aluminum dimethyl chloride,[3] olefin, acetylene, or phosphine adducts. For the applications below, the labile titanocyclobutane **1**, prepared from isobutylene is the most useful.[5] This reaction (eq 2) produces the enolates suitable for isolation with >95% conversion of **1** in the presence of a 50% excess of acid chloride. Other methylene sources such as the Tebbe reagent/pyridine[6] or adducts which require elevated temperatures[5] for the generation of **2**, result in substantially lower yields. Stable enolates can be isolated and characterized by spectroscopic and chemical methods (eq 3).[7]



(3)

Of particular importance is the lack of isomerization of **3** and **4** to their more stable isomers (eq 4). The regiostability of these complexes is further demonstrated by the conversion of an optically active acid chloride to the corresponding methyl ketone with ≤0.5% epimerization (eq 5).[8]



(4)

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(5) Grubbs, R. H.; Straus, D. A. *Organometallics* **1982**, *1*, 1658. This complex and related metallacycles are easily prepared from commercially available $Cp_2TiCH_2AlMe_2Cl$.

(6) Use of the Tebbe reagent ($Cp_2TiCH_2AlMe_2Cl$) results in substantially lower yields (20%), since the aluminum byproducts induce decomposition of the enolate.

(7) All four isolated enolates are in complete agreement with the spectroscopic data. Representative spectroscopic data, that of **4** are as follows: $^1$H NMR ($CD_2Cl_2$, −30 °C) δ 3.27 (s, 2 H), 3.85 (s, 1 H), 3.96 (s, 1 H), 6.20 (s, 10 H), 7.31 (m, 5 H); $^{13}$C NMR ($CD_2Cl_2$, −30 °C) δ 43.4 ($CH_2$), 87.4 ($=CH_2$), 117.2 (Cp), 126.3 (Ph), 128.3 (Ph), 129.4 (Ph), 139.0 (Ph), 173.2 ($=C-O$).

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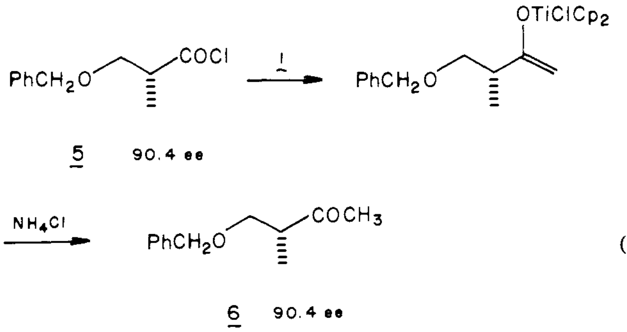


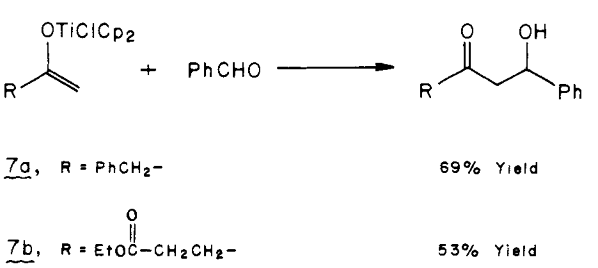
5 90.4 ee

6 90.4 ee

(5)

The optimum conditions for enolate formation with the acid chloride as the limiting reagent were determined by hydrolysis to the methyl ketone without prior isolation.[9] It is evident from Table I that the yields of ketone enolates are near 90% even with a bulky $\alpha$-carbon or potentially reactive functionality present in the molecule.

These enolates undergo standard enolate reactions such as aldol condensation.[10] The reaction of the phenylacetone enolate, **7a**, with benzaldehyde demonstrates the regiostability of the enolate under the reaction conditions. A second example, **7b**, illustrates the selectivity of the reaction when another carbonyl functionality is present. The major byproduct of these reactions is the methyl ketone resulting from protonation of the enolate. In view of the recent development of methods for the synthesis of substituted alkylidenes,[12] this reaction provides a general new tool for organic synthesis.



(6)

7a, $\mathrm{R = PhCH_2-}$ 69% Yield

7b, $\mathrm{R = EtO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{-CH_2CH_2-}$ 53% Yield

**Acknowledgment.** We acknowledge the support of the National Science Foundation and helpful discussions of D. A. Evans.

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(8) The chiral carboxylic acid was obtained 99.2% optically pure from D. J. Mathre and D. A. Evans. The conversion to **5** by oxalyl chloride proceeded with slight epimerization resulting in 95.2% optically pure acid chloride. This was quantified by reaction with the lithium salt of (4*S*)-4-(2-propyl)oxazolidin-2-one and analysis of the resulting diastereomeric mixture by capillary gas chromatography. With correction for the enantiomeric impurity of the acid chloride, the methyl ketone produced an optical rotation $[\alpha]^{25}_{D}$ −19.3 (31 mg/mL). This is identical with that of an independently synthesized sample of the methyl ketone using the $(CH_3)_2CuLi$ reagent, shown not to epimerize the $\alpha$ chiral center of an acid chloride, and the procedure obtained from Posner et al. (Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106).

(9) Typically, 1.2 equiv of **1** was cooled to −20 °C and dissolved (0.4 M solution) in precooled toluene with stirring. The acid chloride was added via syringe, and the mixture was warmed to 0 °C. At this temperature, **1** dissociates into **2** and isobutylene, allowing the reaction to occur. After a short time, as recorded in Table I, the mixture was warmed to a higher temperature to ensure completion of the reaction. Hydrolysis was achieved by cooling the solution to −10 °C and introducing 1.5 equiv of HCl gas into the reaction vessel via syringe. All titanium precipitated from solution as titanocene dichloride. The supernatant was then removed for VPC analysis or isolation of the methyl ketone by silica gel chromatography.

(10) Yield of isolated product based on 1 mmol of acid chloride used for in situ formation of the enolate. Products were characterized by $^1$H NMR, $^{13}$C NMR, IR, and C,H analysis. The aldol product (67% yield), starting from pivaloyl chloride and pivaldehyde, was identified by comparison to literature spectra.[11]

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# Aryl Isomerization during Aliphatic CH Bond Activation

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The transition-metal-stabilized benzyne or *o*-phenylene ($\eta^2$-$C_6H_4$) ligand has been shown to be both an interesting and reactive group.[1-7] The ligand is normally generated in mononuclear systems by $\beta$- (ortho-) hydrogen abstraction from an aryl group, and this synthetic approach has allowed a stable example to be isolated and structurally characterized.[8]

We report here our conclusive identification of a benzyne intermediate during the isomerization of a tantalum–aryl compound. The reaction is interesting in that the ortho hydrogen is transferred to the carbon atom of a cyclometalated chelate, the reverse (isomerization) step thus involving the activation of an aliphatic CH bond by the intermediate benzyne.

We recently reported that alkylation of $Ta(OAr')_2Cl_3$ (I) (OAr′ = 2,6-di-*tert*-butylphenoxide) with LiPh (3 equiv) leads to the room-temperature formation of $Ta(OC_6H_3\text{-}t\text{-}BuCMe_2CH_2)(OAr')(Ph)_2$ (II), in which one of the CH bonds of a *tert*-butyl group has been activated and cleaved.[9] Thermolysis of II (120 °C/toluene) leads to the loss of benzene and formation of $Ta(OC_6H_3\text{-}t\text{-}BuCMe_2CH_2)_2(Ph)$ (III), in which a further CH bond activation has taken place.[9] We have extended this chemistry to the use of the three tolyllithium reagents and have obtained the results shown in Table I.[10] The three products obtained at room temperature, IIo, IIm, and IIp, can be shown by $^1$H NMR spectroscopy to be isomerically pure (>98%). However, the product of thermolysis of these compounds at 125 °C are mixtures of IIIm and IIIp. Hence, isomerization of the tolyl groups is taking place during the second step of the reaction. A possible pathway

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(10) The three isomeric tolyllithium reagents were synthesized from the corresponding bromotoluene and *n*-butyllithium in hexane/toluene. The compounds $Ta(OC_6H_3\text{-}t\text{-}BuCMe_2CH_2)(OAr')(tol)_2$, *o*-tolyl (IIo), *m*-tolyl (IIm), and *p*-tolyl (IIp) were obtained by treating $Ta(OAr')_2Cl_3$ with the corresponding lithium salts in benzene and isolated by using the same procedures outlined in ref 9 for the synthesis of II. In the case of IIo the yield was substantially lower than for the other isomers. The $^1$H NMR spectra of the compounds showed them to be isomerically pure. In particular, the chemical shifts and pattern of the ortho protons was extremely characteristic. $^1$H NMR spectra (470 MHz, toluene-$d_8$) (IIo) $\delta$ 8.62 (d, *o*-H); (IIm) $\delta$ 7.93 (s), 7.90 (d, *o*-H's); (IIp) $\delta$ 7.95 (d, *o*-H). The aryloxide resonances were very similar to those of II; see ref 9. Thermolysis of these compounds was carried out in sealed $^1$H NMR tubes in toluene-$d_8$. Toluene was generated along with a mixture of IIIm and IIIp. No IIIo could be observed. Again, the $^1$H NMR spectrum of the mixtures is distinctive in the aromatic region, allowing a determination of the isomer ratio. $^1$H NMR spectrum (470 MHz, toluene-$d_8$) (IIIm) $\delta$ 7.97 (s), 7.95 (d, *o*-'s); (IIIp) $\delta$ 8.05 (d, *o*-H). The aliphatic chemical shifts of the metalated aryloxide ligands were very similar to those of III; see ref 9.

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