Astonishing Alkylation and Unusual Reduction Reactions of Anionic Titanium(II) Isopropoxide Complexes: Evidence for SET Processes in Transition-Metal Oxidative Additions[‡]

John J. Eisch*[a] and John N. Gitua[a]

Keywords: Titanium / Subvalent compounds / Oxidative addition / Alkylation / Electron transfer

A mixture of titanium(II) isopropoxide and lithium isopropoxide (1:2), generated in THF by the treatment of titanium(IV) isopropoxide with two equivalents of *n*-butyllithium, has been shown to be an unexpected alkylating agent as well as an unusual reducing agent for a wide variety of organic substrates. Since titanium(II) isopropoxide, which is free of any lithium isopropoxide, neither causes alkylation of any of the same substrates nor is such a powerful reductant, it is proposed that the lithium isopropoxide activates titanium(II) isopropoxide for such unusual reactions by the formation of the lithium salt coordination complex $Li_2Ti[OiPr]_4$. Illustrative of the unprecedented alkylations are the transformations, after hydrolysis, of various substituted benzonitriles to isopropyl-substituted phenyl ketones, of (dichloromethyl)benzene to, principally, 2-methyl-1-phenyl-1-propene and of (trichloromethyl)benzene to isopropyl phenyl ketone. By comparing the reducing actions of $Li_2Ti[OiPr]_4$ and $Ti[OiPr]_2$ individually, it has been shown that, generally, the lithium salt is the more powerful reductant for epoxides, benzylic halides and conjugated olefins. From the reactions of $Li_2Ti[OiPr]_4$ with the benzonitriles, styrene, the isomeric stilbene oxides and *cis*-stilbene, cogent evidence is marshaled for the operation of SET processes, sensitive to steric hindrance, in such alkylations and reductions.
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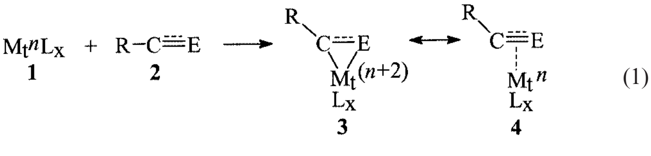
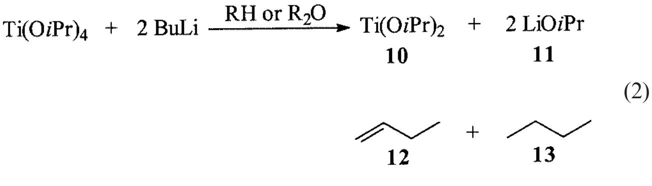
Introduction

The oxidative addition of subvalent transition metals or metal salts, $M_t^nL_x$ (**1**), where *n* is the oxidation number, to π-bonded organic substrates (**2**) with the formation of a metallacyclic intermediate (**3**) has been termed epimetallation [Equation (1)].[2]


(1)

Since metallacycle **3** is one extreme of resonance structures ranging to the other extreme of a π-complex structure **4**, the term epimetallation implies that the adduct of **1** and **2** displays chemical reactions in better accord with **3**, possessing two sigma $C-M_t$ bonds, than with **4**. The chemical behavior of **5** — the adduct of benzophenone and $Li^+CrH_2^-$ — towards D_2O[3] and towards CO_2 [2] illustrates clearly why **5** should be viewed as an oxachromacyclopropane rather than as the π-complex **6**. Were the π-complex **6** involved in the reaction with CO_2, then simple ligand displacement and reduction of CO_2 to **7** should have ensued (Scheme 1). Instead, the observed products of deuterium oxide cleavage (**8**) and of carbonation (**9**) are unambiguous proof for the presence of a C−Cr bond in **5**.

In exploring the applicability of epimetallation for organic synthesis, we have recently generated titanium(II) isopropoxide (**10**) according to Equation (2) and have employed **10** for the epimetallation of terminal alkenes, alkynes and selected carbonyl derivatives.[4]


(2)

Particularly noteworthy are the by-products formed in the production of **10**, namely lithium isopropoxide (**11**), which remains in solution regardless of whether the reaction is conducted in hexane or THF, and the one equivalent of 1-butene (**12**) which is epimetallated in situ by **10** with the formation of **14** (Scheme 2). The presence of **14** was demonstrated by its chemical trapping with benzonitrile

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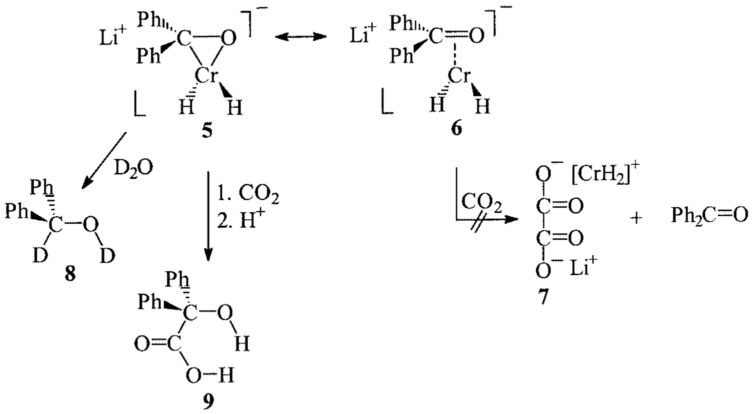
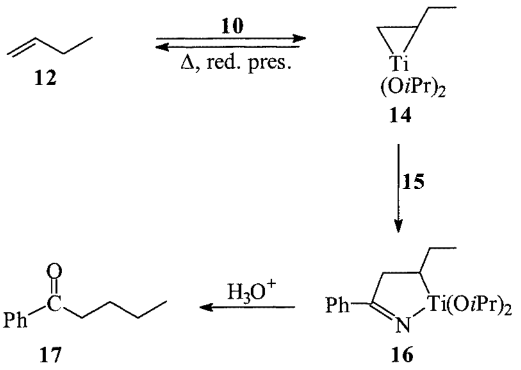
[a] Department of Chemistry, The State University of New York at Binghamton
P. O. Box 6016, Binghamton, New York 13902−6016 U.S.A.
Fax: (internat.) +1-607/777-4865
E-mail: jjeisch@binghamton.edu



Scheme 1

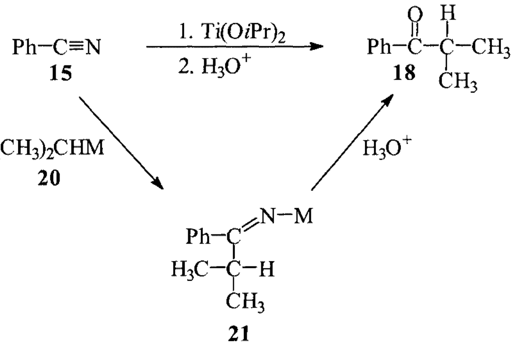
(**15**) to provide **16**, whose subsequent hydrolysis yielded *n*-butyl phenyl ketone (**17**).[4] Only if the solvent is removed by warming and reduced pressure can **14** be decomposed.



Scheme 2

Results and Discussion

In order to learn whether titanium(II) isopropoxide itself, free of any of the adduct **14**, could epimetallate benzonitrile (**15**), a solution of **10** generated in THF was freed of solvent under reduced pressure at 70°. To the black residue of **10** and **11** an equivalent of benzonitrile in toluene was then added and the solution heated at reflux. To our astonishment, upon hydrolytic workup such a reaction mixture gave 92% of isopropyl phenyl ketone (**18**) but only a small amount of **17** and a trace of 2,2-dimethyl-1,3-diphenyl-1,3-propanedione (**19**)[5] [Scheme 3, Table 1]. The formation of **18** raised the possibility that heating solutions of **10** might have produced an isopropylmetallic agent **20**, which would then have added to **15** to yield **21**, a prehydrolysis intermediate to the observed final product. That the lithium isopropoxide by-product **11** plays an essential role in this unexpected reaction was demonstrated in the following way. Recently we have reported that titanium(II) isopropoxide, free of lithium isopropoxide, can be prepared by treating titanium dichloride diisopropoxide (**22**) in hexane with two equivalents of *n*-butyllithium[6] [Equation (3)]. In this case, the lithium chloride formed is a much weaker base and more ionic salt and precipitates completely from the mixture. When this $Ti(OiPr)_2$, free of lithium isopropoxide, was heated with benzonitrile in toluene and then hydrolyzed, analogous to the reaction in Scheme 3, no trace of **18** was found whatsoever.[7] Thus, a combination of **10** and **11** is a prerequisite for the formation of isopropyl phenyl ketone (**18**) from benzonitrile (**15**).



Scheme 3

$$\underset{\mathbf{22}}{Cl_2Ti(O\mathit{i}Pr)_2} + 2\,BuLi \xrightarrow[\mathbf{-12,\,-13}]{Hexane} \underset{\mathbf{10}}{Ti(O\mathit{i}Pr)_2} + 2\,LiCl\downarrow \tag{3}$$

In establishing the role of **11** in activating **10** for this unusual reaction, it should be noted that titanium(II) salts form anionic complexes with alkali metal salts.[8] Therefore, **10** and **11** can be expected to be in equilibrium with complexes such as **23** [Equation (4)].

$$\underset{\mathbf{10}}{Ti(O\mathit{i}Pr)_2} + \underset{\mathbf{11}}{2\,LiO\mathit{i}Pr} \rightleftharpoons \underset{\mathbf{23}}{Li_2\,Ti[O\mathit{i}Pr]_4} \tag{4}$$

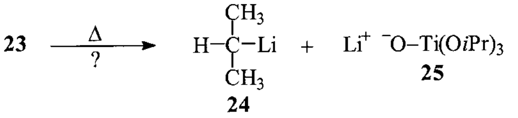
That four isopropoxyl groups can be sterically accommodated around the titanium(II) center in **23** is corroborated by the existence of stable titanium(IV) isopropoxide. One possibility for the formation of the requisite isopropyl-

Table 1. Reactions of the titanium(II) isopropoxide-lithium isopropoxide complex (23) in THF with organic substrates

Entry	Substrate[a]	Products	Yield (%)[b]
1	Benzonitrile (**15**)	Isopropyl phenyl ketone (**18**)	92
		Butyl phenyl ketone (**17**)	7
		2,2-Dimethyl-1,3-diphenyl-1,3-propanedione (**19**)	1
2	2-Methoxybenzonitrile (**26**)	Isopropyl 2-methoxybenzonitrile ketone	90
		1,3-Bis(*p*-anisyl)-2,2-dimethyl-1,3-propanedione	10
3	4-Methoxybenzonitrile (**27**)	Isopropyl 4-methoxyphenyl ketone	99
		1,3-Bis(*p*-anisyl)-2,2-dimethyl-1,3-propanedione	1
4	2,4,6-Trimethylbenzonitrile (**28**)	No Reaction	–
5	(Dichloromethyl)benzene (**29**)	2-Methyl-1-phenyl-1-propene (**30**)	40
		trans-Stilbene	16
		Benzyl chloride	32
		Isopropyl phenyl ketone	8
		1,2-Dichloro-1,2-diphenyl ethane	4
6	(trichloromethyl)benzene (**30a**)[c]	Isopropyl phenyl ketone (**18**)	64
		1,1,2,2-Tetrachloro-1,2-diphenylethane	30
		trans-1,2-Dichlorostilbene	6
7	Benzyl chloride (**31**)[d]	Dibenzyl (**40**)	97
		Toluene	3
8	9-Bromofluorene (**32**)[d]	Fluorene	55
		9,9′Bifluorenyl	45
9	4-Bromoanisole (**38**)	Anisole	40
10	*cis*-Stilbene oxide (**33**)[d]	*trans*-Stilbene (**36**)	91
		cis-Stilbene (**35**)	9
11	*trans*-Stilbene oxide (**34**)[d]	*trans*-Stilbene (**36**)	100
12	Diphenylacetylene (**37**)	*cis*-Stilbene (**35**)	30
		Dibenzyl (**40**)	5
13	*cis*-Stilbene (**35**)	*trans*-Stilbene (**36**)	35
		Dibenzyl (**40**)	25
14	*trans*-Stilbene (**36**)	Dibenzyl (**40**)	25
15	Styrene (**38**)	Polystyrene	100

[a] All reactions involved 10.0 mmol of Ti(O*i*Pr)$_2$ containing the LiO*i*Pr by-product and 5.0 mmol of the organic substrate in 40 mL of THF at 25 °C for 24 h unless otherwise specified. [b] Percent yields of products were obtained from the integrated ^{1}H NMR spectra; recovered starting substrate = 100% −% of products. [c] The reaction was conducted at reflux for 4−8 h. [d] The reaction was conducted at 25 °C for 12 h.

ating agent **20** would be an intraanionic oxidative addition that might occur upon heating **23** that would produce isopropyllithium (**24**) and the lithium salt of the titanium(IV) complex **25** [Equation (5)]. However, the fatal flaw in this proposal is that isopropyllithium is an extremely active lithium reagent that attacks ethers and is thereby destroyed, with lithium alkoxide elimination, even at 25 °C.[9] Under the reaction conditions used to prepare a mixture **10** and **11** for reaction with benzonitrile (**15**), according to Scheme 3, no isopropyllithium would have been expected to survive.



$$\mathbf{23} \xrightarrow[?]{\Delta} \underset{\mathbf{24}}{\mathrm{H{-}C(CH_3)_2{-}Li}} + \underset{\mathbf{25}}{\mathrm{Li^+\ {}^-O{-}Ti(O\mathit{i}Pr)_3}} \qquad (5)$$

The remaining possibility, therefore, is that the ionic complex **23** itself is the actual isopropylating agent for benzonitrile (**15**). In order to evaluate this hypothesis, a series of polar substrates, ranging from substituted benzonitriles through benzylic and aryl halides to epoxides and finally to aryl-conjugated acetylenes and olefins, were individually treated with lithium complex **23**, prepared according to Equation (2). The resulting products are tabulated in Table 1.

Because of the equilibrium possible between **10** and **23** [depicted in Equation (4)], it became important to ascertain which reactions reported in Table 1 are unambiguously attributable to reagent **23** and which could equally be caused by reagent **10**. To this end, titanium(II) isopropoxide, which was essentially free of lithium isopropoxide (**11**) and hence of any **23**, was generated according to Equation (3). Reagent **10** was then individually allowed to react with many of the same polar substrates, which had previously been treated with reagent **23**, and the results are listed in Table 2.

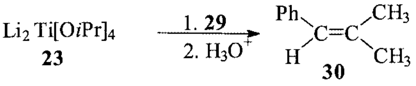
Through a comparison of the reaction products from individual substrates towards reagent **23** (Table 1) and towards reagent **10** (Table 2), the following conclusions can be reached. First of all, only reagent **23**, not reagent **10**, can introduce an isopropyl group into any of the organic substrates, as it does with benzonitriles **15**, **26** and **27** (entries 1,2,3), (dichloromethyl)benzene (**29**, entry 5) and (trichloromethyl)benzene (**30a**, entry 6 in Table 1) [cf. Scheme 3 and Equation (6) and (7)]. Secondly, with respect to the isopropylation of benzonitriles by **23**, it is most noteworthy that some substituted benzonitriles, such as the 2-methoxy (**26**, entry 2, Table 1) and 4-methoxy (**27**, entry 3) derivat-

Table 2. Reactions of the titanium(II) isopropoxide (10, free of LiOiPr) in THF with organic substrates

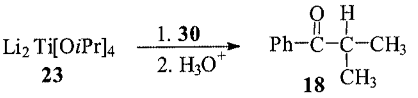
Entry	Substrate[a]	Products	Yield (%)[b]
1	Benzonitrile (**15**)	Benzyl phenyl ketone	1
		Benzaldehyde	1
2	(Dichloromethyl)benzene (**29**)	*trans*-Stilbene	84
		meso-1,2-Dichloro-1,2-diphenylethane	11
		Dibenzyl	5
3	(trichloromethyl)benzene (**30a**)	1,1,2,2-Tetrachloro-1,2-diphenylethane	92
4	Benzyl chloride (**31**)	Dibenzyl	90
		Toluene	10
5	9-Bromofluorene (**32**)	Fluorene	35
		9,9′-Bifluorenyl	65
6	4-Bromoanisole (**38**)	Anisole	95
7	*trans*-Stilbene oxide (**34**)	*trans*-Stilbene (**36**)	68
		Dibenzyl (**40**)	7
8	Diphenylacetylene (**37**)	*cis*-Stilbene (**35**)	31
		Dibenzyl (**40**)	4
9	*cis*-Stilbene (**35**)	*trans*-Stilbene (**36**)	50
		Dibenzyl (**40**)	15
10	Styrene (**38**)	Polystyrene (**42**)	95
		Ethylbenzene	5

[a] Identical reaction conditions involving titanium(II) isopropoxide, prepared according to Equation (3), as those specified in footnote [a] of Table 1. [b] The percent yields of products were obtained from the integrated ^{1}H NMR spectra; recovered starting substrate = 100% − % of products.

ives underwent the isopropylation reaction readily,[5] but the 2,6-dimethyl derivative (**28**, entry 4) did not react at all. The failure of **28** to react with **23** can readily be ascribed to steric hindrance to the close approach of **23** to the C≡N group in **28** because of the flanking CH_3 groups.



(6)

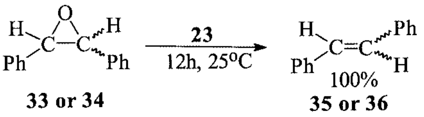


(7)

Thirdly, in those cases where no isopropylation of the organic substrate takes place, reagents **23** and **10** can effect monomolecular and bimolecular reductions, deoxygenations or dehalogenations to various degrees. Although not without exception, the results given in Table 1 and 2 indicate that reagent **23** is a more active reductant than reagent **10**. Thus in the reduction of benzyl chloride (**31**) or of 9-bromofluorene (**32**) the monomolecular and bimolecular reduction depicted in Equation (8) is complete in 12 h with **23** but requires 24 h with **10** (entries 7 and 8, Table 1, versus entries 4 and 5, Table 2). In another instance, the deoxygenation of *cis*- or *trans*-stilbene oxide (**33** or **34**) proceeds more cleanly and rapidly to the stilbenes **35** or **36** with **23** than with **10** (entries 10 and 11, Table 1, versus entry 7, Table 2; Equation (9) and (10)]. But with other substrates, such as diphenylacetylene (**37**) and the stilbenes **35** and **36**, the extent of reduction with either **23** or **10** is not markedly different. The behavior of 4-bromoanisole is anomalous in this regard, being much more readily reduced by **10** than by **23** (entry 6 in Table 2 versus entry 9 in Table 1).

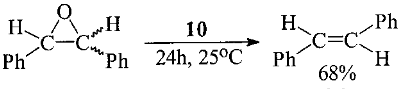
$$2\,R{-}X \xrightarrow[\textbf{23}\text{ or }\textbf{10}]{\text{THF, 25°C}} R{-}H + R{-}R \qquad (8)$$

R = Benzyl (**31**)
9-fluorenyl (**32**)



33 or 34 **35 or 36**

(9)

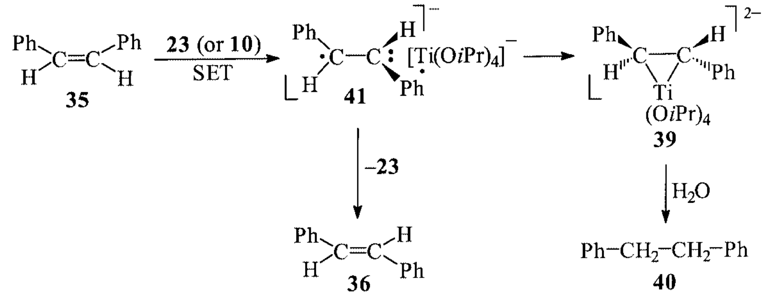


33 or 34 **36**

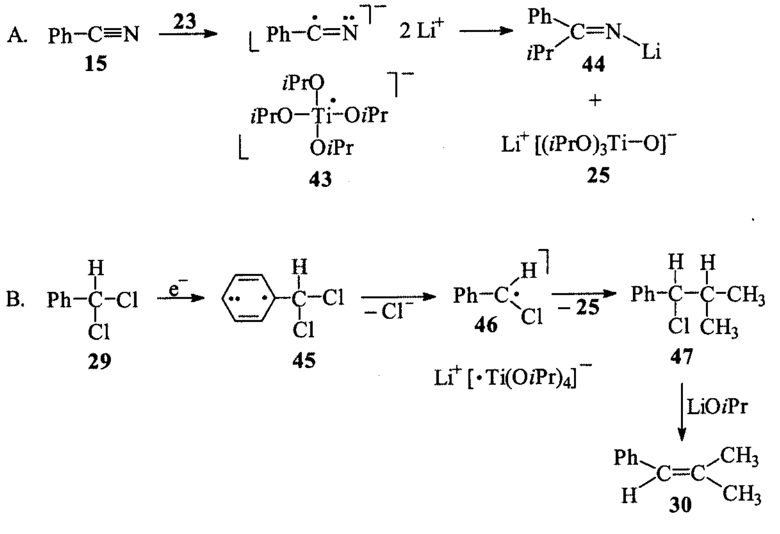
(10)

The final valuable conclusion deducible from these reductions by reagents **10** or **23** concerns their underlying mechanism of reaction. First, that *cis*-stilbene (**35**) undergoes extensive isomerization to *trans*-stilbene (**36**) in the course of epimetallation to **39** is consistent with the formation of the biradical intermediate **41** by single-electron transfer (SET). This intermediate can then either ring-close to **39** or reeliminate **23** to form the *trans*-isomer **36** (Scheme 4).[10]

Furthermore, that the *cis*- and *trans*-stilbene oxides (**33** and **34**) undergo non-stereoselective deoxygenation[11] to give chiefly *trans*-stilbene (**36**) again strongly supports an isomerizable radical ion intermediate (**42**), which can lead principally to the more stable *trans*-olefin **36** [Equation (11)]. Finally, that styrene undergoes polymerization much more rapidly than epimetallation with **23**, compared with **10**, further corroborates the superior SET donor character of **23** in forming the styrene radical-anion intermediate, crucial in such polymerization. Compelling precedents for SET mechanisms for both olefin isomerization and

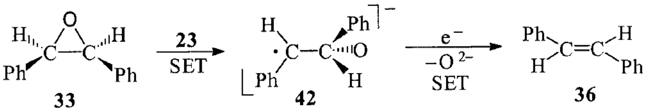


Scheme 4



Scheme 5

conjugated olefin polymerization are available in the work of Swarc and co-workers on the "living polymerizations" of diolefins by alkali metals.[12]



(11)

Conclusions

In light of the foregoing unexpected isopropylations of carbon centers and the nature and stereochemistry of many of the observed reductions, we conclude that the actual reagent in most of these reactions is dilithium tetraisopropoxytitanate(II) (**23**) and not titanium(II) isopropoxide (**10**) alone, and that such processes involve SET pathways. The mode of action of **23** as an isopropylating agent towards benzonitrile (**15**) is proposed in Scheme 5, Part A. The caged radical-anions formed by SET (**43**) can then undergo an isopropyl-radical transfer to the sterically accessible nitrile carbon to form the final adduct **44**. In Part B, (dichloromethyl)benzene (**29**) undergoes SET with **23** to form radical-anion **45**, which loses a Cl anion to form radical **46**. Radical **46** accepts an isopropyl radical from the caged Ti^{III} radical to form **47**. Simple dehydrohalogenation by LiO*i*Pr leads to the final product **30**.

In summary, a most unusual intramolecular oxidative addition of an ionic titanium(II) alkoxide (**23**), leading to a complex of titanium(IV), probably **25**, has been observed to occur with a variety of reducible organic substrates. The organic substrate undergoes either simple reduction or isopropylating reduction via pathways most likely involving SET processes.

Experimental Section

Instrumentation, Analysis and Starting Reagents: All reactions were carried out under a positive pressure of anhydrous, oxygen-free argon. All solvents employed with organometallic compounds were dried and distilled from a sodium metal-benzophenone ketyl mixture prior to use.[13] The IR spectra were recorded with a Perkin−Elmer instrument (model 457) and samples were measured either as mineral oil mulls or as KBr films. The NMR spectra (^1H and ^{13}C) were recorded with a Bruker spectrometer (model EM-360) and tetramethylsilane (Me_4Si) was used as the internal standard. The chemical shifts reported are expressed on the δ scale in parts per million (ppm) from the Me_4Si reference signal. The GC/MS measurements and analyses were performed with a Hewlett−Packard GC 5890/Hewlett−Packard 5970 mass-selectivedetector instrument. The gas chromatographic analyses were carried out with a Hewlett−Packard instrument (model 5880) provided with a 2-m OV-101 packed column or with a Hewlett−Packard instrument (model 4890) having a 30 m SE-30 capillary column. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected.

Preparation of Titanium(II) Isopropoxide (10, Free of LiO*i*Pr): *n*BuLi (1.28 g, 12.5 mL, 1.6 M solution in hexane, 20 mmol) was added slowly at −78 °C to a stirred solution of titanium(IV) chloride (1.89 g, 10 mmol) in THF (40 mL) under an argon atmosphere and the mixture stirred for 30 minutes at this temperature. Then the slow addition of isopropyl alcohol (1.20 g, 1.53 mL, 20 mmol) was performed at the same low temperature. The resulting reaction mixture was allowed to warm to 25 °C over 10 h to yield a dark brown suspension, which was then cooled to −78 °C and a further two equivalents of *n*BuLi (20 mmol) were slowly added at the same temperature. The resulting dark brown suspension was then allowed to warm to 25 °C over a 10 h period to yield a black solution of titanium(II) isopropoxide (1.66 g, 100%) from which white LiCl precipitated on standing.

Preparation of Titanium(II) Isopropoxide (23, Containing LiO*i*Pr): *n*BuLi (1.28 g, 12.5 mL, 1.6 M solution in hexane, 20 mmol) was added slowly at −78 °C to a stirred solution of titanium(IV) isopropoxide (2.84 g, 10 mmol) in THF (40 mL) under an argon atmosphere and the mixture stirred for 2 h at this temperature. The resulting light-brown reaction mixture was then allowed to warm to 25 °C over 10 h to yield a dark brown-black solution of titanium(II) isopropoxide (1.66 g, 100%).

Acknowledgments

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[1] J. J. Eisch, F. A. Owuor, P. O. Otieno, *Organometallics* **2001**, *20*, 4132−4134.

[2] J. J. Eisch, *J. Organomet. Chem.* **2000**, *617−618*, 148−157.

[3] J. J. Eisch, J. R. Alila, *Organometallics* **2000**, *19*, 1211−1213.

[4] J. J. Eisch, J. N. Gitua, P. O. Otieno, X. Shi, *J. Organomet. Chem.* **2001**, *624*, 229−238.

[5] 1,3-Diketone **19** undoubtedly arose from the lithium isopropoxide-promoted addition of isopropyl phenyl ketone (**18**) to benzonitrile (**15**). The small amounts of diketone formed from **26** and **27** (entries 2 and 3, Table 1) were probably generated in a similar manner.

[6] J. J. Eisch, F. A. Owuor, P. O. Otieno, *Organometallics* **2001**, *20*, 4132−4134.

[7] In reactions of benzonitrile with other titanium(II) derivatives, such as $TiCl_2$, considerable amounts (30%) of benzyl phenyl ketone were isolated: J. J. Eisch, X. Shi, unpublished studies.

[8] [8a] Titanium(II) chloride, for example, forms anionic complexes of the types $[TiCl_4]^{2-}$ and $[TiCl_5]^{3-}$: G. W. A. Fowler, T. E. Lester, R. A. Walton, *J. Am. Chem. Soc. A* **1968**, 1081−1085. [8b] More recently characterized anionic titanium(II) complexes include Na_2TiCl_4 (D. J. Hinz, T. Dedecke, W. Urland, G. Meyer, *Z. Anorg. Allg. Chem.* **1994**, *620*, 801−804) and $Na_2Ti_3Cl_8$ (D. J. Hinz, G. Meyer, T. Dedecke, W. Urland, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 71−73).

[9] P. D. Bartlett, S. Friedman, M. Stiles, *J. Am. Chem. Soc.* **1953**, *75*, 1771−1772: Isopropyllithium reacts with diethyl ether exothermally at room temperature to form lithium ethoxide and ethylene:

$$i\text{PrLi} + \text{Et}_2\text{O} \longrightarrow \text{PrH} + \text{LiOEt} + \text{H}_2\text{C=CH}_2$$

The excess *i*PrLi then adds to the ethylene to form isoamyllithium, which can be trapped with CO_2 to give, after hydrolysis, the observed diisoamyl ketone:

$$i\text{PrLi} + \text{H}_2\text{C=CH}_2 \longrightarrow i\text{Pr–CH}_2\text{–CH}_2\text{Li}$$

$$2\ i\text{Pr–CH}_2\text{–CH}_2\text{Li} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. CO}_2} (i\text{Pr–CH}_2\text{–CH}_2)_2\text{C=O}$$

[10] Solutions of **23** and **10** in THF are paramagnetic as shown by ESR spectroscopic measurement at room temperature. In fact, solutions of **23** give a strong triplet signal, consistent with the presence of two unpaired electrons. However, from the magnitude of the spin coupling, the two electrons are not on the same titanium atom, and probably not even on adjacent titanium centers. (Studies in progress with Professor D. C. Doetschman).

[11] One-step deoxygenations of epoxides with polar reagents such as lithium diphenylphosphide lead stereospecifically to the olefin with inverted configuration. Deoxygenations with SET reagents, such as nickel(0) complexes, occur stereoselectively to favor the more stable olefin: J. J. Eisch, K. R. Im, *J. Organomet. Chem.* **1977**, *139*, C45−C50.

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