$Ti(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4{}^tBu)(CH_2Ph)_2$; a Probe of the Course of the Petasis Benzylidenation Reaction

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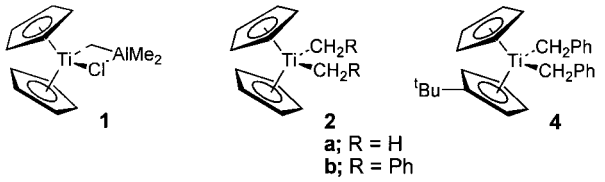
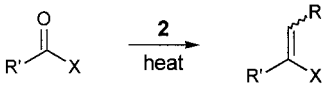
Abstract: The existence of the proposed benzylidene intermediate **11** in the Petasis benzylidenation procedure is supported by the isolation of cyclometallated product **8**. A model is proposed which explains the empirical observation that a large acid residue and a small ester group are needed for good stereoselectivity in benzylidenation reactions.

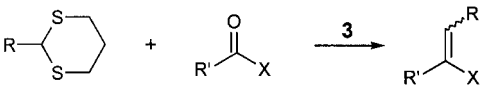
Key words: olefination, alkylidene, titanocene, stereoselectivity

The olefination of ester carbonyl groups is a synthetic challenge to which titanium-based reagents offer the most satisfactory solutions.[1] The Tebbe Reagent **1** is the classic methylidenation agent,[2] although a less well-characterised but very useful alternative has been developed by Takai.[3] More recently, Petasis introduced the stable, readily-prepared compound dimethyltitanocene **2a** as a methylidenation agent for esters and other carbonyl compounds.[4] This method was extended, again by Petasis, to include other alkylidene groups (Scheme 1).[4,5] Very recently, Takeda has reported a more general alkylidenation procedure that employs the reaction of dithioacetals with $Cp_2Ti(P(OEt)_3)_2$ **3** (Scheme 2).[6]





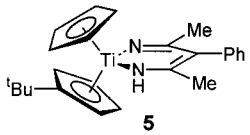
Scheme 1

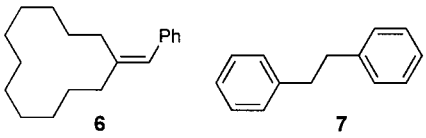


Scheme 2

For ester olefination with unsymmetrical "alkylidenes" both the Petasis and the Takeda methods give E/Z mixtures, limiting their synthetic utility. However, we are not aware of any model for predicting the stereochemical outcome of the reactions, which could permit rational design of superior reagents. We reasoned that the *tert*-butyl group in the Petasis reagent analogue **4**, previously reported by ourselves,[7] would allow us to probe the possible intermediate and origins of stereoselectivity in the Petasis benzylidenation procedure.

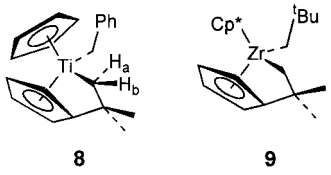
Firstly, we decided to thermolyse **4** in the presence of (i) acetonitrile and (ii) cyclododecanone, under the precise reaction conditions described by Petasis,[5] to establish whether **4** would show similar reactivity. As expected, the double insertion product **5** was isolated from the acetonitrile reaction and characterised by NMR. The olefination reaction of cyclododecanone also proceeded smoothly. Interestingly, although the yield of **6** was lower than with the Petasis reagent, none of the byproduct **7**, always observed in Petasis' work,[5] was detected. Since **7** is thought to arise from a *competing* mechanism, perhaps reductive elimination,[5] its absence in our reactions is no reason to suggest a different mechanism for olefination in our case.





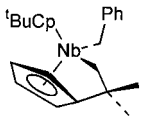
To probe the mechanism of these olefinations, we carried out the thermolysis of **4** in toluene with no trap. The major product, as judged by the crude ^1H NMR, was the cyclometallation product **8**, which results from activation of one of the C-H bonds of the *tert*-butyl group. The chirality of the product is witnessed both by the four distinct signals for the C_5H_4R protons and by the pairs of doublets due to the two diastereotopic methylene groups. In addition, the very low chemical shift of H_a (-3.0 ppm) is consistent with similar values observed for the same proton in both of analogues **9** (which is the precursor to an interesting olefin dimerisation catalyst[8]) and **10**.[9]

The isolation of **8** is entirely consistent with the existence of the benzylidene intermediate **11**. The cyclometallation could also have resulted from homolysis of a titanium-carbon bond to give a titanium (III) species and a benzyl radical or from heterolysis to give a cationic titanium centre.

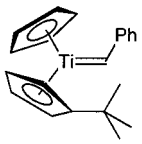


8

9



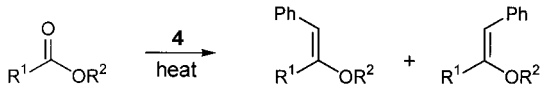
10



11

However, the absence of dibenzyl **7** rules out the former and the latter is unlikely in the absence of a Lewis or protic acid. A mechanism proceeding *via* **11** thus seems reasonable, although, as pointed out by Petasis,[4,5] coordination of the carbonyl compound before elimination of toluene is conceivable in the actual olefination reactions.

To probe the stereoselectivity of the olefination of esters, we thermolysed **4** in the presence of **12a** and of **12b**. With **12a** an E:Z ratio of 10:90 was observed. This 80% isomeric excess is somewhat higher than the 72% isomeric excess observed with the Petasis reagent **2b**. However, with the isomeric ester **12b** very poor stereoselectivity was seen. The isomeric excess was 14%, but we have not yet confirmed which is the major product (Scheme 3).



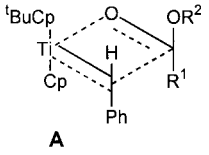
12 *E* : *Z*

a; R^1 = Ph, R^2 = CH_3 10 : 90

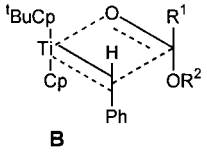
b; R^1 = CH_3, R^2 = Ph 14% isomeric excess

Scheme 3

When these results are added to those of Petasis[5] it emerges that for good stereoselectivity the ester substrate should have a *large acid residue and a small ester group* (as in **12a** but not in **12b**). We believe that simple transition state models can account for these observations. We assume that the substituted cyclopentadienyl Cp' group (if any) will lie *trans* to the phenyl group of the postulated benzylidene intermediate **11**. Transition state **A** would lead to *E* product, whereas **B** would lead to *Z*, the ratio being controlled by steric interactions with the benzylidene phenyl group. With a large R^1 and a small R^2, **B** would be of significantly lower energy than **A** and the Z product would thus predominate. However, the spacer effect of the oxygen in OR^2 means that R^2 interacts less with the phenyl group in **B** than does R^1 in **A**. Hence, with a large R^2 and a small R^1, OR^2 and R^1 would have similar steric requirements and low stereoselectivity would be predicted.



A



B

The presence of a substituted Cp' group would be expected to reduce the conformational flexibility of the cyclic transition state, thus increasing steric interactions. This explains the modest increase in stereoselectivity in the *tert*-butyl case.

Whether this stereochemical model can be applied to the Takeda procedure is uncertain. Unfortunately, only one common substrate was used by both Petasis[5] and Takeda[6] and the stereochemical result was very different (68% *vs* >98% isomeric excess respectively). It should be noted that Takeda used a coordinating solvent (thf) and that the mechanism may in any case be different.[6]

In summary, isolation of compound **8** on thermolysis of benzylidenation agent **4** is consistent with the intermediacy of benzylidene complex **11**. A model is hence proposed which explains the empirical observation that a large acid residue and a small ester group are needed for good stereoselectivity in the Petasis benzylidenation procedure.

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References and Notes

† Deceased
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Experimental procedure for preparation of **4** To a solution of $Ti(h^5\text{-}C_5H_5)(h^5\text{-}C_5H_4{}^tBu)Cl_2$[10] (1g, 0.65mmol) in diethyl ether (30mL) at -40 °C was added benzyl magnesium bromide (6.6mL of a 1M solution in diethyl ether), dropwise with stirring. The mixture was stirred for 5h, allowed to warm to room temperature and the solvent was removed *in vacuo*. The resulting residue was extracted with petroleum ether (15mL) and filtered. The solution was concentrated to 20mL and cooled to -30° C to yield **4** as a brown powder, mp 41° C (dec.). Yield: 0.8g, 60%. ^{1}H NMR (C_6D_6): δ 7.26 (m, 4H, Ph), 6.98 (m, 2H, Ph), 6.90 (m, 4H, Ph), 5.96 (m, 2H, C_5H_4), 5.75 (s, 5H, Cp), 5.67 (m, 2H, C_5H_4), 2.22 (d, *J* = 9.3Hz, 2H, CH_2), 1.91 (d, *J* = 9.3Hz, 2H, CH_2), 0.94 (s, 9H, ^{t}Bu). ^{13}C NMR δ 154.03 (quat. Ph), 139.22 (quat. C_5H_4), 125.53 (2xPh), 121.53 (Ph), 115.38 (Cp), 114.87 (C_5H_4), 113.71 (C_5H_4), 73.73 (CH_2), 32.50 (quat.), 31.14 (CH_3).

General Procedure for Thermolysis of **4.** Thermolysis reactions were carried out according to the procedure described by Petasis,[5] using 0.25 mmol of **4**.

Experimental procedure for preparation of **5.** Acetonitrile was used in place of toluene as solvent. Instead of dilution, the solvent was removed *in vacuo* to leave a dark red residue which was washed with petroleum ether (2 x 15ml) to yield the unstable product **5**. ^{1}H NMR (C_6D_6): δ 7.34 (m, 2H, Ph), 7.02 (m, 2H, Ph), 6.70 (m, 1H, Ph), 5.82 (m, 1H, C_5H_4), 5.67 (m, 1H, C_5H_4), 5.52 (m, 1H, C_5H_4), 5.47 (s, 5H, Cp), 5.42 (m, 1H, C_5H_4), 2.77 (s, 6H, 2xCH_3), 1.28 (s, 9H, ^{t}Bu).

Experimental procedure for preparation of **6.** The crude product was a red/brown oil which was purified by flash chromatography on silica to yield **6** as a yellow oil. Yield: 45%. The NMR data for **6** were identical with those in the literature.[11]

Experimental procedure for reaction of **4** with methyl benzoate**.** Work-up as for **6** gave a mixture of products (Scheme 3). Yield: 42%. ^{1}H NMR ($CDCl_3$)[12] δ 7.89-6.95 (m, 10H, 2xPh from *E* and *Z*), 6.05 (s, 0.9H, *Z* CH), 5.76 (s, 0.1H, *E* CH), 3.81 (s, 0.3H, *E* CH_3), 3.58 (s, 2.7H, *Z* CH_3).

Experimental procedure for reaction of **4** with phenyl acetate**.** Work-up as for **6** gave a mixture of products (Scheme 3). Yield: 55%. ^{1}H NMR ($CDCl_3$) δ 7.65-7.20 (m, 10H, 2xPh), 5.93 (s, 0.57H, CH), 5.88 (s, 0.43H, CH), 2.21 (s, 1.71H, CH_3), 2.01 (s, 1.29H, CH_3).

Experimental procedure for preparation of **8.** No carbonyl compound was added. Instead of dilution, the solvent was removed *in vacuo* to yield **8** as an unstable brown solid. ^{1}H NMR (C_6D_6) δ 7.25 (m, 1H, Ph), 7.04 (m, 2H, Ph), 6.68 (m, 2H, Ph), 6.48 (m, 1H, C_5H_4), 5.88 (m, 1H, C_5H_4), 5.76 (s, 5H, Cp), 4.70 (m, 1H, C_5H_4), 4.34 (m, 1H, C_5H_4), 2.14 (s, 3H, CH_3), 1.63 (d, *J* = 9.8Hz, 1H, CH_2Ph), 1.36 (d, *J* = 9.8Hz, 1H, CH_2Ph), 0.76 (s, 3H, CH_3), 0.52 (d, *J* = 8.9Hz, 1H, H_b), -3.0 (d, *J* = 8.9Hz, 1H, H_a). ^{13}C NMR δ 154.62 (quat. Ph), 137.64 (quat. C_5H_4), 129.84 (Ph), 125.58 (Ph), 125.38 (Ph), 116.96 (C_5H_4), 116.65 (C_5H_4), 112.37 (Cp), 108.97 (C_5H_4), 104.80 (C_5H_4), 51.82 (CH_2Ph), 33.90 (quat.), 31.57 (CH_3), 29.99 (CH_3), 29.96 (CH_2).