Acylation Reactions Mediated by Tantalum Carboxylates

Kiran Joshi, Jiang Bao, Alan S. Goldman,* and Joachim Kohn*

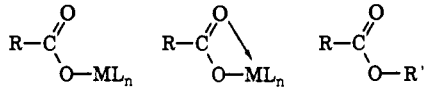
Contribution from the Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903. *Received March 5, 1992*

Abstract: Facile nucleophilic attack on coordinated carboxylate ligands is reported: complexes of tantalum(V) react rapidly with amines and amino acid esters to give the corresponding amides. Cyclopentadienyltantalum(V) amino acid carboxylate complexes have been prepared and reacted with free amino acid esters to give dipeptides in good yield and with high stereochemical purity.

Introduction

Although metal carboxylates have long occupied a central position in coordination chemistry,[1] little is known about the occurrence of nucleophilic substitutions at the metal coordinated carbonyl function. Prior to this work very few well characterized examples of metal carboxylates undergoing nucleophilic attack had been reported.[2-5] Taube found that the aqueous hydrolysis of a cobalt(III) pentaamine trifluoroacetate proceeded under very basic conditions via attack at the carbonyl carbon.[6] Kinetic studies on that system indicated that in spite of the electron-withdrawing effect of the trifluoromethyl group, nucleophilic assistance by a second hydroxide anion was required to effect hydrolysis. Buckingham has reported nucleophilic hydrolysis of a Co(III)-coordinated oxalate ligand and nucleophilic isotopic exchange ($^{18}O/^{16}O$) at a Co(III)-coordinated glycinate; like the Taube system, these reactions proceed slowly even under very basic conditions.[7]

Metal carboxylates (**1a** or **1b**) may be viewed as formally analogous to organic esters (**2**). The important role of "active"



1a **1b** **2**

organic esters (**2**; R′ = electron-withdrawing group) in amide bond formation led us to consider if metal carboxylates could be similarly used as acylating agents as, for example, in eq 1.

$$RC(O)OM + NH_2R'' \rightarrow RC(O)NHR'' + "M(OH)" \quad (1)$$

We presumed that carboxylates of metal centers less electron-rich than cobalt(III) should be more susceptible toward nucleophilic attack. In a preliminary communication[8] we reported the reactivity of dicyclopentadienyltitanium(IV) and -zirconium(IV) carboxylates. These were found to undergo attack by amines and amino acids, giving rise to the corresponding amides.[8] Thus, these complexes are far more electrophilic than the cobalt(III) carboxylates. However, in the context of practical organic synthesis, the required reaction conditions (ca. 24 h in refluxing THF) were fairly severe compared with those required by presently utilized reagents.

To obtain more reactive systems we turned our attention to even higher oxidation state complexes. Tantalum(V) tetrachloroisobutyrate was noted[8] to undergo much faster nucleophilic attack (by benzylamine) than the titanium and zirconium isobutyrates. In this paper we report studies on cyclopentadienyltantalum(V) carboxylates which are conveniently prepared from the corresponding chlorides and which undergo extremely facile nucleophilic attack even at very low temperatures. Consistent with the very mild reaction conditions, acylations using chiral carboxylates afford dipeptides of high stereochemical purity.

Results

Synthesis and Reactions of Complexes of Simple Carboxylates: $CpTaCl_3[O(O)CCHMe_2]$ ($Cp = \eta^5$-C_5H_5; 3a) and $Cp^*TaCl_3[O(O)CCHMe_2]$ ($Cp^* = \eta^5$-C_5Me_5; 3b). Carboxylates **3a** and **3b** were prepared by the addition of 1 equiv of isobutyric acid to toluene solutions of the known[9] $CpTaCl_4$ and Cp^*TaCl_4 complexes, respectively. In both cases, the reaction proceeded rapidly at room temperature with the concomitant liberation of HCl gas. **3a** and **3b** were isolated as orange crystals in high yields (ca. 80%) and characterized by ^1H and $^{13}C\{^1H\}$ NMR and IR spectroscopy. The solution IR spectrum (**3a**, toluene) shows a ν_{COO} asymmetric stretch at 1525 cm^{-1} and a ν_{COO} symmetric stretch at 1496 cm^{-1}. The $\Delta\nu$ (asym–sym) value of 29 cm^{-1} is strongly indicative of the chelating mode of the carboxylate ligand (**2a**).[10]

The ability of these complexes to act as acylating agents for amide bond formation was demonstrated by their reactions with various amines and with alanine methyl ester (Table I). In a typical procedure, 2 or more equivs of an amine were added to the toluene solution of the isobutyrate complex **3a** or **3b** at room temperature. The reaction proceeded rapidly as judged by the disappearance of the yellow color of the tantalum carboxylate and the formation of a white precipitate of the amine·HCl salt. Water was then added to precipitate the tantalum product(s). Workup afforded the corresponding amide in high purity and quantitative yields.

The reaction of **3a** with benzylamine was monitored by ^1H NMR spectroscopy in order to identify the tantalum-containing reaction products. Upon addition of 2 equivs of benzylamine to a benzene-d_6 solution of **3a**, 1 equiv of the amide is observed in the ^1H NMR spectrum, while the second equivalent of amine is

(1) (a) Oldham, C. *Comprehensive Coordination Chemistry*; Pergamon Press: Oxford, 1987; pp 435–459. (b) Mehrotra, R. C.; Bohra, R. *Metal Carboxylates*; Academic Press: London, 1983.

(2) Amide bond formation promoted by metals (most notably, in this context, titanium(IV) species[3,4]) has been reported. Although our work suggests that such reactions may involve the formation of metal carboxylates, there is evidence that the role of the metals in several cases is to form nucleophilic amido complexes which attack the carbonyl group.[4] Also noteworthy are the well developed transition metal systems for amide bond formation which involve coordination to carboxylic esters,[5] thereby enhancing their electrophilicity; these are distinct from the reactions described in this work in which the carboxylate anion is attacked.

(3) (a) Wilson, J. D.; Weingarten, H. *Can. J. Chem.* **1970**, *48*, 983–986. (b) Nordahl, A.; Carlson, R. *Acta Chem. Scand. B* **1988**, *42*, 28–34. (c) Mader, M.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 3049–3052, and references therein.

(4) (a) Chandra, G.; George, T. A.; Lappert, M. F. *J. Chem. Soc. C* **1969**, 2565–2568. (b) George, T. A.; Lappert, M. *J. Chem. Soc. A* **1969**, 992. (c) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174. (d) Beck, W.; Kramer, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1467.

(5) Sutton, P. A.; Buckingham, D. A. *Acc. Chem. Res.* **1987**, *20*, 357 and references therein.

(6) Jordan, R. B.; Taube, H. *J. Am. Chem. Soc.* **1966**, *88*, 4406.

(7) (a) Miskelly, G. M.; Clark, C. R.; Buckingham, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 5202. (b) Boreham, C. J.; Buckingham, D. A. *Aust. J. Chem.* **1980**, *33*, 27. (c) Buckingham, D. A.; Clark, C. R.; Miskelly, G. M. *Comm. Inorg. Chem.* **1988**, *7*, 171.

(8) Recht, J.; Cohen, B. I.; Goldman, A. S.; Kohn, J. *Tetrahedron Lett.* **1990**, 7281.

(9) Bunker, M. J.; Cian, A. D.; Green, M. L. H. *J. Chem. Soc., Chem. Commun.* **1977**, 59.

(10) (a) Deacon, G. B.; Phillips, R. J. *Coord. Chem. Rev.* **1980**, *33*, 227. (b) Kapoor, R.; Sharma, R.; Kapoor, P. *Ind. J. Chem.* **1985**, *24A*, 761.

0002-7863/92/1514-6649$03.00/0

Table I

Ta reagent	amine	product	yield (%)
a. Reactions of Tantalum Carboxylates with Amines and Amino Acids			
$CpTaCl_3(O(O)CCHMe_2)$ (**3a**)	benzylamine	$(Me_2HC)C(O)NHCH_2Ph$	95
$Cp^*TaCl_3(O(O)CCHMe_2)$ (**3b**)	benzylamine	$(Me_2HC)C(O)NHCH_2Ph$	80
3a, **3b**	*S*-(−)-PhCH(Me)NH_2	$(Me_2HC)C(O)NHCH(Me)Ph$	90, 35
3a, **3b**	*R*-(+)-PhCH(Me)NH_2	$(Me_2HC)C(O)NHCH(Me)Ph$	90, 35
3a	HCl·Ala·OMe	$(Me_2HC)C(O)$-Ala-OMe	82
$CpTaCl_3[O(O)CCHMeEt]$ (**4a**)	benzylamine	$(EtMeHC)C(O)NHCH_2Ph$	86
$Cp^*TaCl_3[O(O)CCHMeEt]$ (**4b**)	benzylamine	$(EtMeHC)C(O)NHCH_2Ph$	85
4a	*S*-(−)-PhCH(Me)NH_2	$(EtMeHC)C(O)NHCH(Me)Ph$	86
4a	*R*-(+)-PhCH(Me)NH_2	$(EtMeHC)C(O)NHCH(Me)Ph$	90
$CpTaCl_3(O(O)CCH_2Ph)$ (**5a**)	benzylamine	$(PhH_2C)C(O)NHCH_2Ph$	95
$Cp^*TaCl_3(O(O)CCH_2Ph)$ (**5b**)	benzylamine	$(PhH_2C)C(O)NHCH_2Ph$	100
$CpTaCl_3(O(O)CCHPh_2)$ (**6a**)	benzylamine	$(Ph_2HC)C(O)NHCH_2Ph$	60
$Cp^*TaCl_3(O(O)CCHPh_2)$ (**6b**)	benzylamine	$(Ph_2HC)C(O)NHCH_2Ph$	69

reagent	amino acid/base	product	yield (%)	rac[a] (%)
b. Dipeptide Formation Using Tantalum Carboxylates and Comparisons with the DCC/HOBt Amino Acid Coupling System				
$CpTaCl_3$(Z-Ala) (**7a**)	HCl·Ala·OMe/Et_3N	*N*-Z-Ala-Ala-OMe	81	nd[b]
DCC/HOBt	HCl·Ala·OMe/NMM	*N*-Z-Ala-Ala-OMe	98	nd
7a	HCl·Phe·OMe/Et_3N	*N*-Z-Ala-Phe-OMe	79	nd
DCC/HOBt	HCl·Ala·OMe/NMM	*N*-Z-Ala-Phe-OMe	96	nd
$CpTaCl_3$(*N*-Ac-Ala) (**8a**)	HCl·Phe·OMe/Et_3N	*N*-Ac-Ala-Phe-OMe	76	1.4
8a	HCl·Phe·OMe/NMM	*N*-Ac-Ala-Phe-OMe	72	1.6
8a	HCl·Phe·OMe/NMM[c]	*N*-Ac-Ala-Phe-OMe	73	0.4
DCC/HOBt	HCl·Phe·OMe/NMM	*N*-Ac-Ala-Phe-OMe	87	0.8
DCC/HOBt	HCl·Phe·OMe/NMM[c]	*N*-Ac-Ala-Phe-OMe	85	0.3
8a	HCl·Leu·OMe/Et_3N	*N*-Ac-Ala-Leu-OMe	76	6.8
8a	HCl·Leu·OMe/NMM	*N*-Ac-Ala-Leu-OMe	78	1.8
8a	HCl·Leu·OMe/NMM[d]	*N*-Ac-Ala-Leu-OMe	75	1.1
DCC/HOBt	HCl·Leu·OMe/NMM	*N*-Ac-Ala-Leu-OMe	84	1.2
DCC/HOBt	HCl·Leu·OMe/NMM[d]	*N*-Ac-Ala-Leu-OMe	85	1.5

[a] Racemization, i.e., percent of D,L isomer formed (±0.3%). [b] nd = none detected; detection limit of 0.2%. [c] With 1.4 equiv of HCl·Phe·OMe. [d] With 1.5 equiv of HCl·Leu·OMe.

consumed in the formation of amine·HCl precipitate. The Cp signal at δ 6.10 disappears and a sharp singlet at δ 6.34 ppm is observed, attributable to the cyclopentadienyl protons of the oxo species $CpTa(=O)Cl_2$ (83% yield based on peak integration). The characteristic Ta=O vibration[11] at 852 cm^{-1} in the IR spectrum (toluene solution) supports the characterization of this species (cf. $Cp^*_2Ta(O)Cl$,[11a] ν_{TaO} = 850 cm^{-1}). Attempts to isolate this complex were unsuccessful, probably due to the formation of aggregates of the form $[CpTaCl_2(\mu\text{-}O)]_n$ in analogy with the known chemistry of the hydrolysis of Cp^*TaCl_4.[12]

$$CpTaCl_3[O(O)CCHMe_2] + 2PhCH_2NH_2 \rightarrow CpTa(O)Cl_2 + PhCH_2NH(O)CCHMe_2 + PhCH_2NH_2\cdot HCl \quad (2)$$

Several tantalum-containing products result from the reaction of **3b** with amines including $Cp^*Ta(O)Cl_2$ but only in low yield (<10%).

Synthesis and Reactions of Complexes of Chiral Carboxylates: $CpTaCl_3[O(O)CCHMeEt]$ (4a) and $Cp^*TaCl_3[O(O)CCHMeEt]$ (4b). We investigated complexes containing the chiral *S*-(+)-2-methylbutyrate ligand (2-MBA) as "models" of amino acid complexes. $CpTaCl_3$(2-MBA) (**4a**) and Cp^*TaCl_3(2-MBA) (**4b**) were synthesized from *S*-(+)-2-methylbutyric acid in analogy with the isobutyrate complexes **3a** and **3b** and isolated as yellow crystals in good yields (ca. 75%).

Acylations using **4a** and **4b** (Table I) were conducted analogously to those with **3a** and **3b**. The reaction of **4** with chiral amines *S*-(−)-α-methylbenzylamine or *R*-(+)-α-methylbenzylamine afforded diastereomeric amides, thus allowing racemization evaluation by ^1H and ^{13}C NMR spectroscopy. When **4a**, formed from *S*-(+)-2-methylbutyric acid, was reacted with *S*-(−)-α-methylbenzylamine or *R*-(+)-α-methylbenzylamine at room temperature, diastereomeric mixtures were formed containing 28% and 25% of the *RS* and *RR* diastereomers, respectively, which result from racemization at the methylbutyrate chiral carbon. (Identification and quantitation of the diastereomers was easily achieved, for example, from the variation of the chemical shifts observed for the protons on the methyl group on the chiral carbons. The methyl doublets for the *SS* isomer appeared at 0.92 and 1.26 ppm, whereas in the *RS* isomer, these resonances were shifted to 1.03 and 1.41 ppm.) The same reactions, however, *when conducted at −14 °C gave no observable racemization products* (ca. 1% limit of detection of racemization).

These results as well as related observations described below imply not only that the amide bond formation step is nearly racemization-free but also that the chiral carbon of the carboxylate ligand retains its configuration during the reaction with $CpTaCl_4$. This is not surprising since the synthesis of the carboxylates—in contrast with synthesis of typical active organic esters—does not involve nucleophilic attack at the carbonyl carbon. Instead, formation of the tantalum carboxylates may be viewed as an electrophilic substitution of Ta(V) for the carboxylic acid proton.

Synthesis and Reactions of Tantalum(V) Complexes of Amino Acid Carboxylates. Complexes were derived from amino acids *N*-(benzyloxycarbonyl)-L-alanine (Z-Ala) and *N*-acetyl-L-alanine (*N*-Ac-Ala). For example, $CpTaCl_4$ in toluene was reacted with equimolar amounts of Z-Ala at room temperature. The reaction mixture was allowed to stir for an hour during which the yellow solution turned orange. The complex $CpTaCl_3$(Z-Ala) (**7a**) was prepared and characterized in situ by ^1H NMR spectroscopy. Attempts to isolate the product gave a yellow oil which has not yet been characterized. The Cp* analogue of **7a**, however, was easily crystallized from a toluene/hexanes solution.

Using the Cp amino acid complexes, we have been able to prepare many dipeptides in yields ranging from 75–81% (Table I) at low temperatures (−14 °C) with little accompanying racemization as determined by ^1H NMR spectroscopy[13] and analytical

(11) (a) Asselt, A. V.; Burger, B. J.; Gibson, V. C.; Bercaw, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 5347. (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 3.

(12) (a) Jernakoff, P.; Bellefon, C. D. M. D.; Geoffroy, G. L.; Rheingold, A. L.; Geib, S. J. *Organometallics* **1987**, *6*, 1362. (b) Mata, J. D. L.; Fandos, R.; Gomez, M.; Gomez-Sal, P.; Martinez-Carrera, S.; Royo, P. *Organometallics* **1990**, *9*, 2846.

HPLC. In a typical experiment, the amino acid carboxylate complex was generated in situ and 1.0–1.5 equiv of L-amino acid methyl ester hydrochloride and 1.0 equiv of triethylamine or *N*-methylmorpholine (NMM) was added to the solution at −14 °C. The workup involved washings with water and Na_2CO_3, followed by evaporation of the organic solvent in vacuo which afforded the crude dipeptide as white solid. In order to determine the chemical and chiral homogeneity, the dipeptides were analyzed, without further purification, by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy as well as HPLC, which generally revealed that the products consisted of only small amounts of D,L diastereomers (<2%, see Table I).

Several problems were encountered during the dipeptide synthesis using the Cp* analogues for acylation. For example, on reacting the complex Cp^*TaCl_3(Z-Ala), **7b**, with HCl·Ala·OMe/Et_3N, we did not obtain the corresponding dipeptide methyl ester. Instead, the presence of several different organic species in the crude product was apparent from the ^1H NMR spectrum. Interestingly, cleavage of the O–Me bond had apparently occurred. The reaction with HCl·Ala·OBu^t/Et_3N gave the expected dipeptide, Z-Ala-Ala-OBu^t in 20% yield. However, separation of Cp*Ta products from the dipeptide (as well as from the amide products of other reactions) was tedious because both seemed to possess similar solubility in many solvents.

Reaction of Cp^*TaCl_4 with $PhCH_2NH_2$. As a potential side reaction which could lower acylation yields, the reaction of amines with the Ta–Cl functionality was of interest. When $PhCH_2NH_2$ (1 or 2 equivs) was added to Cp^*TaCl_4, ^1H NMR spectroscopy revealed the clean formation of a single complex, $Cp^*TaCl_4(NH_2CH_2Ph)$, isolated in 84% yield.[14] No evidence for formation of amido ($TaNHCH_2Ph$) complexes was observed. When isobutyric acid was added to the resulting solution, a complex mixture of products was observed in the ^1H NMR spectrum. The formation of benzylisobutyramide, however, was not observed. The failure of this reaction to afford the amide is consistent with the presumed mechanism of eq 1 which involves direct nucleophilic attack by free amine at the coordinated carboxylate carbon.

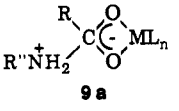
Discussion

Reactivity. Nucleophilic attack at metal-coordinated carboxylate ligands, virtually uncharacterized prior to this work, is demonstrated to be extremely facile with cyclopentadienyl complexes of tantalum(V). Even at −14 °C these species react with amines and amino acids rapidly according to eq 2. Further, even sterically hindered carboxylates such as Cp- and Cp^*TaCl_3(O(O)CCHPh_2), **6a** and **6b**, give good yields of amides (Table I). Thus we observe that while cobalt(III) carboxylates undergo nucleophilic attack only under very basic conditions,[6,15] titanium and zirconium(IV) complexes are far more reactive,[8] and, in turn, their tantalum(V) analogues are several orders of magnitude more so. These results clearly establish that the electrophilicity of the carboxylate ligand is highly sensitive to the oxidation state of the coordinated metal.

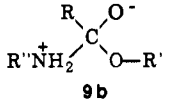
Table II. ^1H NMR Data (in C_6D_6) for Tantalum Carboxylate Complexes

compound	δ (ppm)	assignment	coupling (Hz)
$CpTaCl_3(\eta^2$-OOCCH$Me_2)$	6.10 (s)	C_5H_5	
3a	2.25 (septet)	CH	$^3J_{H,H}$ = 10.9
	0.99 (d)	CH_3	$^3J_{H,H}$ = 11.0
$Cp^*TaCl_3(\eta^2$-OOCCH$Me_2)$	2.22 (s)	$C_5(CH_3)_5$	
3b	2.21 (m)	CH	
	0.96 (d)	CH_3	$^3J_{H,H}$ = 7.7
$CpTaCl_3[\eta^2$-OOCCH(Me)CH_2Me]	6.04 (s)	C_5H_5	
4a	1.61 (m)	CH	
	1.22 (m)	CH_2	
	0.98 (d)	CH_3	$^3J_{H,H}$ = 7.1
	0.82 (t)	CH_3	$^3J_{H,H}$ = 7.3
$Cp^*TaCl_3[\eta^2$-OOCCH(Me)CH_2Me]	2.23 (s)	$C_5(CH_3)_5$	
4b	1.61 (m)	CH	
	1.20 (m)	CH_2	
	0.98 (d)	CH_3	$^3J_{H,H}$ = 8.2
	0.82 (t)	CH_3	$^3J_{H,H}$ = 7.7
$CpTaCl_3(\eta^2$-OOCCH_2Ph)	6.01 (s)	C_5H_5	
5a	3.21 (s)	CH_2	
	7.15 (br)	C_6H_5	
$Cp^*TaCl_3(\eta^2$-OOCCH_2Ph)	2.30 (s)	$C_5(CH_3)_5$	
5b	3.40 (s)	CH_2	
	7.27 (br)	C_6H_5	
$CpTaCl_3(\eta^2$-OOCCH$Ph_2)$	5.96 (s)	C_5H_5	
6a	5.20 (s)	CH	
	7.20 (m)	C_6H_5	
$Cp^*TaCl_3(\eta^2$-OOCCH$Ph_2)$	2.26 (s)	$C_5(CH_3)_5$	
6b	5.02 (s)	CH	
	7.25 (m)	C_6H_5	
$CpTaCl_3$(Z-Ala)	5.97 (s)	C_5H_5	
7a	4.34 (m)	CH	
	5.02 (br)	CH_2	
	5.21 (br)	NH	
	7.12 (m)	C_6H_5	
	1.01 (d)	CH_3	$^3J_{H,H}$ = 7.3
Cp^*TaCl_3(Z-Ala)	2.59 (s)	$C_5(CH_3)_5$	
7b	4.43 (m)	CH	
	5.11 (s)	CH_2	
	5.34 (d)	NH	$^3J_{H,H}$ = 6.0
	7.35 (m)	C_6H_5	
	1.43 (d)	CH_3	$^3J_{H,H}$ = 7.3
$CpTaCl_3$(*N*-Ac-Ala)	6.01 (s)	C_5H_5	
8a	4.28 (m)	CH	
	3.62 (s)	OCH_3	
	5.15 (br)	NH	
	0.99 (d)	CH_3	$^3J_{H,H}$ = 7.3

Presumably, the remarkably high reactivity of the early metal carboxylates vis-a-vis active organic esters can be explained in terms of stabilization of the tetrahedral intermediate (or transition state) of nucleophilic substitutions. The ability of the 12-electron $CpTa(V)Cl_3$ unit to accept electron density (both π and σ-donation) from the gemdioxodiyl dianion ligand of the proposed intermediate (**9a**) is probably much greater than the electron-accepting ability of the analogous R′ cation of the active ester (**9b**). We believe that **9a** represents a likely structure of the intermediate even in cases where the unreacted carboxylate is bound in an η^1 fashion (**1a**).



9a



9b

Accompanying Racemization. Probably the most important example of amide bond formation is formation of the peptide bond, the fundamental reaction of peptide and protein synthesis. The most basic requirement of a useful peptide bond formation system is a very low level of accompanying racemization at the carboxylate α-carbon. In this context, for example, Cp_2TiCl(Z-Ala) was previously reacted with HCl·Phe·OMe/Et_3N (24 hr in refluxing THF) in this laboratory. The dipeptide Z-Ala-Phe-OMe was

(13) It is generally observed that for dipeptides containing an aromatic residue adjacent to a C-terminal alanyl residue, the methyl protons of the L, L stereoisomer are shifted significantly downfield from those of the D, L isomer. This variation is usually sufficient to allow identification and quantitation of the two diastereomers. For example, in *N*-Ac-L-Ala-L-Phe-OMe, the methyl protons of the alanine group are observed as a doublet at 1.30 ppm, whereas for the D, L molecule the analogous resonance occurs at 0.99 ppm. From independently synthesized (DCC/HOBt) *N*-Ac-L-Ala-L-Phe-OMe and *N*-Ac-D-Ala-L-Phe-OMe, we were able to detect as little as 1% of the D, L diastereomer in the mixture using a 400 MHz NMR spectrometer. The dipeptides reported in Table I were also analyzed by $^{13}C\{^1H\}$ NMR spectroscopy and the results were in excellent agreement with the ^1H NMR data. See: (a) Weinstein, B.; Pritchard, A. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1015. (b) Halpern, B.; Chew, L. F.; Weinstein, B. *J. Am. Chem. Soc.* **1967**, *89*, 5051.

(14) Other simple adducts of $CpTaCl_4$ have been reported: Poli, R. *Chem. Rev.* **1991**, *91*, 509–551, and references therein.

(15) It is noteworthy in this context that cobalt(III) has been successfully used in peptide synthesis as a carboxylate *protecting group*: (a) Isied, S. S.; Vassilian, A.; Lyon, J. *J. Am. Chem. Soc.* **1982**, *104*, 3910–3916. (b) Isied, S. S.; Lyon, J.; Vassilian, A. *Int. J. Peptide Protein Res.* **1982**, *19*, 354–360.

formed in moderate yield.[16] Unfortunately, however, a significant amount of the diastereomeric (D,L) dipeptide was formed as revealed by ^1H NMR spectroscopy.[13] Such racemization is not surprising in view of the high temperature and long reaction time, especially in comparison with the conditions required by other "active ester" systems. In contrast, we find that acylation reactions of tantalum complexes of chiral carboxylates can be conducted with very low levels of accompanying racemization.

When tantalum(V) carboxylates were reacted with amines and amino acids at −14 °C, dipeptides of high stereochemical purity were formed (Table I). Particularly encouraging was the low level of racemization found when using the acetyl moiety as the N-protecting group. For example, when **8a** was reacted with 1.4 equiv of HCl·Phe·OMe/NMM the resulting dipeptide, N-Ac-Ala-Phe-OMe, was found to contain only 0.4% of the racemized diastereomer. The reaction of **8a** with HCl·Leu·OMe/NMM (1.5 equiv) gave *N*-Ac-Ala-Leu-OMe with only 1.1% racemization. These racemization levels are comparable to those obtained using a commonly employed and highly optimized standard coupling system, DCC and the racemization suppression agent HOBt,[17] to synthesize the same dipeptides, *N*-Ac-Ala-Phe-OMe and *N*-Ac-Ala-Leu-OMe: 0.3% and 1.5%, respectively (Table I, part b).

Since the acetyl group promotes racemization—and presumably does so in the same manner as an adjoining peptide unit[18]—these unoptimized reactions may augur well for the potential use of tantalum complexes in the coupling of oligopeptides, a reaction class which represents one of the major challenges in peptide synthesis. More generally, this work demonstrates the potential of early d^0 transition metal carboxylates as efficient low-racemization acylating agents. The ability to vary the ligand sphere should present considerable opportunity in the further design of complexes more effective for oligopeptide coupling or other acylation reactions.

Experimental Section

All air-sensitive complexes were handled under argon or nitrogen using standard inert atmosphere techniques. $TaCl_5$ was purchased from Strem Chemicals. $CpTaCl_4$ and Cp^*TaCl_4 were prepared according to literature procedures.[9] The isobutyric and *S*-(+)-2-methylbutyric acids, *R*-(+)- and *S*-(−)-α-methylbenzylamines, and all amino acids and their hydrochloride salts were obtained from Aldrich or Sigma and used without further purification. Benzylamine (Aldrich) was dried and distilled from KOH. C_6D_6 and $CDCl_3$ were purchased from Aldrich and dried by conventional methods. The ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded using Varian 200 or 400 MHz spectrometers. HPLC analyses were performed using reversed phase HPLC-RAININ HPXL system (Dynamax-300 Å C_{18} column; detection at 220 and 260 nm; 0.1% CF_3CO_2H, 10% CH_3CN, 90% H_2O buffer).

Representative Synthesis of Tantalum Carboxylates (3a). Typically, an equimolar amount of isobutyric acid was added to a toluene solution (10 mL) of $CpTaCl_4$ (250 mg, 0.64 mmol) at room temperature. The reaction mixture rapidly changed color from yellow to orange. Also detected was the evolution of HCl gas. The reaction mixture was stirred for an hour. The solvent was removed in vacuo, and the resulting orange oil was crystallized from a toluene/hexanes mixture (2 mL): yield 80%. The product **3a** was characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy (Table II). The same procedure was used for the synthesis of the rest of the complexes, and the isolated yields of the complexes were 70–80%. As noted above, the complexes **7a** and **8a** could not be recrystallized and were therefore prepared and characterized only in situ.

Representative Procedure for Reactions with Amines (3a and Benzylamine). Benzylamine (2 equivs, 11.4 μL, 0.10 mmol) was added to a toluene solution (10 mL) of **3a** at room temperature. A precipitate of benzylamine·HCl formed immediately. The reaction mixture was stirred for 1 h which was followed by addition of water (10 mL). The white precipitates were filtered off, and the clear colorless toluene solution was washed with 1 M HCl (20 mL) and 1 M Na_2CO_3 (20 mL). Solvent was removed under vacuum affording analytically pure benzylisobutyramide.

Representative Procedure for Dipeptide Formation. A freshly prepared in situ toluene solution (10 mL) of **7a** (1.30 mmol) was cooled to −14 °C (acetone/ice). HCl·Ala·OMe (180 mg, 1.30 mmol) and Et_3N (0.18 μL, 1.3 mmol) were then added, and Et_3N·HCl precipitated immediately. The reaction mixture was stirred at −14 °C for 1 h and then slowly warmed to room temperature and stirred for an additional hour. Workup involved addition of water (10 mL), filtration of the precipitates, and washing of the organic phase with 1 M Na_2CO_3 (20 mL) and water (15 mL). The solution was dried over anhydrous $MgSO_4$ for 30 min and then filtered. The solvent was evaporated to yield Z-Ala-Ala-OMe. All of the dipeptides were analyzed by ^1H, $^{13}C\{^1H\}$ NMR spectroscopy, and HPLC, and the data[13] were compared with that of samples synthesized using DCC/HOBt.[17]

Acknowledgment. Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We thank Drs. A. M. Felix and D. R. Bolin (Hoffmann-La Roche, Nutley, NJ) for helpful discussions and for optical purity determinations of some of the dipeptides. We thank Dr. J. A. Maguire for experimental assistance.

(16) Cohen, B. I.; Goldman, A. S.; Kohn, J. unpublished results.

(17) (a) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984. (b) Benoiton, N. L.; Kuroda, K. *Int. J. Peptide Protein Res.* **1981**, *17*, 197–204.

(18) Bodanszky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984; pp 159–173.