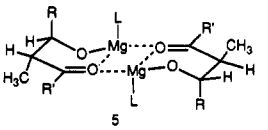
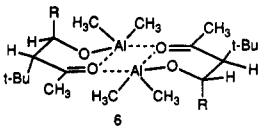
ployed. Using half a molar equiv resulted in both lower diastereomeric ratio and lower yield (entry 1 vs 2). These results differ from those using Zn(II) in equilibration reactions where 0.5 molar equiv of Zn(II) gave better diastereoselectivity.[9b] In one comparative experiment, the use of $ZnBr_2$ in the aldol reaction between propiophenone and benzaldehyde gave a lower anti:syn ratio (92:8) and lower yield (53%) than the reaction with $MgBr_2 \cdot OEt_2$ (98:2, 73%).[3a,9d]

The equilibration of lithium aldolate is often accompanied by lower yields of aldol products as a result of retro-aldol reaction.[3a,9b] This complication is effectively eliminated with the use of Mg(II). We postulate that the strongly chelating magnesium ion permits isomerization around the C_2–C_3 bond without requiring the complete dissociation of the adduct from the metal. However, this still leaves a pivotal question unanswered, i.e., why are the observed anti selectivities as high as they are? As House pointed out almost twenty years ago,[9b] anti adducts are thermodynamically more stable than their syn counterparts, *but only to the extent of having one less skew butane interaction.* We suggest that bis-adducts, such as **5**, may provide a mechanism for amplifying what might otherwise be small energy differences between monomeric aldolate diastereomers. For example, a hypothetical equilibrium mixture of 5:1 anti–anti:anti–syn bis-aldolates would result in an 11:1 anti–syn product ratio. Support for the intermediacy of dimeric aldolate comes from the work of Jeffery et al., who have isolated and characterized aluminum aldolate dimers of general structure **6**.[13]



5



6

Experimental and theoretical studies aimed at establishing the intermediacy of bis-magnesium adducts in these reactions is underway. In addition, we are also exploring the potential of this procedure with regard to simple aldol selectivity and double asymmetric induction.

Acknowledgment. Financial support for this study was provided by a grant from the National Institutes of Health, the donors of the Petroleum Research Fund, administrated by the American Chemical Society, and a grant from the R. W. Johnson Pharmaceutical Research Institute.

(13) See: Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373 and references contained therein.

Stereoselective Synthesis of Trisubstituted α,β-Unsaturated Esters and Amides via Reactions of Tantalum–Alkyne Complexes Derived from Acetylenic Esters and Amides with Carbonyl Compounds

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Summary: Treatment of acetylenic esters with low-valent tantalum ($TaCl_5$ and Zn) in DME and benzene produces tantalum–alkyne complexes (not isolated), which react with carbonyl compounds regioselectively at the α-position of the esters to give *Z* isomers of trisubstituted α,β-unsaturated esters in a stereoselective manner. In contrast, tantalum–alkyne complexes derived from acetylenic amides react with carbonyl compounds at the β-position of the amides predominantly.

Tri- or tetrasubstituted α,β-unsaturated carbonyl compounds, in particular, esters and amides, are an important class of compounds as synthetic intermediates of many natural products. Stereoselective construction of such compounds is a fundamental challenge in organic synthesis.[1,2] Olefination of carbonyl compounds using Horner–Emmons reagents or the carbanions stabilized by silicon and ester groups usually produces a mixture of *E* and *Z* isomers of α,β-unsaturated esters.[3] Carbometalation of a propiolate ester with lithium dialkylcuprates followed by addition of carbonyl compounds affords (*Z*)-2-alkylidene-3-hydroxy esters stereoselectively in the case of ketones, while its condensation reaction with aldehydes affords mixture of *E* and *Z* isomers.[4]

Recently we found a convenient procedure for the preparation of tantalum–alkyne complexes[5,6] and employed the complexes as a cis-fixed vicinal alkene dianion reagent.[7] We disclose here novel access to trisubstituted α,β-unsaturated esters and amides by the reaction of tantalum–alkyne complexes, derived from acetylenic esters or amides, with carbonyl compounds.

(1) (a) Arora, A. S.; Ugi, I. K. *Methoden der Organic Chemie*; Houben-Weyl, Bd. V/1b.

(2) For intramolecular reactions between acetylenic esters and carbonyl compounds, see: Smith, A. B., III. *Strategies and Tactics in Organic Synthesis*; Academic Press Inc.: Orlando, 1984; Chapter 9, p 252.

(3) (a) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849. (b) Crimmin, M. J.; O'Hanlon, P. J.; Rogers, N. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 541.

(4) For copper-catalyzed conjugate addition of Grignard reagents to acetylenic esters, see: Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1983**, *48*, 4621 and references cited therein. See also: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

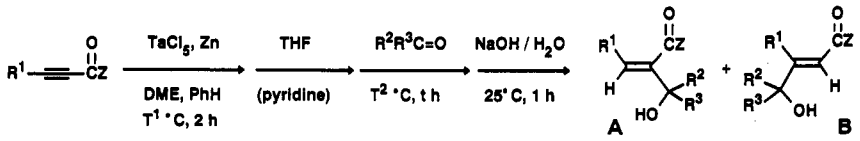
(5) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 365.

(6) For representative reactions of metallacyclopropenes with unsaturated compounds, see: (a) Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441. (b) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (c) Takahashi, T.; Swanson, D. R.; Negishi, E. *Chem. Lett.* **1987**, 623. (d) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (e) Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (f) Hartung, J. B., Jr.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 5468. (g) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 369. (h) Strickler, J. R.; Bruck, M. A.; Wexler, P. A.; Wigley, D. E. *Organometallics* **1990**, *9*, 266.

(7) (a) Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707. (b) Takai, K.; Miyai, J.; Kataoka, Y.; Utimoto, K. *Organometallics* **1990**, *9*, 3030.

0022-3263/91/1956-5980$02.50/0

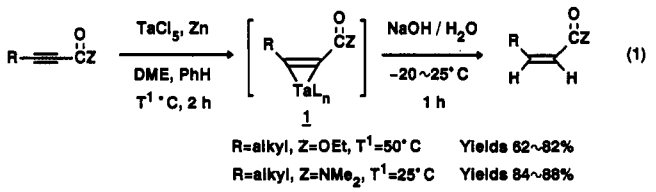
Table I. Reactions of Acetylenic Esters or Amides with Carbonyl Compounds[a]



run	R^1	Z	R^2	R^3	T^1/°C	T^2/°C	t/h	yield/%[b]	A/B[c]
1	n-$C_{10}H_{21}$	OEt	Pr	H	50	25	0.5	76	95/5 (2a) (2b)
2			c-C_6H_{11}	H	50	25	0.5	63	96/4
3			CH_2=CH	H	50	0	0.3	65[d]	78/22
4			-$(CH_2)_5$-		50	25	0.5	72	97/3
5			CH_2=CH	Me	50	25	1	61[d]	72/28
6	c-C_6H_{11}	OEt	Pr	H	50	25	0.5	76	98/2
7			c-C_6H_{11}	H	50	25	0.5	69	97/3
8			CH_2=CH	H	50	0	0.3	64[d]	83/17
9			-$(CH_2)_5$-		50	25	0.5	72[e]	>99/<1
10	n-C_6H_{13}	NMe_2	Pr	H	25	50	2	79	10/90 (3a) (3b)
11			c-C_6H_{11}	H	25	50	2	57	<2/>98
12			CH_2=CH	H	25	50	2	73	14/86
13			-$(CH_2)_5$-		25	50	3	33[f]	<2/>98
14	c-C_6H_{11}	NMe_2	Pr	H	25	50	2	73	24/76
15			c-C_6H_{11}	H	25	50	3	31	<2/>98
16	Bu	$N(CH_2)_3CH_2$	Pr	H	25	50	2.5	80	10/90

[a] All reactions were performed on a 1.0-mmol scale. Acetylenic ester (runs 1–9): Two moles of $TaCl_5$, 3.0 mol of zinc, and 1.2 mol of a carbonyl compound were employed per mol of the alkyne, unless otherwise noted. THF and pyridine (4.0 mmol) were used as additives. Acetylenic amide (runs 10–16): 1.2 mol of $TaCl_5$, 1.8 mol of zinc, and 2.0 mol of a carbonyl compound were employed per mol of the alkyne. THF was used as an additive. [b] Isolated yields. [c] The regioisomer ratios were determined by isolation or ^{1}H NMR analysis. [d] Two equivalents of acrolein (or methyl vinyl ketone) was employed. [e] Cyclohexanone (2.4 equiv) was used. [f] Cyclohexanone (3.0 equiv) was used.

Reaction of an acetylenic ketone with low-valent tantalum gave a complex mixture containing a pinacol-type coupling product.[8] However, treatment of acetylenic esters with 2.0 equiv of $TaCl_5$ and 3.0 equiv of zinc produced the tantalum–alkyne complexes. As complexation of acetylenic esters with low-valent tantalum proceeded slower than that of dialkyl acetylenes, the mixture of low-valent tantalum and an acetylenic ester was heated at 50 °C to accomplish the complexation.[9] Hydrolysis of the tantalum–alkyne complexes with aqueous sodium hydroxide solution (15%) afforded (*Z*)-α,β-unsaturated esters in 80–82% yields (eq 1).[10] In contrast to acetylenic



(1)

esters, complexation of acetylenic amides with low-valent tantalum proceeded smoothly at 25 °C and the corresponding (*Z*)-α,β-unsaturated amides were obtained in 84–88% yields after aqueous alkaline workup (eq 1).[10]

Tantalum–alkyne complexes derived from acetylenic esters reacted with carbonyl compounds smoothly at 25 °C and two regioisomeric adducts **A** and **B** were produced in 61–76% combined yields (Table I, runs 1–9). One of the regioisomers (**A**), generated by insertion of a carbonyl group into the tantalum–α-carbon bond of **1**, was produced under high regio- and stereocontrol, especially in the case of saturated carbonyl compounds.[11] On the other hand, reactions between tantalum–acetylenic amide complexes and carbonyl compounds gave predominantly the opposite regioisomers **B**.[12] As the reaction proceeded very slowly and required heating to complete, the amount of the low-valent tantalum was reduced to avoid the consumption of carbonyl compounds (runs 10–16).

Regioselectivity of the reaction of metallacyclopropenes is an important problem especially from a synthetic point of view. Tantalum–alkyne complexes can be produced from not only dialkyl acetylenes[7a] but also heterosubstituted ones,[7b] and they react with carbonyl compounds to afford two regioisomeric allylic alcohols. Although the complexes derived from such alkynes and the $TaCl_5$–Zn system are not well characterized, the regioselectivities are varied with the following factors. (i) Steric effects of the substituents on acetylenes: Reaction takes place at the less hindered side of the tantallacyclopropene.[7a] (ii) Electronic effects of the substituents: When electron-donating groups, such as SMe and SPh,[7b] are attached to the acetylenes, β-adducts are produced predominantly. In contrast, α-adducts are obtained as a main product in the case of electron-withdrawing groups, such as SO_2Me[7b] and CO_2Et. (iii) These two factors, however, could not account for the regiochemistry, β-selectivity, of the reaction between tantalum–acetylenic amide complexes and aldehydes. Complexation of acetylenic amides with the low-valent tantalum proceeded exceptionally fast, while reactivity of the formed tantalum–alkyne complexes toward

(8) Ketone and aldehyde groups were reduced smoothly with the low-valent tantalum to produce pinacol-type 1,2-diols.

(9) Diethyl acetylenedicarboxylate remained unchanged after heating with low-valent tantalum at 50 °C for 3 h.

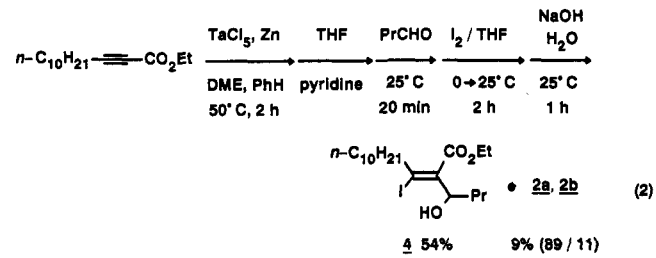
(10) Authentic samples of the opposite isomers, (*E*)-α,β-unsaturated esters were prepared with the Horner–Emmons reagents. (*E*)-α,β-Unsaturated amides were obtained from the corresponding esters. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 492.

(11) Stereochemistries of trisubstituted α,β-unsaturated esters were confirmed by comparison with the ^{1}H NMR data on the literature; see ref 4.

(12) Treatment of a TBDMS ether of (*Z*)-α,β-unsaturated ester **2a'** (R^1 = n-C_6H_{13}) with Me_2AlNMe_2 afforded the corresponding α,β-unsaturated amide, which was identical with the TBDMS ether of **3a**.[10] Reduction of a TBDMS ether of α,β-unsaturated amide **3b** with $LiEt_3BH$ in THF gave the corresponding monoprotected allylic diol. This sample was identical to the reduction product derived from a TBDMS ether of **2b'** (R^1 = n-C_6H_{13}).

aldehydes was low. The observed reactivities and the β-selectivity could be attributed to the coordination of the nitrogen of amide to tantalum.[13]

Quenching the reaction mixture of a tantalum–ethyl tridecenoate complex and butanal with iodine in THF at 0 °C for 15 min and 25 °C for 2 h afforded β-iodo-α,β-unsaturated ester **4** in 54% yield[14] along with untrapped allylic alcohols **2a** and **2b** in 9% combined yields (**2a**/**2b** = 89/11, eq 2). None of the α-iodo unsaturated ester was obtained. The carbon(sp²)–iodine bond of **4** is a clue to develop further transformations.[15]



(2)

Supplementary Material Available: Experimental procedures and spectral data for all new compounds (13 pages). Ordering information is given on any current masthead page.

(13) When an acetylenic amide was added to the mixture of low-valent tantalum, the color of the mixture changed from greenish dark blue to ultramarine. Similar color change was observed after the addition of TMEDA to the low-valent tantalum.

(14) Reduction of β-iodo ester **4** with $Et_3NH^+HCO_2^-$ under palladium catalysis ($Pd(PPh_3)_4$) produced **2a** in 87% yield. The following method was modified: Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(15) For some examples, see: (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (b) Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 4926. (c) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

Enantiocontrolled Total Syntheses of (−)-Physovenine and (−)-Physostigmine

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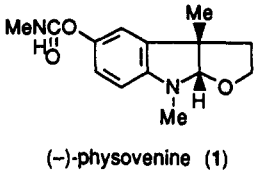
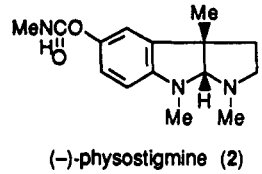
Summary: Enantiocontrolled total syntheses of the Calabar bean alkaloid (−)-physovenine (**1**) and (−)-physostigmine (**2**) have been achieved in a concise manner starting from the optically active tricyclic enone **3** employing a Fischer indolization reaction under nonacidic conditions as the key step.

There is currently considerable interest in compounds having central stimulatory activity such as the anti-cholinergic Calabar bean alkaloids[1] due to their therapeutic potential in Alzheimer's disease[1] and cholinergic disorders.[2,3] We report here the first total syntheses of (−)-physovenine (**1**) and a formal total synthesis of (−)-physostigmine (**2**), both members of the alkaloids of current interest, based on a new strategy exploiting a structurally biased polycyclic ketone **4** as a stereochemical control element in the key Fischer indolization step.



(−)-physovenine (**1**)



(−)-physostigmine (**2**)

Alkylation of the optically active (−)-tricyclic enone[4] **3**, prepared from racemic dicyclopentadiene in a four-step sequence of reactions including lipase-mediated resolution,[5] afforded the monomethyl ketone **4** in 86% yield as a mixture of epimers. When this compound was refluxed with *p*-methoxyphenylhydrazine hydrochloride in aqueous pyridine[6] (1:10), a facile diastereoselective reaction occurred to furnish the carbinol amine **7**, mp 109–111 °C, $[\alpha]^{28}_D$ −144.6° (*c* 1.95, $CHCl_3$), as a single product, in 82% yield. This compound is presumably generated via [3,3]-sigmatropic rearrangement of the diaza-1,5-diene intermediate **5** to afford the imine **6** via introduction of the aryl group from the convex face of the molecule. The imine **6** is then hydrolyzed under the reaction conditions to give the carbinolamine **7** instead of giving the pentacyclic indolenine.

On acetylation followed by methylation, **7** afforded the tertiary amide **9**, $[\alpha]^{29}_D$ −147.1° (*c* 1.21, $CHCl_3$), in 86% overall yield via **8**, mp 163–164 °C, $[\alpha]^{27}_D$ −100.3° (*c* 1.19, $CHCl_3$). Compound **9** was refluxed in *o*-dichlorobenzene to initiate a retro-Diels–Alder reaction to give the cyclopentenone **10**, $[\alpha]^{31}_D$ −64.6° (*c* 1.41; $CHCl_3$), in 66% yield. The enone **10**, on sequential one-flask ozonolysis, borohydride reduction, and periodate cleavage, furnished the lactol **14** in 62% yield via **11**–**13**. Refluxing **14** in methanol containing a trace of hydrochloric acid caused concomitant deacetylation and cyclization to give the tricyclic amino acetal[7] **15**, $[\alpha]^{32}_D$ − 96.2° (*c* 0.35, $CHCl_3$), in 71% yield. Treatment of **15** with boron tribromide[3a] followed by carbamoylation of the resulting phenol **16** afforded (−)-physovenine[7] (**1**), mp 126–127.5 °C, $[\alpha]^{30D}$ −90.0° (*c* 0.09,

(1) A recent review: Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 36, p 225.

(2) Cf. Brossi, A. *J. Med. Chem.* **1990**, *33*, 2311.

(3) Enantiocontrolled syntheses: (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641. (b) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109. (c) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411. (d) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872. (e) Node, M.; Hao, X.-j.; Fuji, K. *Chem. Lett.* **1991**, 57.

(4) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462.

(5) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271. Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636.

(6) Welch, W. M. *Synthesis* **1977**, 645.

(7) Enantiomeric excess was determined to be ≥97% by HPLC [CHIRACEL OJ, ^{i}PrOH–hexane (1:9)]. Spectral data (IR, ^{1}H NMR, and MS) of **15** were identical with those of racemic material: Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007.

0022-3263/91/1956-5982$02.50/0