JOC*Note*

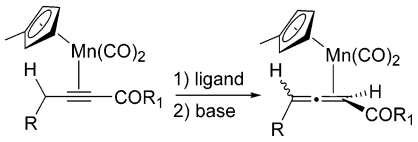
Studies on the Manganese-Mediated Isomerization of Alkynyl Carbonyls to Allenyl Carbonyls

Salvatore D. Lepore,* Anita Khoram, Deborah C. Bromfield, Pamela Cohn, Vinod Jairaj, and Maximilian A. Silvestri

Department of Chemistry, Florida Atlantic University, Boca Raton, Florida 33431-0991

slepore@fau.edu

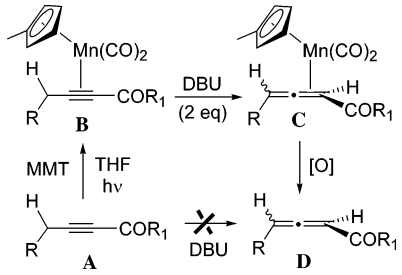
Received May 24, 2005



A study of the role of base in the isomerization of manganese-coordinated conjugated alkynyl carbonyls to the corresponding allenyl carbonyls is described. The use of phosphine additives indicates that manganese requires a ligand prior to isomerization with amine bases. A series of amine bases were also examined for their efficacy in this isomerization reaction revealing a strong dependence on pK_a. By contrast, potassium *tert*-butoxide led to rapid isomerization in the absence of added manganese ligand.

We are currently developing synthetic methods involving the use of allenyl carbonyls as heterodienes in an inverse electron demand Diels–Alder reaction for applications in the synthesis of pyran bicyclic natural products. A limiting factor in utilizing this new Diels–Alder methodology is the general paucity of methods to prepare allenyl carbonyl precursors from alkynyl carbonyls.[1] Recently we reported the development of an efficient method for the conversion of a variety of conjugated alkynyl esters to α-substituted conjugated allenyl esters (racemic) through the use of strong amide bases and metal halide salt additives.[2] However, after unsuccessful attempts to apply this strong-base method to the synthesis of allenyl ketones and aldehydes, we turned our attention to a reaction developed by Franck-Neumann involving the use of manganese complexes.[3] In this note, we describe a series of experiments that elucidate the role of base in the isomerization mechanism of manganese coordinated alkynes. Based on these mechanistic findings, conditions were developed to significantly enhance the rate of isomerization through the use of potassium *tert*-butoxide.

SCHEME 1. MMT-Mediated Conversion of Alkyne to Allenyl Ester



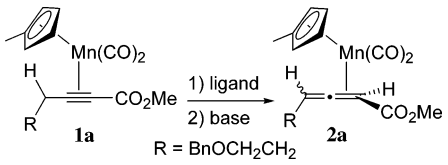
The mechanism of methylcyclopentadienyl manganese tricarbonyl (MMT) complexation to alkyne **A** has been investigated and is believed to involve an initial loss of a manganese carbonyl under UV irradiation to form a manganese–THF complex (Scheme 1).[3a] Subsequent base-mediated isomerization of manganese–alkyne species **B** affords the corresponding allene **C** with exclusive coordination of the α,β-double bond. However, the mechanism of the manganese-coordinated alkyne/allene isomerization reaction has received little comment in the literature. We hypothesize that the role of the manganese is to reverse the thermodynamic preference for the alkyne in favor of the allene in the isomerization reaction. Although no energetic comparisons between alkynyl and allenyl carbonyls have been reported, studies of related compounds suggest a thermodynamic preference for the alkyne. For example, a comparison of the reported heats of formation of 2-butyne[4] and 1,2-butadiene[5] indicates a 7 kcal/mol preference for the alkyne. In a manner analogous to the MMT isomerization reaction, Casey has shown that the stability of rhenium-complexed 2-butyne and 1,2-butadiene favors the complexed allene under thermodynamic conditions.[6] The importance of the use of manganese to alter the thermodynamic preference for alkyne is highlighted by our failed attempts to isomerize alkynyl **A** (R = $BnOCH_2CH_2$, R_1 = CH_3O) to the corresponding allene **D** using DBU in the absence of MMT coordination even after a prolonged reaction time (4 days).[7]

We were intrigued by the use of stoichiometric amounts of DBU in previous reports[3] involving the isomerization of manganese-coordinated alkynyl carbonyls to the corresponding allenyl carbonyls. An initial assessment of the mechanism of this isomerization reaction suggests that DBU should serve as a base by abstracting the γ-proton and shuttling it to the α-position in this equilibrium reaction. In this mechanistic conception, only a catalytic amount of DBU should be necessary to effect the alkyne/allene transformation and obtain the more thermodynamically stable isomer. However, attempts to form the coordinated allene **2a** from its coordinated alkynyl ester precursor **1a** using a catalytic amount of DBU failed

(1) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1993**, *58*, 3233.
(2) (a) Lepore, S. D.; He, Y. J.; Damisse, P. *J. Org. Chem.* **2004**, *69*, 9171. (b) Lepore, S. D.; He, Y. J. *J. Org. Chem.* **2005**, *70*, 4546.
(3) (a) Franck-Neumann, M.; Brion, F. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 688. (b) Franck-Neumann, M.; Neff, D.; Martina, D.; Nouali, H.; de Cian, A. *Synlett* **1994**, 657. (c) Franck-Neumann, M.; Martina, D.; Neff, D. *Tetrahedron*: *Asymmetry* **1998**, *9*, 697.
(4) Goldstein, E.; Buyon, G. M.; Jenn-Huei, L. I.; Norman, L. A. *J. Phys. Org. Chem.* **1996**, *9*, 191.
(5) Cowperthwaite, M.; Bauer, S. H. *J. Chem. Phys.* **1962**, *36*, 1743.
(6) Casey, P. C.; Brady, J. T. *Organometallics* **1998**, *17*, 4620.
(7) The use of a stronger base such as potassium *tert*-butoxide in this isomerization reaction gave a variety of condensation products.

10.1021/jo051040u CCC: $30.25
Published on Web 08/09/2005

TABLE 1. Role of Base and Ligand in the Isomerization of Alkyne Complex 1a to Allenyl Carbonyl 2a



entry	base	equiv of base	ligand[a]	reaction time (h)	yield[b] (%)
1	DBU	0.30		24	trace
2		1.4		24	68
3		2.0		24	61
4		0.40	TEA	30	62
5		0.40	TMEDA	22	88
6		0.40	DIPEA	24	64
7		0.40	pyridine	24	56
8		0.40	PPh_3	22	62
9		0.40	PMe_3	23	46
10	*t*-BuOK	2.0		1	55
11		1.0		1	62
12		0.40		24	15

[a] 1.0 equiv of ligand used. [b] Isolated yields.

(Table 1, entry 1). By contrast, the use of 1.4 or 2.0 equiv of DBU led to complete isomerization of coordinated alkynyl ester **1a** (Table 1, entries 2 and 3) to coordinated allene **2a** in reasonable isolated yields. Since an excess of DBU was required to isomerize the coordinated alkynyl ester **1a** to allenyl ester **2a**, we hypothesize that the first equivalent of DBU acts as a ligand for the manganese complex while the remaining 0.4 or 1.0 equiv of DBU served as a proton shuttle.

The isomerization of the coordinated alkynyl ester **1a** to coordinated allenyl ester **2a** was attempted with other amine bases. Initially, 2.0 equiv of amine bases such as triethylamine (TEA), tetramethylethylenediamine (TMEDA), diisopropylethylamine (DIPEA), and pyridine were used in the reaction; however, all of the bases failed to yield manganese-coordinated allenyl ester **3a** (data not shown). However, when a substoichiometric amount of DBU (0.4 equiv) was added to the alkyne/allene isomerization reactions containing 1.0 equiv of the weaker bases described above, complete isomerization to the coordinated allenyl carbonyl **2a** was observed (Table 1, entries 4−7). This lack of reactivity appears to correlate with the lower basicity of these amines relative to DBU. The approximate pK_a values in DMSO for the conjugate acid of TEA (9.0),[8] TMEDA (9.4),[9] DIPEA (8.5),[10] and pyridine (3.3)[8] are clearly lower than the estimated value for DBU (13.9).[10] These experiments suggest that the first equivalent of the weaker amine bases served as a manganese ligand and that the catalytic amount of DBU most likely functioned as a proton shuttle. The use of the weak bases TEA, DIPEA, and pyridine as ligands for manganese gave roughly the same isolated yields for the isomerization reaction 56−64%. Interestingly, the use of a bidentate ligand (TMEDA) in conjunction with catalytic DBU led to the highest isolated yield (88%) that we have observed for this isomerization reaction. Nonbasic triphenylphosphine and trimethylphosphine ligands were also utilized as potential chelates to the manganese complex[11] in the alkyne/allene isomerization reaction (Table 1, entries 8 and −9). In the presence of catalytic DBU complete conversion to allene **2a** was observed again suggesting that a manganese ligand is required for the isomerization reaction.

Studies of $Cp(CO)_2Mn$ bonding with related α,β-unsaturated ketones reveal that the metal−olefin bond is a combination of σ-donation of the alkene π-bonding electrons to vacant orbitals on the metal and π-back-bonding of metal α electrons to the antibonding π* orbital of the alkene.[12] Although the use of a ligand is required for the isomerization of manganese-coordinated alkyne **1a**, the ligand does not appear in final product **2a**. Based on this finding, we surmise that added amine[13] and phosphine ligands (Table 1 entries 4−9) coordinate the manganese center by an associative mechanism leading to an η^5 to η^3 cyclopentadienyl ring slippage[14] or folding.[15] Subsequent isomerization of the η^3 cyclopentadienyl complex[16] to give the complexed allene is followed by amine ligand dissociation leading to η^5 cyclopentadienyl manganese allene complex **2a**. It is unclear how the amine or phosphine ligands promote the isomerization reaction. Perhaps by reorganizing the ligand sphere of the manganese, the coordinated amine serves to weaken the alkyne−manganese bond either from diminished π-back-bonding of the metal or reduced σ-donation of the α,β-allene π-bond. A weakening of the alkyne−manganese bond should partially restore conjugation between the carbonyl group and the adjacent alkyne. We anticipate that the improved conjugation increases the acidity of the γ protons such that DBU, a relatively weak base, can be used to effect the isomerization reaction.

On the basis of the above discussion, we argued that a stronger base may obviate the requirement for a manganese ligand in the isomerization of **1** to **2**. The treatment of complex **1a** with 1 equiv of potassium *tert*-butoxide (pK_a = 31)[8] gave complete isomerization in reasonable isolated yield (Table 1, entry 11). A catalytic amount (40%) of potassium *tert*-butoxide (entry 12) gave

(8) (a) Kolthoff, I. M.; Chatooni, M. K.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23. (b) Chmurznski, L. *J. Heterocycl. Chem.* **2000**, *37*, 71. (c) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295. (d) Arnett, E. M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808.

(9) Bruice, P. Y. *J. Am. Chem. Soc.* **1983**, *105*, 4982. It is not clear from this reference where the pK_a value of TMEDA was obtained or in which solvent the value was determined.

(10) (a) Streitwieser, A.; Kim, Y. J. *J. Am. Chem. Soc.* **2000**, *122*, 11783. (b) Kelly-Rowley, A. M.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1995**, *117*, 3438. (c) Data from the Streitwieser and Anslyn publications were used to estimate the pK_a of DBU and DIPEA in DMSO. A linear correlation plot (R^2 = 0.994) of pK_a values (DMSO) vs pK_a values (ACN) for a variety of bases was used to estimate the pK_a of DBU and DIPEA in DMSO.

(11) (a) Loim, N. M.; Khruscheva, N. S.; Lukashov, Yu. S.; Sokolov, V. I. *Russ. Chem. Bull.* **1999**, *48*, 984. (b) Le Plouzennec, M.; Le Moigne, F.; Dabard, R. *J. Organomet. Chem.* **1977**, *132*, 409. (c) Le Moigne, F.; Dabard, R.; Le Plouzennec, M. *J. Organomet. Chem.* **1976**, *122*, 365.

(12) Giffard, M.; Gentric, E.; Touchard, D.; Dixneuf, P. *J. Organomet. Chem.* **1977**, *129*, 371. Giffard, M.; Dixneuf, P. *J. Organomet. Chem.* **1977**, *85*, C26.

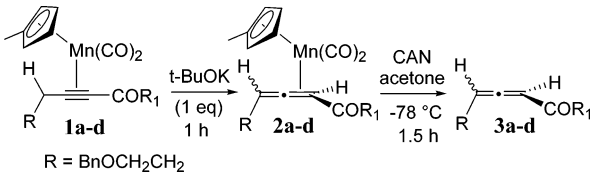
(13) (a) Koelle, U.; Aechen, A. *J. Organomet. Chem.* **1977**, *133*, 58. (b) Hershberger, J. W.; Kochi, J. K. *Polyhedron* **1983**, *2*, 929.

(14) (a) O'Connor, J. M.; Casey, C. P. *Chem. Rev.* **1987**, *87*, 307. (b) Veiros, L. F. *Organometallics* **2000**, *19*, 3127. (c) Veiros, L. F. *J. Organomet. Chem.* **1999**, *587*, 221.

(15) Veiros, L. F. *Organometallics* **2000**, *19*, 3127.

(16) In a related system, cyclopentadienyl ruthenium alkyne complexes have been isomerized to give the corresponding vinylidenes in the presence of phosphine ligands via an η^5 to η^3 slippage mechanism. Bassetti, M.; Alvarez, P.; Gimeno, J.; Lastra, E. *Organometallics* **2004**, *23*, 5127.

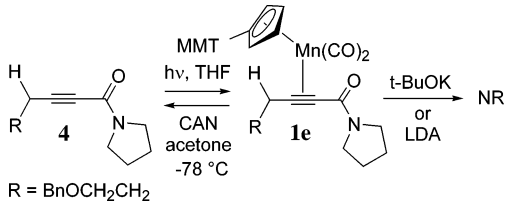
TABLE 2. Coordination of MMT to Alkynyl Carbonyls Followed by Isomerization and Oxidative Decomplexation



		% yield[a]	
entry	R_1	**2**	**3**
1	OMe	62	72
2	OPh	68	44[b]
3	Me	46	71[b]
4	*t*-Bu	58	65

[a] Isolated yields. [b] Based on recovered starting material.

SCHEME 2. Base Stability of MMT-Complexed Alkynyl Amide



partial conversion to product (15%), suggesting that the alkoxide does not act as a manganese ligand. Importantly, the alkoxide-mediated isomerization reaction reached completion in less than 1 h whereas the use of DBU required 24 h.

We next examined the conversion of complexed alkynyl carbonyls **1** to their corresponding coordinated allenyl carbonyls **2** using *tert*-butoxide base (Table 2, entries 1−5). The identity of complexed allenes **2** was then confirmed by oxidative manganese decomplexation to give **3** which were fully characterized (Table 2, entries 1−5). Methyl ester **1a**, phenyl ester **1b**, and *tert*-butyl ketone **1d** were rapidly (1 h) converted to the corresponding allenes **2** in similar yields. The isomerization of complexed methyl ketone **1c** afforded a lower yield (46%) of the allene product leading to a variety of condensation products most likely arising from deprotonation of the enolizable methyl protons.[17]

Finally, the synthesis of allenyl amides using the MMT-coordinated isomerization method has not been reported prompting us to attempt this transformation using both DBU and *tert*-butoxide with this class of compounds. The light-mediated coordination of MMT with alkynyl amide **4** was far more sluggish than the analogous ester and ketone systems requiring 3 days to achieve reasonable yields of complex **1e** (Scheme 2). However, once complex **1e** was formed it exhibited remarkable stability surviving silica gel purification and long-term storage.[18] Furthermore, complex **1e** failed to undergo isomerization in the presence of either DBU or *tert*-butoxide nor did the use of lithium diisopropyl amide (a significantly stronger base) yield the desired product.

(17) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328.
(18) The complexed alkynyl amide proved more stable when stored as a neat oil and protected from light.

In light of its considerable base stability, the manganese-containing unit of complexes such as **1e** may find applications as transition metal solid-phase linkers.[19] The removal of this "protecting group" was accomplished in 66% yield using the CAN oxidation procedure.

In summary, we have demonstrated that the isomerization of manganese-chelated alkynyl carbonyls to the corresponding allenyl carbonyls using catalytic DBU requires a manganese ligand. The use of a stoichiometric bidentate ligand (TMEDA) in conjunction with catalytic DBU led to the highest isomerization yield. With a stronger base such as potassium *tert*-butoxide, complete and rapid isomerization is accomplished using 1 equiv of the base in the absence of added ligand.

Experimental Section

Representative Procedure: MMT Coordination of Methyl 6-Benzyloxyhexa-2,3-dienoate (2a). An oven-dried vial (20 mL) was equipped with a rubber septa and a magnetic stir bar and charged with argon. Methylcyclopentadienyl manganese tricarbonyl (MMT) (0.100 mL, 0.64 mmol) was added to the vial via syringe. The argon atmosphere was evacuated from the reaction vessel and reintroduced into the vial. The process was repeated three times. Dry THF (4 mL) was added into the vial via syringe and the resulting solution was stirred at ambient temperature followed by irradiation with long-wave ultraviolet light (365 nm) for 30 min. The carbon monoxide released during the coordination reaction was then removed via purging with argon. Methyl 6-benzyloxy-hex-2-ynoate (0.112 g, 0.48 mmol) was dissolved in THF (4 mL) and added to the reaction vial via syringe. The resulting solution was stirred at ambient temperature and irradiated with long-wave ultraviolet light for 12 h. Analysis via TLC (eluant 20% EtOAc/hexanes) revealed that complexation of the alkyne (complexed alkyne R_f 0.42, free alkyne R_f 0.47) was complete. The reaction vessel was wrapped in tin foil and a THF solution of potassium *tert*-butoxide (0.60 mL, 0.53 mmol) was added followed by stirring for 1 h at ambient temperature. Analysis via TLC (eluant 20% EtOAc/hexanes) revealed that complete isomerization to the allene had occurred. A crude oil (reddish) was obtained after solvent removal, which was purified by silica flash chromatography (50 g, 3 × 15 cm) with a gradient elution (0−15% EtOAc in hexanes) to yield a yellow oil (125 mg, 62%): R_f 0.29 (20% EtOAc in hexanes). LRMS (CI) $[M + H]^+$ 423.

Representative Procedure: Manganese Decomplexation of Methyl 6-Benzyloxyhexa-2,3-dienoate (3a). A round-bottomed flask containing MMT-coordinated methyl 6-benzyloxyhexa-2,3-dienoate (**3a**) (480 mg, 1.13 mmol) dissolved in acetone (10 mL) under an argon atmosphere was cooled to −78 °C for 5 min. Cerium ammonium nitrate (2.00 g, 3.66 mmol) dissolved in acetone (70 mL) was added dropwise to the flask via syringe. The resulting reaction mixture was stirred at −78 °C for an additional 1.5 h. The reaction mixture was then concentrated in vacuo and passed through a plug of silica gel (90 g) to remove excess cerium salts flushing with EtOAc. Following solvent removal, the crude product (an oil) was purified via flash column chromatography using silica (20 g, 2 × 14 cm) with gradient elution (4−12% EtOAc/hexanes). Like fractions were combined and solvent removed in vacuo to yield a colorless oil (187 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5 H), 5.72−5.67 (m, 1H), 5.63−5.60 (m, 1H), 4.52 (s, 2H), 3.72 (s, 3H), 3.59 (t, J = 6.5 Hz, 2H), 2.49−2.43 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.5, 166.5, 138.2, 128.4, 127.6, 92.3, 88.2, 73.0, 68.9, 52.0, 28.1; HRMS (CI) $[M + H]^+$ 233.1101, calculated for $C_{14}H_{16}O_3$ $[M + H]^+$ 233.1178.

Phenyl 6-Benzyloxyhexa-2,3-dienoate (3b). The crude oil was purified via flash column chromatography using silica (30 g, 3 × 10 cm) with gradient elution (6−20% EtOAc−hexanes)

(19) Zhang, Z.; Lepore, S. D. *Tetrahedron Lett.* **2002**, *43*, 7357.

to yield a colorless oil (129 mg, 44%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.33 (m, 7 H), 7.24−7.21 (m, 1 H), 7.11−7.09 (m, 2 H), 5.83−5.78 (m, 2H), 4.54 (s, 2H), 3.63 (t, J = 6.4 Hz, 2H), 2.55−2.49 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.4, 164.5, 150.8, 138.1, 129.3, 128.4, 127.7, 125.7, 121.5, 92.8, 88.1, 73.1, 68.9, 28.1; HRMS (CI) $[M + H]^+$ 295.1339, calculated for $C_{19}H_{18}O_3$ $[M + H]^+$ 295.1334.

7-Benzyloxyhepta-3,4-dien-2-one (3c). The crude oil was purified via flash column chromatography using silica (40 g, 3 × 11 cm) with gradient elution (0−10% EtOAc/hexanes) to yield a colorless oil (105 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5 H), 5.75−5.66 (m, 2H), 4.52 (s, 2H), 3.61 (t, J = 6.2 Hz, 2H), 2.48 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.7, 199.2, 138.0, 128.4, 127.7, 98.1, 92.3, 73.1, 68.7, 28.4, 26.5; HRMS (CI) $[M + H]^+$ 217.1232, calculated for $C_{14}H_{16}O_2$ $[M + H]^+$ 217.1229.

8-Benzyloxy-2,2-dimethylocta-4,5-dien-3-one (3d). The crude oil was purified via flash column chromatography using silica (50 g, 3 × 12 cm) with gradient elution (4−12% EtOAc/hexanes) to yield a colorless oil (164 g, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5 H), 6.08−6.05 (m, 1H), 5.66−5.61 (m, 1H), 4.52 (s, 2H), 3.59 (t, J = 6.6 Hz, 2H), 2.49−2.43 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.9, 208.6, 144.1, 128.4, 127.7, 127.6, 91.7, 73.0, 69.1, 28.3, 26.6. HRMS (CI) $[M + H]^+$ 259.1698, calculated for $C_{17}H_{22}O_2$ $[M + H]^+$ 259.1698.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This work was also supported by a grant from the National Institute of General Medical Science (GM067635-01) and the National Science Foundation Division of Undergraduate Education (NSF-0311369) for the 400 MHz NMR used in this study. Finally, we thank the Ethyl Corporation for a generous donation of MMT.

Supporting Information Available: Copies of ^{1}H NMR spectra for compounds **3a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051040U