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Manganese η^2-Complexes as Auxiliaries for Stereoselective Aldol Synthesis of Allenyl Carbinols

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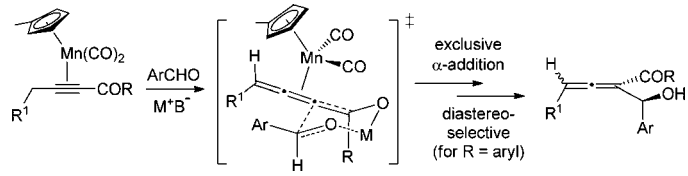
ABSTRACT



A convenient and robust manganese auxiliary was linked via an η^2-bond to alkynyl esters and ketones using a mild complexation reaction with methylcyclopentadienyl manganese tricarbonyl. This complex readily underwent aldol reactions with exclusive α-substitution and in good diastereoselectivities especially with aryl ketone substrates. This selectivity has been rationalized using a cyclic transition state model in which the manganese auxiliary plays a critical role in promoting *E*(*O*)-geometry of the cumulenolate intermediate.

Neutral η^2-complexed transition metals are virtually unknown as auxiliaries for the mild and stereoselective formation of carbon−carbon bonds. Certainly the use of allylmolybdenum complexes by Liebeskind in 1,5-Michael-type additions serves as a tantalizing and rare example of the potential for unprecedented control in bond formation afforded by transition metal η^3-auxiliaries.[1] We are particularly interested in developing mild and stereoselective methods for the preparation of allenyl esters from easily accessible alkynes. Allenyl esters and ketones have taken on increased importance as intermediates in organic synthesis.[2] We have recently exploited the potential of functionalized allenyl esters for a highly abbreviated synthesis of [3.2.1] bridged bicyclic compounds.[3] In this regard, we required a regio- and diastereoselective method for the preparation of α-carbinol allenyl esters. Hammond[4] and Miesch[5] have recently reported the synthesis of γ-carbinol allenoates from propargyl and allenyl esters; however, these reported methods are not well-suited to the preparation of the α-carbinol analogue. Others have demonstrated that allenyl ketones can be further functionalized at the α-position by condensation with aldehydes.[6] These methods suffer from concomitant formation of β-alkynyl ketones and dehydration products. In all reported cases, the aldol reactions proceed with little or no diastereoselectivity.

In our attempts to address this shortcoming, we turned to a pioneering report by Franck-Neumann demonstrating that alkynyl esters η^2-complexed to methylcyclopentadienyl manganese dicarbonyl (MMD) could be isomerized to the corresponding allene in the presence of a stoichiometric

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(3) Maity, P.; Lepore, S. D. *J. Am. Chem. Soc.* **2009**, *131*, 4196.

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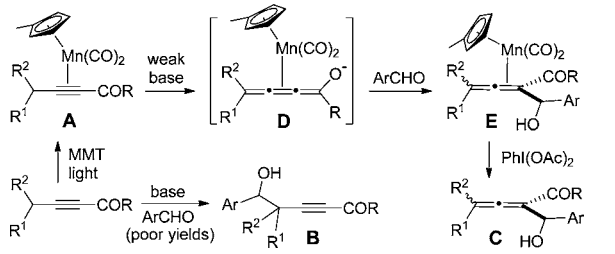
amine base.[7] The work of Franck-Neumann and others[8] have clearly established that MMD coordinates the more electron-deficient α,β-bond of the allenyl carbonyl system. We have previously hypothesized that MMD coordinates alkenes and alkynes with an η^2-bond that exhibits significant metallocyclic character leading to a preference for bonding with carbon−carbon double bonds (metallocyclopropane) relative to triple bonds (more strained metallocyclopropene) and thus reversing thermodynamic preferences to shift equilibrium toward allene formation.[9] On the basis of this conception, we reasoned that the preference of manganese for double bonds could be used to solve the long-standing problem of selective addition reactions to alkynyl esters and ketones. Thus under very mild light activation, the MMD group is introduced to an alkyne to give intermediate **A** (Scheme 1).

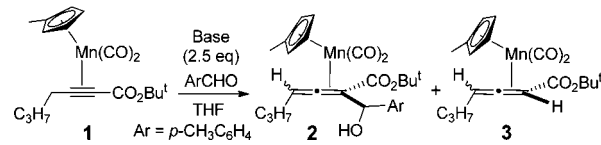
Scheme 1. Manganese as an α-Directing Group in Aldol Additions



A subsequent deprotonation leads to cumulenolate **D** with preferred addition of aldehyde at the α-position to give **E** affording the more favorable manganese allene complex. Importantly, similar reactions with noncomplexed alkynyl esters lead to α-carbinol products often in low yields.[10,11] A final mild oxidation of **E** then reveals desired allenyl α-carbinol **C**. In this communication, we describe our validation of this designed aldol addition reaction as a potentially general solution to the stereoselective synthesis of α-substituted allenes.

Our initial studies involved the addition of aldehyde MMD-complex **1**,which was conveniently generated in good yields using inexpensive and commercially available methylcyclopentadienyl manganese tricarbonyl (MMT) under the action of a very low energy UV lamp.[12] Complex **1** was then treated with a variety of bases to identify suitable conditions for the aldol addition. We quickly noted that excess base (2.5 equiv) generally led to improved yields. Among the various bases examined (Table 1), ^{t}BuOK at 0 °C gave the best yield of aldol

Table 1. Optimization of MMD-Mediated Aldol Additions



entry	base	T (°C)	time (h)	ArCHO (equiv)	**2**:**3**[a]	% yield[b]
1	LDA	−55 to rt	20	1.5	100:0	20
2	TBAF	0 to rt	48	1.5	0:100	10
3	LiHMDS	−78 to rt	24	1.5	50:50	25
4	KHMDS	−78	3	1.5	0:100	65
5	DBU	−78 to rt	12	1.5	50:50	40
6	NaH	0 to rt	24	1.5	100:0	10
7	KH	0 to rt	12	1.5	50:50	68
8	^{t}BuOLi	−78 to rt	12	1.5	0:100	55
9	^{t}BuOK	−78	4	1.5	50:50	67
10	^{t}BuOK	−55	3	1.5	60:40	55[c]
11	^{t}BuOK	0	3	1.5	70:30	70[c]
12	^{t}BuOK	0	3	2.5	84:16	74[c]
13	^{t}BuOK	0	3	5.0	80:20	67[c]
14	^{t}BuOK	0	3	10	82:18	67[c]

[a] Based on isolated yields of Mn-complexed products. [b] Combined isolated yields. [c] Isolated yields of decomplexed **2**.

product **2**. Lower temperatures appeared to depress reaction yields and lead to greater amounts of isomerization product **3**. We also examined the reaction using varying equivalents of an aromatic aldehyde and found that 2.5 equiv led to optimal yields. The use of aliphatic aldehydes in this reaction primarily led to isomerized product **3**. Although these complexed allenyl α-carbinol products are rather stable toward silica gel chromatography, a slight improvement in product yield was realized when the crude products were first treated with a mild oxidant to remove the MMD auxiliary prior to column purification (Table 1, entries 10−14). Thus a variety of complexed alkynoates **4** were converted to allenoates **6** in good two-step isolated yields (Table 2).

The reagent of choice for the oxidative removal of MMD from crude products **5** was $PhI(OAc)_2$. The use of 2 equiv of this oxidant provided good overall yield of aldol product within 1.5 h at room temperature. The aldol/oxidation reaction of **4** also gave good yields with a variety of electron-rich and electron-deficient aromatic aldehydes. Alkynyl ketones are well-known for their propensity to act as Michael acceptors; indeed, in previous alkylation studies, we have observed dimerization products arising from unwanted conjugate additions.[10a] By contrast, substrates **4** (R = Ph) were converted exclusively to aldol products in good two-step yields (Table 2, entries 9−23). In this context, MMD appears to act as an alkyne protecting group.

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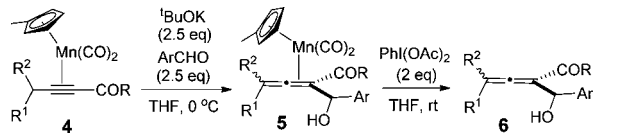
(10) Our early studies in this vein revealed that a direct alkylation of an alkynyl ester to give allene product is usually not possible except in the presence of multiple equivalents of strong amide bases leading to dianion intermediates. Even under these forcing conditions, the method was limited to the formation of allenyl esters with α-silyl, stannyl, and methyl substitution: (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.
(11) Our attempts to obtain α-substituted allenyl esters from β-keto esters using an efficient dehydrative protocol also suffered similar limitations: Maity, P.; Lepore, S. D. *J. Org. Chem.* **2009**, *74*, 158.
(12) The MMD complexes are air- and light-stable and amenable to flash chromatography. The auxiliary is introduced by replacing a carbon monoxide ligand on methylcyclopentadienyl manganese tricarbonyl (MMT) with the alkynyl ketone or ester substrate. The MMT reagent is inexpensive and widely available (e.g., Bosche Scientific, Inc. for less than $1/g).

Table 2. Generality of One-Pot Aldol Addition/Oxidation Reactions



entry	R	R^1	R^2	Ar	%Yield (dr)
1	^{t}BuO	n-C_3H_7	H	C_6H_5	84 (1.5:1)
2	^{t}BuO	n-C_3H_7	H	p-$MeOC_6H_4$	72 (2.0:1)
3	^{t}BuO	n-C_3H_7	H	p-$NO_2C_6H_4$	88 (1.8:1)
4	MeO	n-C_3H_7	H	C_6H_5	88 (1.8:1)
5	MeO	n-C_3H_7	H	p-$CH_3C_6H_4$	76 (2.0:1)
6	MeO	n-C_3H_7	H	p-$MeOC_6H_4$	72 (1.5:1)
7	MeO	n-C_3H_7	H	p-$NO_2C_6H_4$	70 (2.0:1)
8	MeO	n-C_3H_7	H	p-ClC_6H_4	90 (1.8:1)
9	Ph	n-C_3H_7	H	C_6H_5	76 (13:1)
10	Ph	n-C_3H_7	H	p-$CH_3C_6H_4$	80 (12.6:1)
11	Ph	n-C_3H_7	H	p-$MeOC_6H_4$	81 (9.0:1)
12	Ph	n-C_3H_7	H	p-$NO_2C_6H_4$	83 (12.5:1)
13	Ph	n-C_3H_7	H	p-ClC_6H_4	73 (10:1)
14	Ph	PhC_2H_4	H	C_6H_5	79 (12:1)
15	Ph	PhC_2H_4	H	p-$CH_3C_6H_4$	82 (10.5:1)
16	Ph	PhC_2H_4	H	p-$MeOC_6H_4$	76 (14:1)
17	Ph	PhC_2H_4	H	p-$NO_2C_6H_4$	78 (12:1)
18	Ph	PhC_2H_4	H	p-ClC_6H_4	92 (9.5:1)
19	Ph	C_5H_{10}	C_5H_{10}	C_6H_5	60
20	Ph	C_5H_{10}	C_5H_{10}	p-$CH_3C_6H_4$	65
21	Ph	C_5H_{10}	C_5H_{10}	p-$MeOC_6H_4$	52
22	Ph	C_5H_{10}	C_5H_{10}	p-$NO_2C_6H_4$	55
23	Ph	C_5H_{10}	C_5H_{10}	p-ClC_6H_4	71

[a] Isolated two-step yields; dr based on proton NMR.

A crystal structure of product *rac*-**8** (major diastereomer) was obtained to determine its relative stereochemistry (Figure 1). We believe the relatively high diastereoselectivity of **8**

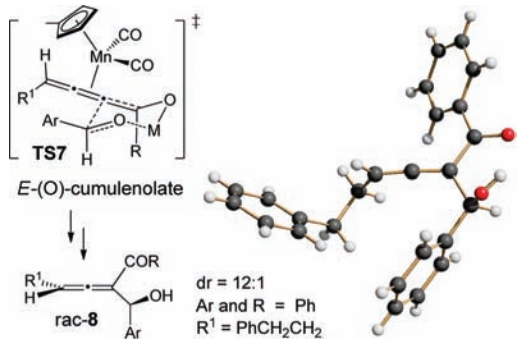
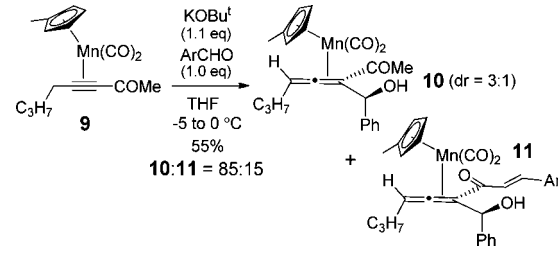


Figure 1. Mechanistic rationale for diastereoselectivity with allenyl ketones and crystallographic evidence.

(and those of entries 9−18 in Table 2) to be the result of the selective formation of an *E*(*O*)-cumulenolate. Specifically, the bulky MMD auxiliary is thought to lead to an intermediate favoring an *anti* orientation with respect to the R and R^1 groups. The *rel*-(*S*,*S*) configuration of **8** can then be rationalized on the basis of a metal chelated cyclic transition state (**TS7**) that positions the aryl group of the aldehyde in a pseudoequatorial orientation (Figure 1). In this mechanistic conception, large R groups (e.g., R = Ph), in addition to affording high *E*(*O*) selectivity, promote the positioning of the aldehyde substituent in **TS7** to avoid 1,3-diaxial repulsions.

The MMD auxiliary can also be used to induce a third level of control (i.e., chemoselectivity). Thus, even in an aldol reaction with alkynyl methyl ketone **9** (this class of substrate is well-known to react primarily at the methyl position),[13] α-carbinol allenoate **10** was the major product giving only a small amount of condensation product **11** (Scheme 2). The

Scheme 2. MMD Auxiliary Favors the α- over the α′-Position



modest diastereoselectivity of product **10** (3:1) accords with our transition state model as the small size of the ketone methyl group would not be expected to exert selectivity in cumulenolate formation.

In conclusion, we have introduced a new transition metal auxiliary in aldol additions of alkynyl esters and ketones leading to allene products with exclusive α-substitution. These alkyne substrates have traditionally proven to be problematic in terms of stereocontrol in bond formation. The key feature of this method is the use of a convenient and inexpensive alkyne-chelating reagent (MMT) that alters the thermodynamic preference of the reaction in favor of allene formation and provides a basis for diastereoselectivty especially with alkynyl ketones. With a mechanistic framework in place for understanding the observed regio- and diastereoselectivity in this system, efforts are now being put forth for the development of a catalytic asymmetric synthesis of allenes taking advantage of the manganese auxiliary as a chelating center.

Acknowledgment. We thank the National Institutes of General Medical Science (073621-01) and NSF (0311369) for financial support.

Supporting Information Available: Experimental procedures and characterization data of all new compounds; copies of ^{1}H and ^{13}C NMR spectra; X-ray crystallographic studies of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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