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A New Reaction Motif: "Homo-S_N2'-Like" Direct Nucleophilic Addition to Neutral η^3-Allylmolybdenum Complexes. Total Synthesis of the Antimalarial (+)-Isofebrifugine

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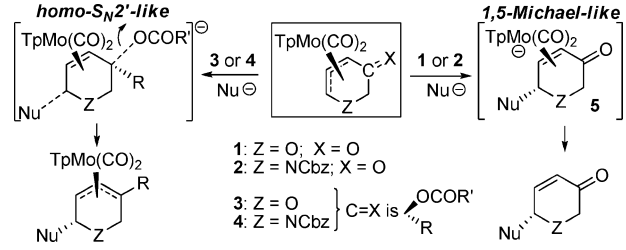
Enantiomerically pure, air- and moisture-stable $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes, **1** and **2** (Scheme 1), are powerful scaffolds for the enantiocontrolled construction of substituted heterocycles.[1] Readily available in multigram quantities,[1m] they not only provide new bond construction strategies to access a variety of natural products but also constitute platforms from which to explore novel reactivity. A survey of the literature shows that a $TpMo(CO)_2$-stabilized carbocation is a requisite intermediate in almost all synthetic transformations of the scaffolds.[1a−i,k,l,n] It was only recently that a new, noncationic pathway taking place through the direct nucleophilic addition of an internal enolate to a terminal π-carbon of a neutral 5-oxo-η^3-pyranyl (and pyridinyl) moiety was reported.[1j,o] This synthetically useful 1,5-Michael-like functionalization mode was explained, in part, by the tendency of $TpMo(CO)_2$ systems to favor six-coordinate over seven-coordinate structures[2] and also because the nucleophilic addition generates a characterizable anionic $TpMo(CO)_2$ intermediate (**5** in Scheme 1), which possesses three good π-back-bonding ligands to delocalize the anionic charge: 2 terminal CO's and the η^2-enone ligand. These observations led us to wonder if the preference for six-coordinate over seven-coordinate structures alone would be sufficient to enhance a more general nucleophilic addition pathway by which $TpMo(CO)_2(\eta^3$-allyl) systems that are less-activated than the 5-oxo-η^3-pyranyl/pyridinyl complexes could be functionalized. Following these considerations, we report herein the first examples of the "homo-S_N2'-like" intermolecular nucleophilic substitution of charge neutral $TpMo(CO)_2$(5-acyloxy-η^3-pyranyl) and $TpMo(CO)_2$(5-acyloxy-η^3-pyridinyl) complexes (**3** and **4**, Scheme 1). This mechanistically new enantiocontrolled carbon−carbon bond forming reaction occurs enantiospecifically with excellent anti stereoselectivity.

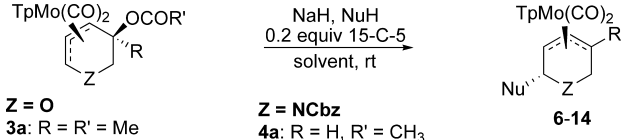
The requisite substrates **3a**−**c**, **4a,b** (Table 1) are prepared in high yields from the readily available $TpMo(CO)_2$(5-oxo-η^3-pyranyl) and $TpMo(CO)_2$(5-oxo-η^3-pyridinyl) complexes **1** and **2** through hydride or Grignard reagent addition to the carbonyl group followed by acylation.[3] Initial experiments were conducted on the racemic forms of $TpMo(CO)_2$(5-acetoxy-η^3-pyranyl) and $TpMo(CO)_2$(5-acetoxy-η^3-pyridinyl) complexes. Treatment of **3a**−**c**,**4a,b** with anionic carbon nucleophiles (pK_a range = 13.3−18.0 in DMSO)[4] in the presence of catalytic 15-crown-5 ether afforded substitution products **6**−**14** in good to excellent yields (Table 1). Moreover, as indicated in entry 1, the use of the high enantiopurity scaffold **3a** led to the corresponding substitution product without loss of enantiopurity. Reactions of carbanions generated from precursors that are more acidic than dimethyl malonate benefited from the use of acetonitrile rather than THF as solvent (compare entry 2 and 3). When R on the scaffold is hydrogen, higher product yields were obtained using *p*-nitrobenzoate rather than acetate as the leaving group.

Scheme 1. Nucleophilic Functionalization of Neutral $TpMo(CO)_2(\eta^3$-pyranyl/pyridinyl) Complexes



The homo-S_N2'-like process does not appear to proceed by way of an *in situ* generated Mo-stabilized carbocation that is then trapped by the nucleophile. Exposure of **3a** to $TrPF_6$ generates the molybdenum-stabilized carbocation **15**, which upon treatment with sodium dimethylmalonate and 15-crown-5-ether shows a different reaction profile from the reactions in Table 1: only 18% of nucleophilic addition compound **6** is produced (Scheme 2). The reaction mostly forms the elimination product **16** in 55% yield. Additional observations are consistent with the postulate of direct attack of the nucleophile at the neutral η^3-allylmolybdenum moiety: (1) compound **3a** is recovered unchanged after stirring overnight in THF/Et_3N; (2) the homo-S_N2'-like substitution reaction proceeds faster with less substituted substrates: both **3b** and the acetate corresponding to **3b** (S2 in the Supporting Information) are faster reacting than the more substituted **3a**; and (3) most reactions are significantly accelerated by the use of 15-crown-5 ether.

Table 1. "Homo S_N2'-Like" Substitution Reactions



Z = O
3a: R = R' = Me
3b: R = H, R' = *p*-$C_6H_4NO_2$
3c: R = Ph, R' = CH_3

Z = NCbz
4a: R = H, R' = CH_3
4b: R = H, R' = *p*-$C_6H_4NO_2$

entry	reactant	NuH	solvent	% yield
1	**3a**	$CH_2(COOMe)_2$	THF	**6**, 99[a]
2	**3a**	CH_3COCH_2COOMe	ACN	**7**, 69(99)[b,c]
3	**3a**	CH_3COCH_2COOMe	THF	**7**, 31(99)[b,c]
4	**3a**	$CH_3CH(COOEt)_2$	THF	**8**, 66(94)[b]
5	**3a**	CH_3NO_2	DMSO	**9**, 80[d]
6	**3b**	CH_3COCH_2COOMe	ACN	**10**, 94[c]
7	**3b**	CH_3COCH_2COMe	ACN	**11**, 68
8	**3c**	$CH_2(COOMe)_2$	THF	**12**, 90
9	**4a**	$CH_2(COOMe)_2$	ACN	**13**, 94
10	**4b**	CH_3COCH_2COOMe	ACN	**14**, 91[c]

[a] 96% ee product from 96% ee starting material. The enantiopurity was determined by chiral HPLC. [b] The number in the parentheses is the yield based on the recovery of starting material. [c] An approximate 1.5:1 ratio of diastereomers was observed according to crude NMR. [d] No 15-crown-5-ether was added.

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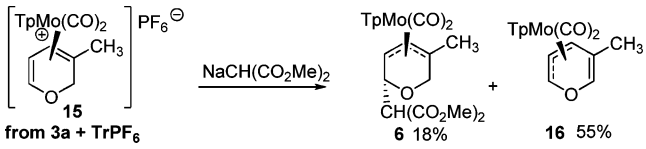
Scheme 2. Control Experiment: Reaction of Molybdenum-Stabilized Carbocation **15** with Sodium Dimethyl Malonate



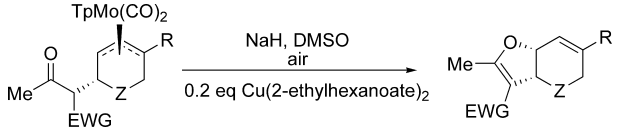
An X-ray crystal structure of **8** (Table 1) unambiguously established direct *anti* nucleophilic attack at the neutral η^3-allylmolybdenum (details are provided in the Supporting Information). In contrast some Mo-catalyzed allylic alkylations occur through a metal-centered attack,[5] and Green has disclosed results consistent with the direct attack of a nucleophile *at the molybdenum moiety* of a neutral η^3-lactonylmolybdenum complex.[6]

A represenative sampling of product molybdenum complexes were cleanly converted to bicyclic annulation products in high yields and with excellent stereoselectivity (Table 1). For example, treatment of **7**, **10**, **11**, and **14** with NaH in DMSO in the presence of a catalytic amount of copper(II) 2-ethylhexanoate[7] open to air provided the annulation products **17**−**20** in 83−92% isolated yields (Table 2). In earlier work, Pearson used different nonbasic annulative demetalation reagents such as I_2[8] or $NOBF_4$[9] for related transformations, but exposing our substrates to these reagents (as well as prolonged standing in $CDCl_3$) yielded only the undesired elimination product (i.e., **16**, Scheme 2) through ionization of the carbon nucleophile[10] and subsequent proton loss. Mechanistically, we suggest that the reactions of Table 2 proceed through one-electron oxidation of the stabilized enolate to a radical[11] that then reacts with the adjacent η^3-allylmolybdenum moiety.

The synthetic potential of this methodology was demonstrated by an asymmetric synthesis of the antimalarial alkaloid (+)-isofebrifugine (Scheme 3).[12]

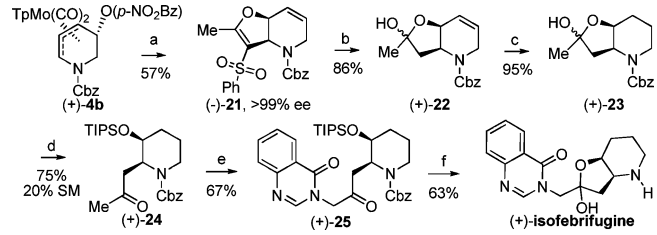
Upon treatment of high enantiopurity (+)-**4b**[3] in one pot with phenyl sulfonyl acetone anion in DMSO followed by a copper-catalyzed annulative demetalation, the bicyclic product (−)-**21** was obtained in good yield without loss of enantiopurity. Desulfonylation with 10% Na/Hg and an acidic workup afforded the hemiketal (+)-**22** in 86% yield. Hydrogenation on PtO_2 yielded (+)-**23** which was subjected to standard TIPS protection conditions to furnish (+)-**24** selectively in 75% yield (along with the recovery of 20% of the starting material). The ketone (+)-**24** was monobrominated by subjecting its *in situ* generated silyl enol ether to NBS. The crude α-bromoketone was directly treated with 4-hydroxyquinazoline to afford (+)-**25**. Finally, deprotection with 6 M HCl delivered (+)-isofebrifugine, **26**, in 63% yield ($[\alpha]_D^{20} = +129$, $c = 0.3$, $CHCl_3$, Lit.[12a] $[\alpha]_D^{20} = +131$, $c = 0.35$, $CHCl_3$).

Table 2. Cu-Catalyzed Aerobic Annulative Demetalation



entry	reactant	Z	EWG	R	% yield
1	**7**	O	COOMe	Me	**17**, 85
2	**10**	O	COOMe	H	**18**, 83
3	**11**	O	COMe	H	**19**, 92
4	**14**	NCbz	COOMe	H	**20**, 83

Scheme 3. Enantiocontrolled Synthesis of (+)-Isofebrifugine[a]



[a] (a) NaH, $CH_3COCH_2SO_2Ph$, DMSO, rt, overnight then NaH, Cu(ethylhexanoate)$_2$, air, overnight. (b) (1) 10% Na/Hg,THF/MeOH, Na_2HPO_4, −35 °C to rt; (2) HCl, acetone. (c) PtO_2, H_2. (d) TIPSCl, imidazole, DMF. (e) (1) TMSOTf, TEA, DCM then NBS; (2) 4-hydroxyquinazoline, NaH, THF, 15-C-5. (f) 6 M HCl, reflux, 90 min.

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Note Added after ASAP Publication. Due to a production error the graphics in Tables 1 and 2 were incorrect in the version published ASAP August 10, 2009; the correct version was published ASAP August 14, 2009.

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

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