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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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Abstract

Charge neutral $\text{TpMo}(\text{CO})_2(5\text{-acyloxy-}\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(5\text{-acyloxy-}\eta^3\text{-pyridinyl})$ scaffolds undergo a novel intermolecular “homo-S_N2’-like” reaction with a variety of carbon nucleophiles. Combined with an annulative demetalation, the homo-S_N2’-like substitution/annulative demetalation sequence rapidly generates 2,7-dioxabicyclo[4.3.0]nonane and 2-aza-7-oxabicyclo[4.3.0]nonane frameworks in good to excellent yields with high enantiopurity. An enantiocontrolled total synthesis of the antimalarial alkaloid (+)-isofebrifugine was achieved utilizing this reaction cascade.

Enantiomerically pure, air and moisture-stable $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(\eta^3\text{-pyridinyl})$ complexes, **1** and **2** (Scheme 1), are powerful scaffolds for the enantiocontrolled construction of substituted heterocycles.¹ Readily available in multigram quantities,^{1m} they provide not only new bond construction strategies to access a variety of natural products, but they also constitute platforms from which to explore novel reactivity. A survey of the literature shows that a $\text{TpMo}(\text{CO})_2$ -stabilized carbocation is a requisite intermediate in almost all synthetic transformations of the scaffolds. 1a–i, 1k, 1l, 1n It was only recently that a new, non-cationic pathway taking place through the direct nucleophilic addition of an internal enolate

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Supporting Information Available: Experimental procedures, synthesis and characterization of all new compounds and X-ray crystallographic studies of **8** (55 pages), scanned copies of ¹H and ¹³C NMR spectra of all new compounds (64 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

to a terminal π -carbon of neutral 5-oxo- η^3 -pyranyl (and pyridinyl) moiety was reported.^{1j,1o} This synthetically useful 1,5-Michael-like functionalization mode was explained, in part, by the tendency of $\text{TpMo}(\text{CO})_2$ systems to favor 6-coordinate over 7-coordinate structures,² and also because the nucleophilic addition generates a characterizable anionic $\text{TpMo}(\text{CO})_2$ 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 6-coordinate over 7-coordinate structures alone would be sufficient to enhance a more general nucleophilic addition pathway by which $\text{TpMo}(\text{CO})_2(\eta^3\text{-allyl})$ 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- $\text{S}_{\text{N}}2'$ -like" intermolecular nucleophilic substitution of charge neutral $\text{TpMo}(\text{CO})_2(5\text{-acyloxy-}\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(5\text{-acyloxy-}\eta^3\text{-pyridinyl})$ 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 $\text{TpMo}(\text{CO})_2(5\text{-oxo-}\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(5\text{-oxo-}\eta^3\text{-pyridinyl})$ 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 $\text{TpMo}(\text{CO})_2(5\text{-acetoxy-}\eta^3\text{-pyranyl})$ and $\text{TpMo}(\text{CO})_2(5\text{-acetoxy-}\eta^3\text{-pyridinyl})$ 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.

The homo- $\text{S}_{\text{N}}2'$ -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- $\text{S}_{\text{N}}2'$ -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.

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 SI). 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 representative 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-ethylhexanoate⁷ open to air provided the annulations products **17–20** in 83–92% isolated yields (Table 2). In earlier work, Pearson used different non-basic

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 nucleophile¹⁰ and subsequent proton loss. Mechanistically, we suggest that the reactions of Table 2 proceed through 1-electron oxidation of the stabilized enolate to a radical¹¹ 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} $[\alpha]_D^{20} = +131$, $c = 0.35$, $CHCl_3$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Scheme 2.

Control Experiment. The Reaction of Molybdenum-Stabilized Carbocation **15** with Sodium Dimethyl Malonate

Scheme 3. Enantiocontrolled Synthesis of (+)-Isofebrifugine

a/NaH, $\text{CH}_3\text{COCH}_2\text{SO}_2\text{Ph}$, DMSO, rt, overnight then NaH, $\text{Cu(ethylhexanoate)}_2$, 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/6M HCl, reflux, 90 min.

Table 1

“Homo S_N2’-Like” Substitution Reactions

entry	reactant	NuH	solvent	% yield
1	3a	CH ₂ (COOMe) ₂	THF	6 , 99 ^a
2	3a	CH ₃ COCH ₂ COOMe	ACN	7 , 69(99) ^{b,c}
3	3a	CH ₃ COCH ₂ COOMe	THF	7 , 31(99) ^{b,c}
4	3a	CH ₃ CH(COOEt) ₂	THF	8 , 66(94) ^b
5	3a	CH ₃ NO ₂	DMSO	9 , 80 ^d
6	3b	CH ₃ COCH ₂ COOMe	ACN	10 , 94 ^c
7	3b	CH ₃ COCH ₂ COMe	ACN	11 , 68
8	3c	CH ₂ (COOMe) ₂	THF	12 , 90
9	4a	CH ₂ (COOMe) ₂	ACN	13 , 94
10	4b	CH ₃ COCH ₂ COOMe	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.

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	NChz	COOMe	H	20, 83