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Organometallic Enantiomeric Scaffolding. Sequential Semipinacol / 1,5-"Michael-like" Reactions as a Strategic Approach to Bridgehead-Quaternary Center Aza[3.3.1]Bicyclics: Application to the Total Synthesis of (-)-Adaline

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> TpMo(CO)₂(5-oxo- η^3 -pyranyl) and TpMo(CO)₂(5-oxo- η^3 -pyridinyl) complexes 1 and 2 (Scheme 1, Tp = hydridotrispyrazolylborate) and their progeny have been developed as organometallic enantiomeric scaffolds for the asymmetric construction of a wide variety of heterocyclic systems.¹ Readily available and easily synthesized,² single enantiomers of these simple air-stable organometallic π -complexes function as scaffolds from which widely differing families of complex organic structures can be elaborated in an enantiospecific fashion. The organometallic nature of these enantiomeric scaffolds provides opportunities to implement conceptually unique synthetic design strategies. Herein is described one such strategy: a new molybdenum-mediated semipinacol rearrangement delivering α -quaternary pyranyl and pyridinyl systems that, when coupled sequentially with a molybdenum-mediated intramolecular 1,5-"Michael-like" reaction of 5-oxopyridinyl molybdenum complexes, ^{1m} can provide a novel enantiocontrolled entry to heteroatom-bridged [3.3.1]bicyclic systems bearing quaternary centers^{3,4,5} adjacent to the ring heteroatom (Scheme 1). The concept is highlighted via a synthesis of the azabicyclo[3.3.1]nonane natural product, (-)-adaline.⁶ Adaline possesses the 9-azabicyclo[3.3.1]nonane skeleton common to several insect- and plant-derived alkaloids, including pseudopelletierine, 7 (+)-euphococcinine, 8 and porantherine. 9 This structure is a higher homolog of the medicinally-important tropane skeleton. A number of racemic¹⁰ and enantiospecific syntheses¹¹ of adaline have been reported.

> The molybdenum scaffold-based synthesis of heteroatom-bridged [3.3.1]bicyclics bearing ring junction quaternary centers suggested in Scheme 1 first requires the stereocontrolled construction of α -quaternary 5-oxopyranyl and 5-oxopyridinyl molybdenum complexes. This was accomplished through the agency of the molybdenum-mediated semipinacol reaction shown in Table 1. The requisite semipinacol precursors 5-12 were prepared from 5-oxopyranyl scaffold $\mathbf{1}$ and 5-oxopyridinyl scaffold $\mathbf{2}$ (both readily available in racemic and high enantiopurity forms on multigram scale in 2-3 isolation steps from furfuryl alcohol and furfuryl amine, respectively²) by conversion of 1 and 2 into the corresponding 6-alkylidene-5-oxo complexes 3 and 4 via a Mukaiyama aldol-dehydration reaction sequence. 12 Specific data points for both the pyranyl and pyridinyl series scaffolds are provided in Table 1.

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Supporting Information Available. Experimental procedures, and characterization data for all compounds (41 pages); copies of ${}^{1}\mathrm{H}$ and ¹³C NMR spectra of all compounds (86 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

Coombs et al.

Selective 1,2-addition of Grignard reagents to the enones **3** and **4** took place *anti* to the TpMo $(CO)_2$ moiety in good to excellent yields, except with the more hindered *i*-Pr and *t*-Bu reagents. Treatment of adducts **5-12** with HCl in dioxane induced a rapid and stereospecific semipinacol reaction for those R² substituents with good migratory aptitudes such as allyl, phenyl, vinyl, and *t*-Bu, but not for R² = Me or *i*-Pr. The geometry of the alkylidene residue influenced the outcome of the semipinacol reaction for the pyridinyl series scaffolds, but not for the pyranyl scaffolds. For example, in the pyranyl series, both *E*-**5** and *Z*-**5** gave excellent yields of the same semipinacol product **13**, but of the analogous pyridinyl series complexes *E*-**11** and *Z*-**11**, only *E*-**11** rearranged in excellent yield to the expected semipinacol product **20**. In stark contrast, treatment of *Z*-**11** with HCl in dioxane led to decomposition. Presumably, *Z*-**11** experiences destabilizing non-bonded steric interactions between the Cbz protecting group on nitrogen and the *syn* R¹ substituent of the alkylidene during sp²—sp³ hybridization changes resident at alkylidene moiety during the semipinacol reaction.

To showcase the utility of the strategic coupling of the molybdenum mediated semipinacol and the 1,5-"Michael-like" bond forming reaction, a total synthesis of (-)-adaline was undertaken. Terminal alkene (-)-**20** (97.7% ee) was oxidized to the methyl ketone **21** in 93% yield using the classical Wacker reaction.¹³ Treatment of **21** with KOSiMe₃ induced a 1,5-"Michael-like" reaction, ^{1m} proceeding *via* attack of the tethered potassium enolate at the neutral η^3 - allylmolybdenum. Direct treatment of the crude anionic intermediate **22**¹⁴ with NOPF₆ in DME provided bicyclic enone **23** in 80% yield over the two steps.

Selective ketalization of the saturated ketone in compound **23** gave **24** in 85% yield. Luche reduction of enone **24** provided a single diastereoisomeric equatorial alcohol in 98% yield, resulting from 1,2-hydride addition to the carbonyl from the less-hindered, convex face of the bicycle.¹⁵ Barton-McCombie conditions¹⁶ were employed to remove the hydroxyl group, providing a single alkene **25** in 63% overall yield, whose structure was confirmed by COSY NMR. Hydrolysis of the ketal protecting group with catalytic Pd(MeCN)₂Cl₂ in wet acetone delivered the corresponding ketone (95%), which was subjected to simultaneous hydrogenation of the alkene and hydrogenolysis of the Cbz protecting group providing (-)-adaline in 90% yield { $[\alpha]_D^{25}$ -13 (*c* 0.73, CHCl3); Lit.⁶ [α]_D -13 (CHCl3)}. The enantiomeric excess of precursor (+)-**25** was determined by HPLC (97.6%); therefore, (-)-adaline produced by this method is assumed to have a 97.6% ee.

In conclusion, the organometallic enantiomeric scaffold-based semipinacol/1,5-"Michaellike" sequence represents a new strategy for the stereocontrolled construction of biologicallyrelevant heteroatom-bridged [3.3.1]bicyclic ring systems bearing quaternary carbons adjacent to the heteroatom. The asymmetric total synthesis of (-)-adaline demonstrates one application of this methodology. Full details pertaining to the scope and application of the metal-mediated semipinacol rearrangement will be provided in a future disclosure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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JAm Chem Soc. Author manuscript; available in PMC 2010 January 28.

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- 12. The aldol-dehydration sequence was accomplished through a Mukaiyama aldol reaction (Mahrwald R. Chem. Rev 1999;99:1095–1120. [PubMed: 11749441]) on the in situ generated OTBS silyl enol ethers of 1 and 2. β-Hydroxy ketones were obtained in good to excellent yields. The pyridinyl scaffold provided significant anti aldol selectivity (6-8:1), the pyranyl scaffold less so (2:1). The Mukaiyama-aldol adducts were easily dehydrated to the alkylidenes shown in Table 1 through the corresponding mesylates. The anti aldol adducts provided the E-alkylidenes preferentially, whereas the syn aldol adducts led to the Z-alkylidenes. No loss of enantiopurity was observed using chiral, non-racemic substrates. Relevant details are provided in the Supporting Information. Full details of the aldol-dehydration sequence will be disclosed in a subsequent publication.
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- 14. Analysis of the metal carbonyl stretches of the anion 22 by FT-IR showed significantly lower stretching frequencies (1891/1855 cm⁻¹) relative to those for neutral 21 (1956/1868 cm⁻¹) due to increased backbonding from the electron-rich metal to the CO ligands. Upon quenching 22 with H⁺ or Meerwein's reagent, the metal carbonyl absorptions shifted back to higher wavenumbers (1974/1888 cm⁻¹ and 1922/1814 cm⁻¹, respectively). See the SI for additional details.
- 15. The stereochemical outcome of this reduction was confirmed: after the Luche reduction, if the ketal was deprotected and the alkene hydrogenated, an intramolecular hemiketal was formed. This can only result from condensation of an equatorial alcohol with the ketone. See the SI for additional details.
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JAm Chem Soc. Author manuscript; available in PMC 2010 January 28.



Scheme 1. Scaffold-based Sequential Semipinacol/1,5-"Michael-like" Approach to Aza[3.3.1]bicyclics

Coombs et al.



Scheme 2. Total Synthesis of (-)-Adaline.

J Am Chem Soc. Author manuscript; available in PMC 2010 January 28.

or Manusc	NIH-PA Autho		uthor Manuscript	NIH-PA Au	script	NIH-PA Author Manu:	
	Semipinacol Route	to α-Quater	Ta nary Carbon Pyranyl and	able 1 l Pyridinyl Scaffolds			
	TpMo(CO)2		pMo(CO)2	TpMo(CO)2	НО	TpMo(CO)2	
		 ∑	X X R -	X ² MgX	'''R ² HCI	×	
	1: X = 0 2: X = NCb	z	3: X = O 4: X = NCbz	5-10: X 11,12: X =	= O = NCbz	R 13-18: X = O 19,20: X = NCbz	
	x	R ¹	enone	R ²	1,2-adduct (%) semi-pinacol (9	
_	0	CH ₃	E -3 a^{tl}	allyl	E-5 , 81	13, 94	
2	-	-	z -3 a^b	allyl	Z-5 , 87	13, 95	
3	-	-	-	vinyl	Z-6 , 81	14 , 99 ^c	
4	÷	÷	F	phenyl	Z-7 , 64	15, 98	
5	z	=	-	Me	Z-8 , 71	$16, 0^d$	
6	÷	÷	÷	<i>i</i> -Pr	Z-9 , 21	$17, 0^{d}$	
7	÷	÷	÷	<i>t</i> -Bu	Z-10 , 25	18, 98	
8	NCbz	CH_3	E -4a e	allyl	E-11 , 99	19 , 96	
6	F	=	Z-4a ^f	allyl	Z-11 , 99	19 , 0^d	
10	NCbz	C_5H_{11}	E-4b ^{g}	allyl	E-12, ^h	20 , ⁱ 78j	
11	-	÷	\mathbf{Z} -4b k	allyl	Z-12 , 93%	20 , 0 ^d	
^a Prepared in 63%	yield from the <i>anti</i> aldol add	duct.					
^b Prepared in 79%	yield from the syn aldol add	luct.					
^c 97.1% ee from a !	97.1% ee sample of Z-(-)- 3a	-i					
dIR analysis of the semipinacol rearra	e crude reaction mixture shown ngement in these cases. Dec	ws an initial shi composition to n	ft to higher wavenumbers for the umerous products ensues (accor-	metal carbonyls indicating ding to TLC).	g that ionization of the ter	rtiary hydroxyl group is likely occurri	g, instead of
¢	•	¢					

J Am Chem Soc. Author manuscript; available in PMC 2010 January 28.



 $f_{\rm Prepared in 83\%}$ yield from the *syn* aldol adduct.

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 $^{g}\mathrm{Prepared}$ in 70% yield from the anti aldol adduct.

h Allylic alcohol E-(-)-12 contained an inseparable impurity passed through from the synthesis of E-(-)-4b. For practical reasons, the Grignard addition/semipinacol rearrangement sequence was performed in one pot, leading to (-)-20 in very good overall yield. See the Supporting Information for more details.

Coombs et al.

 $^i\!97.7\%$ ee from a 97.8% ee sample of E-(-)-**12**.

jIsolated yield over 2 steps.

 $k_1^{\rm L}$ soluted in 5% yield as the minor product from dehydration of the *anti*-aldol product.