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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

Thomas C. Coombs, Yongqiang Zhang,[§] Ethel C. Garnier-Amblard, and Lanny S. Liebeskind*

Sanford S. Atwood Chemistry Center, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322;

Received October 30, 2008; E-mail: chemLL1@emory.edu

$TpMo(CO)_2$(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,[1k] can provide a novel enantiocontrolled entry to heteroatom-bridged [3.3.1]bicyclic systems bearing quaternary centers[3−5] 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 homologue of the medicinally important tropane skeleton. A number of racemic[10] and enantiospecific syntheses[11] 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 required 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 **1** and 5-oxopyridinyl scaffold **2** (both readily available in racemic and high enantiopurity forms on multigram scale in two to three isolation steps from furfuryl alcohol and furfuryl amine, respectively[2]) 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.

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 R^2 substituents with good migratory aptitudes such as allyl, phenyl, vinyl, and *t*-Bu,

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

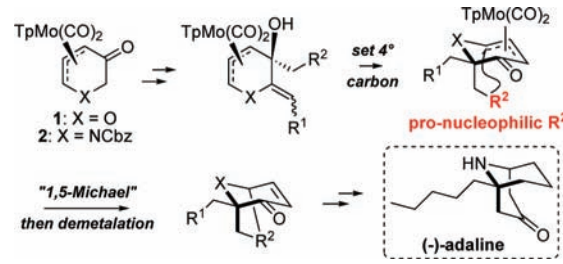
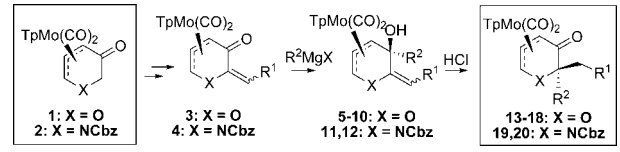


Table 1. Semipinacol Route to α-Quaternary Carbon Pyranyl and Pyridinyl Scaffolds



	X	R^1	enone	R^2	1,2-adduct (%)	semipinacol (%)
1	O	CH_3	*E*-**3a**[a]	allyl	*E*-**5**, 81	**13**, 94
2	O	CH_3	*Z*-**3a**[b]	allyl	*Z*-**5**, 87	**13**, 95
3	O	CH_3	*Z*-**3a**[b]	vinyl	*Z*-**6**, 81	**14**, 99[c]
4	O	CH_3	*Z*-**3a**[b]	phenyl	*Z*-**7**, 64	**15**, 98
5	O	CH_3	*Z*-**3a**[b]	Me	*Z*-**8**, 71	**16**, 0[d]
6	O	CH_3	*Z*-**3a**[b]	*i*-Pr	*Z*-**9**, 21	**17**, 0[d]
7	O	CH_3	*Z*-**3a**[b]	*t*-Bu	*Z*-**10**, 25	**18**, 98
8	NCbz	CH_3	*E*-**4a**[e]	allyl	*E*-**11**, 99	**19**, 96
9	NCbz	CH_3	*Z*-**4a**[f]	allyl	*Z*-**11**, 99	**19**, 0[d]
10	NCbz	C_5H_{11}	*E*-**4b**[g]	allyl	*E*-**12**,[h] −	**20**,[i] 78[j]
11	NCbz	C_5H_{11}	*Z*-**4b**[k]	allyl	*Z*-**12**, 93	**20**, 0[d]

[a] Prepared in 63% yield from the *anti* aldol adduct. [b] Prepared in 79% yield from the *syn* aldol adduct. [c] 97.1% ee from a 97.1% ee sample of *Z*-(−)-**3a**. [d] IR analysis of the crude reaction mixture shows an initial shift to higher wavenumbers for the metal carbonyls indicating that ionization of the tertiary hydroxyl group is likely occurring, instead of semipinacol rearrangement in these cases. Decomposition to numerous products ensues (according to TLC). [e] Prepared in 77% yield from the *anti* aldol adduct. [f] Prepared in 83% yield from the *syn* aldol adduct. [g] 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. [i] 97.7% ee from a 97.8% ee sample of *E*-(−)-**12**. [j] Isolated yield over two steps. [k] Isolated in 5% yield as the minor product from dehydration of the *anti*-aldol product.

but not for R^2 = 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

[§] Current address: Displaytech Inc. 2602 Clover Basin Dr. Longmont, CO 80503.

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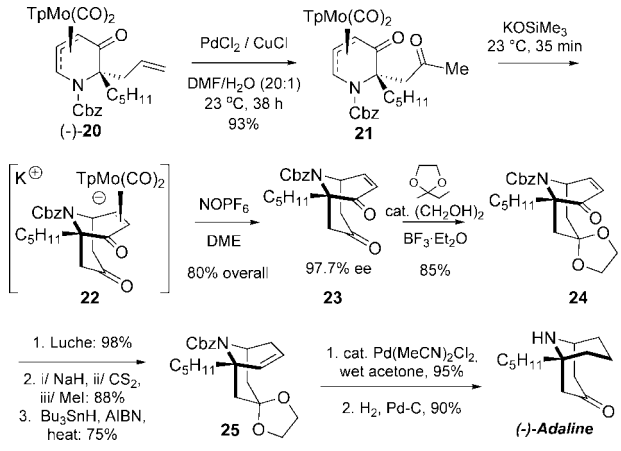
Scheme 2. Total Synthesis of (−)-Adaline



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 **19**. In stark contrast, treatment of *Z*-**11** with HCl in dioxane led to decomposition. Presumably, *Z*-**11** experiences destabilizing nonbonded steric interactions between the Cbz protecting group on nitrogen and the *syn* R^1 substituent of the alkylidene during $sp^2 \rightarrow sp^3$ hybridization changes resident at the 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 $KOSiMe_3$ induced a 1,5-Michael-like reaction,[11] proceeding *via* attack of the tethered potassium enolate at the neutral η^3-allylmolybdenum. Direct treatment of the crude anionic intermediate **22**[14] with $NOPF_6$ 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 conditions[16] 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 $Pd(MeCN)_2Cl_2$ 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 {$[\alpha]^{25}_D$ −13 (*c* 0.73, $CHCl_3$); Lit.[6] $[\alpha]_D$ −13 ($CHCl_3$)}. 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-Michael-like sequence represents a new strategy for the stereocontrolled construction of biologically relevant 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.

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

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(12) The aldol-dehydration sequence was accomplished through a Mukaiyama aldol reaction (Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095–1120) 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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