# 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 (-)-AdalineThomas C. Coombs, Yongqiang Zhang§, Ethel C. Garnier-Amblard, and Lanny S. Liebeskind Sanford S. Atwood Chemistry Center, Emory University, 1515 Dickey Drive, Atlanta, GA 30322


#### Abstract

$\mathrm{TpMo}(\mathrm{CO})_{2}\left(5-\right.$ oxo- $\eta^{3}$-pyranyl) and $\mathrm{TpMo}(\mathrm{CO})_{2}\left(5\right.$-oxo- $\eta^{3}$-pyridinyl) complexes $\mathbf{1}$ and $\mathbf{2}$ (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 $\pi$-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 $\alpha$-quaternary pyranyl and pyridinyl systems that, when coupled sequentially with a molybdenum-mediated intramolecular 1,5-"Michael-like" reaction of 5-oxopyridinyl molybdenum complexes, 1 m 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 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 requires the stereocontrolled construction of $\alpha$-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 2 (both readily available in racemic and high enantiopurity forms on multigram scale in 2-3 isolation steps from furfuryl alcohol and furfuryl amine, respectively ${ }^{2}$ ) by conversion of $\mathbf{1}$ and $\mathbf{2}$ into the corresponding 6-alkylidene-5-oxo complexes $\mathbf{3}$ and $\mathbf{4}$ via a Mukaiyama aldol-dehydration reaction sequence. ${ }^{12}$ Specific data points for both the pyranyl and pyridinyl series scaffolds are provided in Table 1.

[^0]Selective 1,2-addition of Grignard reagents to the enones $\mathbf{3}$ and $\mathbf{4}$ took place anti to the TpMo $(\mathrm{CO})_{2}$ moiety in good to excellent yields, except with the more hindered $i$ - $\operatorname{Pr}$ and $t$-Bu reagents. Treatment of adducts $\mathbf{5 - 1 2}$ with HCl in dioxane induced a rapid and stereospecific semipinacol reaction for those $\mathrm{R}^{2}$ substituents with good migratory aptitudes such as allyl, phenyl, vinyl, and $t$ - Bu , but not for $\mathrm{R}^{2}=\mathrm{Me}$ 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 $E-\mathbf{1 1}$ and $Z-\mathbf{1 1}$, only $E-\mathbf{1 1}$ rearranged in excellent yield to the expected semipinacol product 20. In stark contrast, treatment of $\mathbf{Z - 1 1}$ with HCl in dioxane led to decomposition. Presumably, $Z-\mathbf{1 1}$ experiences destabilizing non-bonded steric interactions between the Cbz protecting group on nitrogen and the syn $\mathrm{R}^{1}$ substituent of the alkylidene during $\mathrm{sp}^{2} \rightarrow \mathrm{sp}^{3}$ 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 $\mathbf{2 1}$ in $93 \%$ yield using the classical Wacker reaction. ${ }^{13}$ Treatment of 21 with $\mathrm{KOSiMe}_{3}$ induced a 1,5-"Michael-like" reaction, ${ }^{1 \mathrm{~m}}$ proceeding via attack of the tethered potassium enolate at the neutral $\eta^{3}$ allylmolybdenum. Direct treatment of the crude anionic intermediate $\mathbf{2 2}^{14}$ with NOPF $_{6}$ in DME provided bicyclic enone $\mathbf{2 3}$ in $80 \%$ yield over the two steps.

Selective ketalization of the saturated ketone in compound $\mathbf{2 3}$ 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 $\mathbf{2 5}$ in $63 \%$ overall yield, whose structure was confirmed by COSY NMR. Hydrolysis of the ketal protecting group with catalytic $\mathrm{Pd}(\mathrm{MeCN})_{2} \mathrm{Cl}_{2}$ 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 $\left\{[\alpha]_{\mathrm{D}}{ }^{25}-13(c 0.73, \mathrm{CHCl} 3)\right.$; Lit. $\left.{ }^{6}[\alpha]_{\mathrm{D}}-13(\mathrm{CHCl} 3)\right\}$. 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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## References

1. (a) Shu C, Liebeskind LS. J. Am. Chem. Soc 2003;125:2878-2879. [PubMed: 12617646] (b) Gomez Arrayás R, Liebeskind LS. J. Am. Chem. Soc 2003;125:9026-9027. [PubMed: 15369354] (c) Alcudia

A, Gomez Arrayás R, Liebeskind LS. J. Org. Chem 2002;67:5773-5778. [PubMed: 12153279] (d) Shu C, Alcudia A, Yin J, Liebeskind LS. J. Am. Chem. Soc 2001;123:12477-12487. [PubMed: 11741410] (e) Gomez Arrayás R, Liebeskind LS. J. Am. Chem. Soc 2001;123:6185-6186. [PubMed: 11414856] (f) Yin J, Llorente I, Villanueva LA, Liebeskind LS. J. Am. Chem. Soc 2000;122:1045810459. (g) Moretto AF, Liebeskind LS. J. Org. Chem 2000;65:7445-7455. [PubMed: 11076602] (h) Malinakova HC, Liebeskind LS. Org. Lett 2000;2:3909-3911. 4083-4086. [PubMed: 11101451] (j) Yin J, Liebeskind LS. J. Am. Chem. Soc 1999;121:5811-5812. (k) Gomez Arrayás R, Yin L, Liebeskind LS. J. Am. Chem. Soc 2007;129:1816-1825. [PubMed: 17284010] (1) Zhang Y,
Liebeskind LS. J. Am. Chem. Soc 2005;127:11258-11259. [PubMed: 16089451] (m) Zhang Y, Liebeskind LS. J. Am. Chem. Soc 2006;128:465-472. [PubMed: 16402833] (n) Garnier EC, Liebeskind LS. J. Am. Chem. Soc 2008;130:7449-7458. [PubMed: 18479131]
2. Coombs TC, Lee MD IV, Wong H, Armstrong M, Cheng B, Chen W, Moretto AF, Liebeskind LS. J. Org. Chem 2008;73:882-888. [PubMed: 18171075]
3. Douglas CJ, Overman LE. Proc. Natl. Acad. Sci 2004;101:5363-5367. [PubMed: 14724294]
4. Peterson EA, Overman LE. Proc. Natl. Acad. Sci 2004;101:11943-11948. [PubMed: 15232003]
5. Ramon DJ, Yus M. Curr. Org. Chem 2004;8:149-183.
6. Tursch B, Braekman JC, Daloze D, Hootele C, Losman D, Karlsson R, Pasteels JM. Tetrahedron Lett 1973;3:201-202.
7. (a) Hess E. Ber 1917;50:380, 1391, 1395. (b) Tanret C. C. R. Hebd. Seances Acad. Sci 1879;88:716.
8. Hart NK, Johns SR, Lamberton JA. Aust. J. Chem 1967;20:561-563.
9. (a) Denne WA, Johns SR, Lamberton JA, Mathieson AM, Suares H. Tetrahedron Lett 1971:31073108. (b) Denne WA, Johns SR, Lamberton JA, Mathieson AM, Suares H. Tetrahedron Lett 1972:1767-1770. (c) Tursch B, Chome C, Braekman JC, Daloze D. Bull. Soc. Chim. Belg 1973;82:699-703. (d) Gossing E, Witkop B. Monatsh. Chem 1980;111:803-811. (e) Gnecco Medina DH, Grierson DS, Husson H-P. Tetrahedron Lett 1983;24:2099-2102.
10. (a) Holmes AB, Bourdin B, Collins I, Davison EC, Rudge AJ, Stork TC, Warner JA. Pure Appl. Chem 1997;69:531-536. (b) Davison EC, Holmes AB. Tetrahedron Lett 1995;36:9047-9050.
11. (a) Yue C, Royer J, Husson H-P. J. Org. Chem 1992;57:4211-4214. (b) Hill RK, Renbaum LA. Tetrahedron 1982;38:1959-1963. (c) Itoh T, Yamazaki N, Kibayashi C. Org. Lett 2002;4:2469-2472. [PubMed: 12123353]
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 $\mathbf{1}$ and 2. $\beta$-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 Mukaiyamaaldol 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 aldoldehydration sequence will be disclosed in a subsequent publication.
13. Tsuji, J. Addition Reactions with Formation of Carbon-Oxygen Bonds: The Wacker Oxidation and Related Reactions. In: Trost, BM.; Fleming, I., editors. Comprehensive Organic Synthesis. Vol. Vol. 7. Pergamon; Oxford: 1991. p. 449-468.
14. Analysis of the metal carbonyl stretches of the anion 22 by FT-IR showed significantly lower stretching frequencies ( $1891 / 1855 \mathrm{~cm}^{-1}$ ) relative to those for neutral $21\left(1956 / 1868 \mathrm{~cm}^{-1}\right)$ due to increased backbonding from the electron-rich metal to the CO ligands. Upon quenching 22 with $\mathrm{H}^{+}$or Meerwein's reagent, the metal carbonyl absorptions shifted back to higher wavenumbers ( $1974 / 1888 \mathrm{~cm}^{-1}$ and $1922 / 1814 \mathrm{~cm}^{-1}$, 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.
16. Hartwig W. Tetrahedron 1983;39:2609-2645.


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


Scheme 2.
Total Synthesis of (-)-Adaline.
Id!usnuew 10 !ın $\forall \forall d$-HIN

|  | X | $\mathbf{R}^{1}$ | enone | $\mathbf{R}^{2}$ | 1,2-adduct (\%) | semi-pinacol (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | O | $\mathrm{CH}_{3}$ | E-3a ${ }^{\text {a }}$ | allyl | E-5, 81 | 13, 94 |
| 2 | " | " | Z-3a ${ }^{\text {b }}$ | allyl | Z-5, 87 | 13, 95 |
| 3 | " | " | " | vinyl | Z-6, 81 | 14, $99^{\text {c }}$ |
| 4 | " | " | " | phenyl | Z-7, 64 | 15, 98 |
| 5 | " | " | " | Me | Z-8, 71 | 16, $0^{d}$ |
| 6 | " | " | " | $i-\operatorname{Pr}$ | Z-9, 21 | $17,0^{d}$ |
| 7 | " | " | " | $t$-Bu | Z-10, 25 | 18, 98 |
| 8 | NCbz | $\mathrm{CH}_{3}$ | $E-4{ }^{e}$ | allyl | E-11, 99 | 19, 96 |
| 9 | " | " | Z-4a ${ }^{f}$ | allyl | Z-11, 99 | $19,0{ }^{d}$ |
| 10 | NCbz | $\mathrm{C}_{5} \mathrm{H}_{11}$ | $\boldsymbol{E - 4 b}{ }^{g}$ | allyl | E-12, ${ }^{h}$--- | $\mathbf{2 0}{ }^{i} 78 j$ |
| 11 | " | " | $\mathbf{Z - 4 b}{ }^{k}$ | allyl | Z-12, 93\% | 20, $0^{d}$ |
| ${ }^{a}$ Prepared in $63 \%$ yield from the anti aldol adduct. |  |  |  |  |  |  |
| $b_{\text {Prepared in }} 79 \%$ yield from the syn aldol adduct. |  |  |  |  |  |  |
| ${ }^{\prime} 97.1 \%$ 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. |  |  |  |  |  |  |
| $f_{\text {Prepared in }} 83 \%$ yield from the syn aldol adduct. |  |  |  |  |  |  |


[^0]:    Correspondence to: Lanny S. Liebeskind.
    Email: chemLL1@emory.edu.
    §Current address: Displaytech Inc. 2602 Clover Basin Dr. Longmont, CO 80503
    Supporting Information Available. Experimental procedures, and characterization data for all compounds ( 41 pages); copies of ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of all compounds ( 86 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

