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Organometallic Enantiomeric Scaffolding: A Strategy for the Enantiocontrolled Construction of Regio- and Stereodivergent Trisubstituted Piperidines from a Common Precursor

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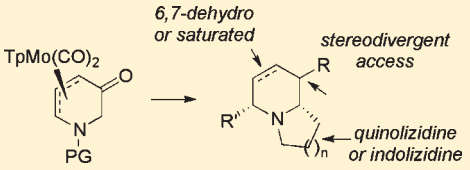
Supporting Information

ABSTRACT: Reported herein is a general and efficient method to construct 2,3,6-trisubstituted piperidines in a substituent-independent fashion. From the high enantiopurity organometallic scaffold (−)-Tp(CO)$_2$[(η-2,3,4)-(1*S*,2*S*)-1-benzyloxycarbonyl-5-oxo-5,6-dihydro-2*H*-pyridin-2-yl)molybdenum (Tp = hydridotrispyrazolylborato), a variety of TpMo(CO)$_2$-based 2,3,6-trifunctionalized complexes of the (η-3,4,5-dihydropyridinyl) ligand were easily obtained in 5 steps through a sequence of highly regio- and stereospecific metal-influenced transformations (15 examples). From the 2,3,6-trifunctionalized molybdenum complexes, either 2,6-*cis*-3-*trans* or 2,3,6-*cis* systems were selectively obtained through the choice of an appropriate stereodivergent demetalation protocol. The potential of this strategy in synthetic chemistry was demonstrated by the short total synthesis of four natural and one non-natural alkaloids: indolizidines (±)-209I and (±)-8-*epi*-219F in the racemic series, and enantiocontrolled syntheses of (−)-indolizidine 251N, (−)-quinolizidine 251AA, and (−)-dehydroindolizidine 233E.



INTRODUCTION

"Molecular scaffolding" provides a means to rapidly probe biological function through the systematic variation of structure. The scaffold is typically a small organic molecule whose periphery can be easily adorned with molecular fragments of diverse shapes, electronegativities, polarizabilities, and hydrogen-bonding capabilities, thus allowing chemical space around the scaffold to be investigated and varied for maximum biological effect. In decorating a scaffold to take an early screening hit to an actual lead drug candidate, or in a more basic research environment to probe biological function, a variety of well-developed and dependable synthetic methods are now routinely used to predictably probe two-dimensional space around the border of aromatic and heteroaromatic scaffolds (i.e., cross coupling,[1] C−H functionalization,[2] electrophilic aromatic substitution,[3] and directed metalation[4]). Since the practice of drug discovery is influenced by ease of use and dependability of available synthetic organic tools, it is not a surprise that much of the activity in small molecule hit-to-lead drug development of the past 1/2 century has been significantly focused within the "flat world" found around the periphery of (hetero)aromatic scaffolds.

It is surprising, however, that there exists no family of correspondingly general synthetic tools that allow the site-specific and enantiospecific probing of three-dimensional space fully about the periphery of biomedically important nonplanar scaffolds in a systematic fashion (Figure 1), even though drugable platforms such as piperidines and 2*H*-tetrahydropyrans are commonly found in a vast array of important pharmacophores that possess broad-ranging biological activities.[5] Such general 3D scaffolding tools, if as easy to use and as broadly applicable as the tools used to elaborate 2D space, would play an important role in taking an early screening hit to an actual lead drug candidate or in using chemical synthesis to probe biological function.

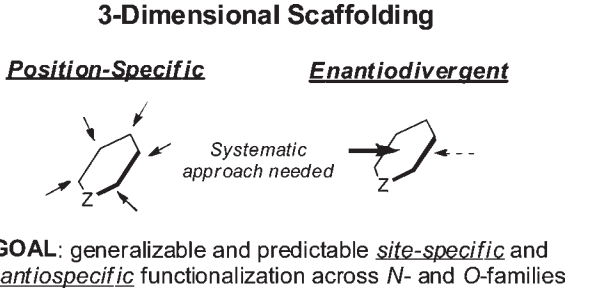


Figure 1. 3-Dimensional scaffolding: systematic exploration of 3D chemical space.

Much effort has been focused on the development of synthetic approaches to various specific substitution families of piperidines.[6] The Comins[6k,7] and Amat/Bosch[6i] laboratories have come closest to achieving the goal of systematic scaffolding around the piperidine ring. Additional piperidine functionalization tools that fall under the rubric of "scaffolding" have also been described by other laboratories, most notably those of Marazano,[6l,8] Husson/Royer,[6m] and Charette[6n] (Figure 2). These scaffolding methods are sometimes restricted to a single scaffold antipode and are applicable only to systems bearing a piperidine core. Furthermore, since these strategies rely on a preexisting sp^3-stereocenter to induce control over subsequently generated

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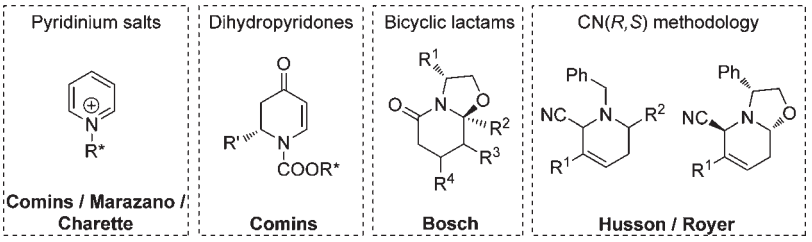

Figure 2. Enantiomeric scaffolding for substituted piperidine synthesis.

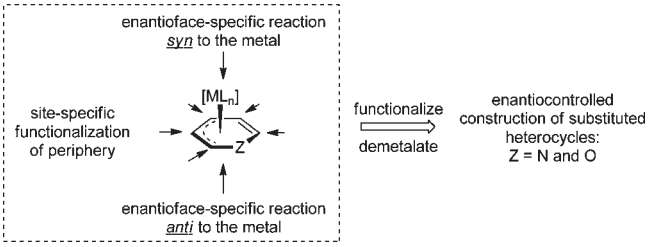

Figure 3. Organometallic enantiomeric scaffolding: elements of regio- and stereocontrol.

stereocenters, high stereocontrol in the final target is predicated upon the realization of efficient substrate- or reagent-based stereocontrol tactics. Not surprisingly, stereoselectivities vary and depend on the identity of previously established stereocenters.

Complementing the scaffolding efforts mentioned above, organometallic enantiomeric scaffolds offer strategic advantage for the systematic variation of structure in three dimensions about the periphery of not just N- but also O-based six-membered ring heterocycles. Here, conceptually simple, readily available, single enantiomers of air- and moisture-stable organometallic π-complexes of unsaturated heterocyclic ligands function as enantiomeric scaffolds for the regio-, stereo-, and enantiocontrolled construction of substituted heterocycle derivatives (Figure 3). Functionalization of the organometallic scaffold periphery uses some elements of reaction control that are standard in synthetic organic chemistry, but owing to the organometallic nature of the system, strategically novel approaches to bond formation and regio- and stereocontrol not achievable using traditional organic systems are also feasible. The scaffolds provide a single source of planar chirality that controls, in a predictable and systematic fashion, the regio- and stereocontrolled introduction of multiple substituents about nonplanar heterocycles over multiple steps. Also, in contrast to traditional metal catalysis where one metal atom influences one step of many turnovers, in organometallic enantiomeric scaffolding efficiency is achieved with one metal atom influencing multiple, different steps, each of one turnover, for the controlled introduction of many substituents and many stereocenters. Not insignificantly, the organometallic auxiliary can provide a dominant yet highly tunable form of "substrate control" over both regio- and stereochemistry, overriding perturbations by existing substituents on stereo- and regiochemistry.

Our laboratory has studied the easily prepared, highly enantiopure, air- and moisture-stable complexes $TpMo(CO)_2$-(5-oxo-η^3-dihydropyranyl/η^3-dihydropyridinyl), **1**−**2**,[9] and $TpMo(CO)_2$(2-oxo-η^3-dihydropyranyl/η^3-dihydropyridinyl), **3**−**4**,[10] where Tp = hydridotrispyrazolylborato[11] (Figure 4).

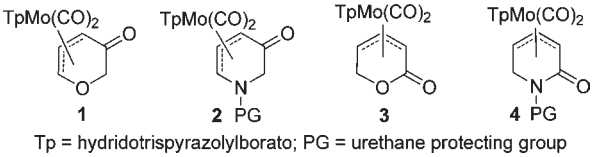

Figure 4. Key organometallic enantiomeric scaffolds.

These π-complexes of unsaturated *O*- and *N*-heterocyclic ligands function as organometallic enantiomeric scaffolds.[10,12] Analogous $CpMo(CO)_2$-based variants have also been investigated.[13] Because the reactivity and selectivity traits of the organometallic enantiomeric scaffolds are (mostly) independent of the nature of the heterocycle ring, those common traits allow a single synthetic strategy to be equally applied to the regio- and stereocontrolled elaboration of both piperidine and tetrahydropyran heterocycle families.[14]

Organometallic enantiomeric scaffolds should be particularly well-suited for the construction of focused libraries employed toward the exploration of structure−activity relationships in 3D chemical space. To exemplify this concept, we demonstrate herein the use of 5-oxo-dihydropyridinyl scaffold **2** for (1) the easy variation of critical substituents at different piperidine ring positions throughout a synthetic sequence, (2) substituent independent reactivity, diastereoselectivity, and enantioselectivity, and (3) the stereodivergent introduction of substituents at the 3-position of the piperidine ring. The potential of this strategy for the synthesis of variously substituted piperidines is specifically demonstrated by the stereodivergent construction of 2,3,6-*cis* and 2,6-*cis*-3-*trans* piperidines from the same high enantiopurity organometallic scaffold (−)-$Tp(CO)_2$-[(η-2,3,4)-(2*S*)-1-benzyloxycarbonyl-5-oxo-5,6-dihydro-2*H*-pyridin-2-yl)molybdenum **2** in a substituent-independent fashion (Scheme 1). These studies include the total syntheses of 5 alkaloids: (±)-indolizidine 209I,[15] (±)-8-*epi*-indolizidine 219F,[16] and enantiocontrolled syntheses of indolizidine (−)-251N,[17] (−)-quinolizidine 251AA,[18] and (−)-dehydroindolizidine 233E.[19] The Harman group has recently described a novel and elegant stereocontrolled approach to substituted piperidines using a tungsten-mediated dearomatization of the pyridine ring.[20]

RESULTS AND DISCUSSION

In an earlier disclosure from this laboratory,[12j] a highly regioselective abstraction (>84:1) of methoxide carried out on 3-methyl 2,6-dimethoxy-(η-3,4,5)-dihydropiperidinyl molybdenum complex **6** derived from the η^3-pyridinylmolybdenum complex **5** was described (Scheme 2). From scaffold **6**, various nucleophiles were sequentially introduced, first at the 2- and then

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at the 6-position. This methodology, coupled with effective demetalation procedures, proved useful for the enantiocontrolled construction of substituted piperidines and the natural product (−)-indolizidine 209B (Scheme 2).[21] However, the first generation preparation of organometallic dihydropyridinyl scaffolds such as **5** had clear tactical deficiencies: it was limited by a substrate-specific enzymatic resolution to achieve high enantiopurity material and involved a lengthy synthetic sequence (8 steps from *N*-benzyl glycine).[12j]

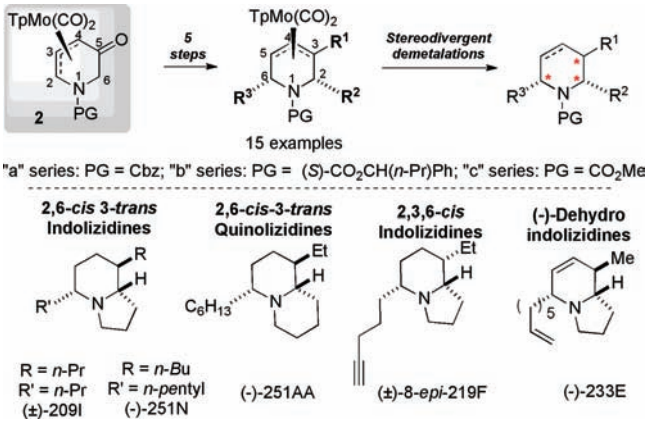
This initial scaffolding strategy for constructing substituted piperidines has now been rendered efficient, general, and substituent-independent. Rather than beginning with a substituent-specific scaffold, the new strategy relies on the *N*-protected 5-oxo-η^3-dihydropyridinyl scaffold **2**, a general enantiomeric platform (Scheme 3) that is easily prepared using an aza-Achmatowicz tactic.[9]

Thus, Scheme 3 provides an overview of how 2,3,6-trisubstituted piperidine-based alkaloids are obtained from scaffold **2** beginning with the generalized 1,2-introduction of a carbanionic substituent at the 5-position, providing the adducts **7**−**12** (refer to Table 1 for specific structures). Dehydration provides the stable η^3-pyridinyl complexes **13**−**18** that undergo a novel and high-yielding 2,6-oxidation of the scaffold with bromine in methanol, generating intermediates **I**. Highly regio- and stereoselective synthetic protocols are then used to transform the dimethoxy intermediates into the trisubstituted dihydropyridinylmolybdenum complexes **30**−**41** (see Table 2 and Table 3 for structures). Finally, two different stereodivergent demetalation procedures can provide either 2,6-*cis*-3-*trans* or 2,3,6-*cis* trisubstituted dehydropiperidines in a fully stereocontrolled fashion (see Table 4 for specific structures).

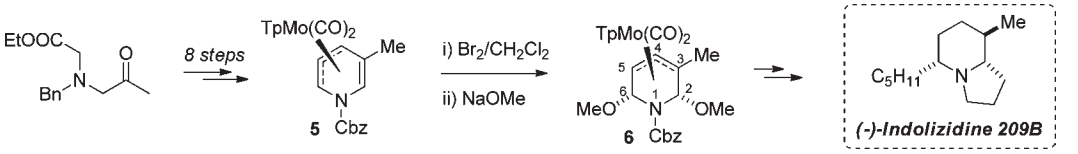
Preparation of the Organometallic Scaffolds. Using a rapid-throughput *aza*-Achmatowicz-based sequence, simple and scalable procedures were recently disclosed for the preparation of racemic (±)-**2a**, as well as the related diastereomers (−)-**2b** and (+)-**2b′**, which represent the functional equivalents of the separate antipodes of **2a** (Figure 5).[9]

That synthetic procedure comprises treatment of *N*-protected furfurylamines with *m*-CPBA followed by metalation of the crude reaction mixture with $Mo(DMF)_3(CO)_3$[22] and finally ligand exchange with KTp.[23] Although isolated yields are modest, this sequence can be conducted on a large scale without rigorous purification of the intermediates and reproducibly provides 45% isolated yields of the 5-oxopyridinyl molybdenum scaffold (±)-**2a**. Applying the same sequence to furfurylamine (*S*)-$CO_2CH(n\text{-Pr})Ph$ urethane[9] provided 36−39% isolated yields of a 1:1 diastereomeric mixture of the *N*-protected oxopyridinyl scaffolds (−)-**2b** and (+)-**2b′**. These diastereoisomers were

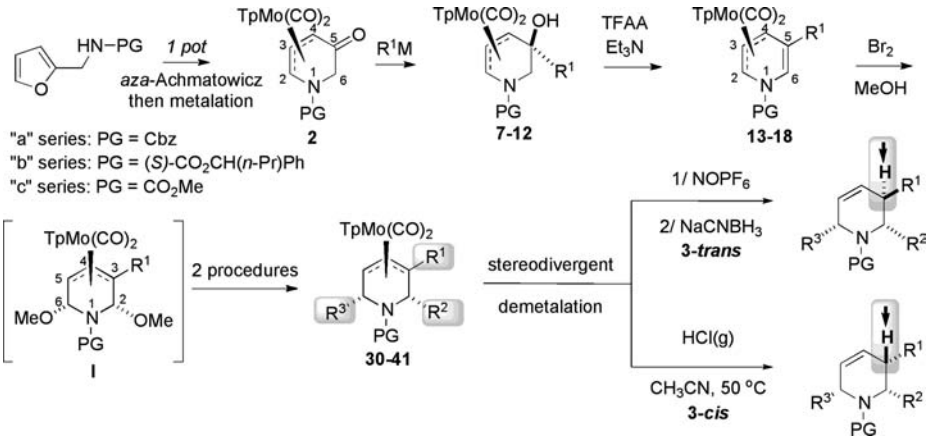
Scheme 1. Organometallic Enantiomeric Scaffolding: Concise Stereodivergent Syntheses of Indolizidine, Dehydroindolizidine, and Quinolizidine Alkaloids from a Common Precursor



Scheme 2. First Generation Organometallic Enantiomeric Scaffolding



Scheme 3. Overview: Substituent Independent Trifunctionalization Sequence Starting from Scaffold 2



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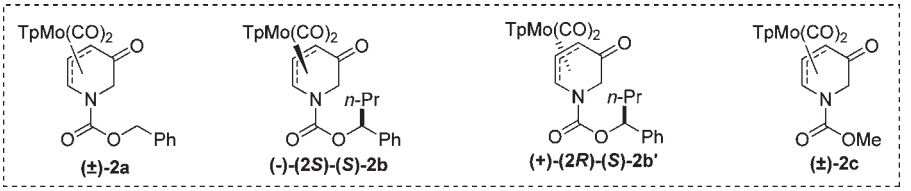
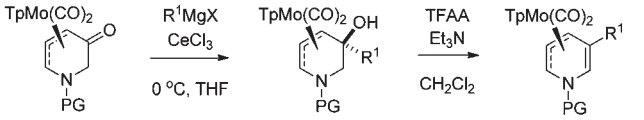


Figure 5. Oxopyridinylmolybdenum scaffolds.

Table 1. First Functionalization of the Scaffold; 5-Substituted η^3-Pyridinyl Complexes



"a" series: PG = Cbz; "b" series: PG = (*S*)-$CO_2CH(n\text{-}Pr)Ph$; "c" series: PG = CO_2Me

entry	#	R^1	no.	yield (%)[a]	dr	#	yield (%)[a]	dr
1	**2a**	Me	**7a**	69		**13a**[12j]	99	
2	**2b**	Me	**7b**	69	>99.5:0.5[b]	**13b**	99	99.5:0.5
3	**2c**	Me	**7c**	71		**13c**	99	
4	**2a**	Et	**8a**	68		**14a**	91	
5	**2b**	Et	**8b**	68	>99.5:0.5[b]	**14b**	91	99.5:0.5
6	**2c**	Et	**8c**	75		**14c**	99	
7	**2a**	*n*-Pr	**9a**	67		**15a**	91	
8	**2c**	*n*-Pr	**9c**	71		**15c**	99	
9	**2b**	*n*-Bu	**10b**	67	99.5:0.5	**16b**	84	99.5:0.5
10	**2a**	but-3-enyl	**11a**	66		**17a**	99	
11[c]	**2a**	Ph	**12a**	49		**18a**	99	

[a] Isolated yield. [b] As a surrogate for possible π-face racemization, epimerization of the products derived from the high purity (>99.5:0.5 dr) diastereomer **2b** was monitored by chromatography (HPLC column, Zorbax Eclipse C_8). [c] The reaction was conducted without cerium using PhMgBr with dichloromethane as the reaction solvent.

easily separated and obtained in excellent stereochemical purity (>99.7:0.3 dr) on large scale by a simple chromatographic separation on silica gel eluting with 15:1 toluene/EtOAc.[24] Since the oxopyridinyl scaffolds bearing either the *N*-Cbz or the *N*-(*S*)-$CO_2CH(n\text{-}Pr)Ph$ urethane protecting groups display identical reaction profiles in all synthetic manipulations explored to date, the chiral, nonracemic urethane can be retained and used as a Cbz equivalent. The availability of both of the π-facial antipodes (−)-**2b** and (+)-**2b′** ensures accessibility to both enantiomers of piperidine-based alkaloids.

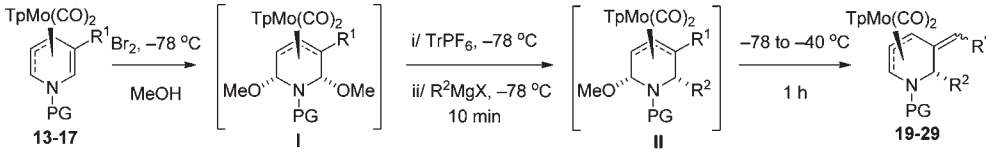
For the current study, in order to obtain somewhat simpler ^1H NMR spectra to allow more rapid screening of reaction conditions and reaction product analysis, racemic scaffold (±)-**2c** bearing a simple -CO_2Me protecting group was also prepared and used in a number of reaction sequences described within.

First Functionalization of the Scaffold. Installation of a substituent at the 5-position was conducted on scaffolds **2** bearing three different *N*-protecting groups: (±)-**2a**, PG = Cbz; (−)-(1*S*, 2*S*)-**2b**, PG = (*S*)-$CO_2(n\text{-}Pr)CHPh$; and (±)-**2c**, PG = CO_2Me. The addition of Grignard reagents to the ketonic functionality of **2a** under standard reaction conditions (THF, −78 °C) consistently gave the corresponding alcohol in low isolated yields (<35%) along with recovery of the starting material. Using less polar reaction solvents, such as dichloromethane[25] or toluene, with commercially available solutions of Grignard reagents in diethyl ether produced the corresponding alcohols in 45−55% yield, with the remainder of the mass balance representing recovery of the starting material **2a**. Since competitive deprotonation alpha to the ketone was likely responsible for the recovered starting material (after a protic workup), the benefit of less basic organocerium reagents was explored.[26] Using a cerium-modified reagent derived from alkyl Grignard reagents, alcohols **7**−**11** were obtained in 66−75% yields (Table 1, entries 1−10). However, the cerium-modified protocol did not improve the reaction with PhMgBr, which still gave product in the 25−35% yield range using THF as solvent. In this case, conversion to the alcohol **12a** using PhMgBr was improved to near 50% yield (Table 1, entry 11) when dichloromethane was the reaction solvent.

The outcome of the carbanion addition was independent of the nature of the N-protecting group (Table 1, compare entries 1−3 and 4−6), and no epimerization[27] of **7b**, **8b**, or **10b** was observed when the functionalization reaction was performed using the chiral, nonracemic starting material **2b** (Table 1, entries 2, 5, and 9). Finally, dehydration of alcohols **7**−**12** to the crucial η^3-pyridinylmolybdenum complexes **13**−**18** was easily achieved upon their exposure to TFAA/Et_3N. When using the chiral, nonracemic system, excellent yields were obtained and full retention of stereochemistry was observed[27] for **13b**, **14b**, and **16b** (Table 1). Therefore, in contrast to the previously reported substituent-specific scaffold,[12j] the 5-oxopyridinyl scaffold **2** allows access to a broad range of 5-substituted η^3-pyridinyl complexes (**13**−**18** in Table 1) that are suitable for further functionalization.

Second Functionalization of the Scaffold. With a general route to 5-substituted η^3-pyridinylmolybdenum complexes in hand, the next challenge was to develop a versatile, regio- and stereodefined procedure for the introduction of additional substituents about the heterocycle ring. We had previously established that η^3-pyranyl-[12l] and η^3-pyridinylmolybdenum[12j] complexes dissolved in CH_2Cl_2 reacted with bromine at −78 °C followed by the addition of sodium methoxide to provide 2,6-dimethoxy-functionalized molybdenum complexes in excellent yields, a transformation analogous to the bromine-induced oxidative dimethoxylation of furan.[28] Unfortunately, this same procedure when applied to the η^3-pyridinylmolybdenum complexes **13**−**17** led predominantly to decomposition of the molybdenum complexes. However, by carrying out the bromination in neutral methanol as solvent, the 3-substituted-2,6-dimethoxy-η^3-dihydropyridinyl complexes, **I**, depicted in Table 2 were obtained with high efficiency. The bromine-mediated 2,6-dimethoxylation was compatible with alkyl, phenyl (shown in Scheme 4), and alkene-bearing substituents as R^1.

Table 2. 6-Substituted 5-Alkylidene-η-2,3,4-Dihydropyridinylmolybdenum Complexes



"a" series: PG = Cbz; "b" series: PG = (*S*)-$CO_2CH(n\text{-Pr})Ph$; "c" series: PG = CO_2Me

entry	#	PG	R^1	#	R'	R^2	yld (%)[a]
1	**13b**	(*S*)-$CO_2CH(n\text{-Pr})Ph$	Me	**19**	H	$BnO(CH_2)_3$	74
2	**13c**	CO_2Me	Me	**20**	H		82
3	**14a**	Cbz	Et	**21**	Me	$BnO(CH_2)_3$	73
4	**14a**	Cbz	Et	**22**	Me	$BnO(CH_2)_4$	75
5	**14b**	(*S*)-$CO_2CH(n\text{-Pr})Ph$	Et	**23**	Me	$BnO(CH_2)_4$	76
6	**14c**	CO_2Me	Et	**24**	Me		83
7	**14c**	CO_2Me	Et	**25**	Me	$BnO(CH_2)_3$	83
8	**14c**	CO_2Me	Et	**26**	Me	Me	83
9	**15a**	Cbz	*n*-Pr	**27**	Et	$BnO(CH_2)_3$	89
10	**16b**	(*S*)-$CO_2CH(n\text{-Pr})Ph$	*n*-Bu	**28**	*n*-Pr	$BnO(CH_2)_3$	73
11	**17a**	Cbz	but-3-enyl	**29**	allyl	vinyl	65

[a] Isolated yield.

The η^3-dihydropyridinyl complexes possessing ionizable methoxy groups *anti* to the molybdenum, such as **I**, are typically somewhat sensitive, so that their careful purification is of limited general value. Therefore, with the exception of intermediate **I**, R^1 = Et, rather than purify, the crude materials were not analyzed but were carried on without purification through the next functionalization steps.

Consistent with previously described results,[12j] the −78 °C addition of 1 equiv of triphenylcarbenium hexafluorophosphate to the oxidative dimethoxylation adducts **I** of compounds **13**−**17** induced a highly regioselective abstraction of the methoxide group adjacent to the R^1 substituent. Subsequent addition of a Grignard reagent produced the sensitive monosubstitution derivatives **II** depicted in the graphic of Table 2. The instability of these Grignard adducts under the reaction conditions, and to subsequent chromatography, precluded their purification and full characterization. As a practical alternative, rather than quenching the reaction mixture 10 min after addition of the Grignard reagent, the reaction mixture was allowed to warm to −40 °C for 1 h in the presence of the Lewis acidic magnesium salts generated under the reaction conditions. This process stimulated loss of methanol from intermediates **II** and caused the formation of stable exocyclic olefins **19**−**29** in very good yields (Table 2). This one-pot reaction sequence was used for the introduction of alkyl, functionalized alkyl, and alkenyl chains at the 2-position of the molybdenum scaffolds.[29] The resulting 6-substituted 5-alkylidene-η^3-dihydropyridinylmolybdenum complexes were stable, and the majority of the complexes (**21**−**28**) were characterized by ^{1}H NMR spectroscopy (urethane rotamers and double bond stereoisomers rendered full spectroscopic characterization at this stage difficult; full compound characterization took place at the next reaction step). The very high regio- and stereocontrol shown by the examples listed in Table 2 follows earlier precedent[12j] and is fully supported by the synthesis of the various natural products described below.

The exocyclic olefins **19**−**29** were isolated as mixtures of *E* and *Z* isomers,[30] the *E*-isomer predominating in all cases. Assignment of stereochemistry to the exocyclic double bond isomers was accomplished through a NOE experiment performed on compound (*E*)-**28**: the proton H_b can clearly be assigned by ^{1}H NMR and, when irradiated, did not show any correlation with H_c, whereas strong interactions were observed between H_b and the terminal allylic proton H_a (Figure 6; refer to the Supporting Information for the NOE experiment). Although the exocyclic olefin isomers were found to equilibrate during slow silica gel column chromatography and upon SiO_2 thin-layer chromatography (but not during flash chromatography[31]), no isomerization was observed during the ^{1}H NMR NOE experiment.

Third Functionalization of the Scaffold. As a model reaction to probe additional functionalizations about the scaffold

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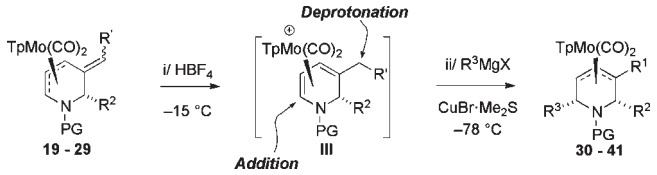
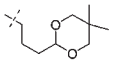
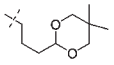
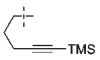
Table 3. Introduction of Functional Groups at the Scaffold 6-Position Using Copper-Modified Grignard Reagents



entry	#	PG	R'	R^1	R^2	R^3	#	yld %[a] (dr)
1	**19**	(*S*)-CO_2CH(*n*-Pr)Ph	H	Me	$BnO(CH_2)_3$-		**30**	81 (>99.5:0.5[b])
2	**20**	CO_2Me	H	Me		*n*-Pr	**31**	90
3	**21**	Cbz	Me	Et	$BnO(CH_2)_3$-		**32**	90
4	**22**	Cbz	Me	Et	$BnO(CH_2)_4$-		**33**	90
5	**22**	Cbz	Me	Et	$BnO(CH_2)_4$-	*n*-hexyl	**34**	91
6	**23**	(*S*)-CO_2CH(*n*-Pr)Ph	Me	Et	$BnO(CH_2)_4$-	*n*-hexyl	**35**	92 (>99.5:0.5[b])
7	**24**	CO_2Me	Me	Et		*n*-Pr	**36**	90
8	**25**	CO_2Me	Me	Et	$BnO(CH_2)_3$-		**37**	90
9	**26**	CO_2Me	Me	Et	Me	*n*-Bu	**38**	92
10	**27**	Cbz	Et	*n*-Pr	$BnO(CH_2)_3$-	*n*-Pr	**39**	90
11	**28**	(*S*)-CO_2CH(*n*-Pr)Ph	*n*-Pr	*n*-Bu	$BnO(CH_2)_3$-	*n*-pentyl	**40**	82 (>99.5:0.5[b])
12	**29**	Cbz	allyl	but-3-enyl	vinyl	Ph	**41**	80

[a] Isolated yield. [b] As a surrogate for possible π-face racemization, epimerization of the products derived from the high enantiopurity (>99.5:0.5 dr) diastereomers **19**, **23**, and **28** was monitored by chromatography (HPLC column, Zorbax Eclipse C_8).

periphery, protonation of the exocyclic double bond of molybdenum complex **20** with tetrafluoroboric acid proceeded smoothly[32] to generate the corresponding cationic η^4-diene intermediate **III** (Table 3).[33] Subsequent nucleophilic functionalization of the cationic complex using *n*-propylMgCl took place adjacent to the ring nitrogen and *anti* to the $TpMo(CO)_2$ moiety. Unfortunately, with a Grignard reagent as the nucleophile, the desired product **31** was always accompanied by recovery of some starting material. These observations are consistent with a competition between nucleophilic addition at C2 of the cation diene complex **III** and its deprotonation by the basic Grignard reagent to regenerate the material **20** (Table 3). The undesired deprotonation, a side reaction observed in related systems,[34] was minimized by a switch to *in situ* generated, copper-modified Grignard reagents (RMgX and CuBr·DMS). Using this reagent system the expected products **30**–**41** were obtained from the 5-alkylidene dihydropyridinyl complexes **19**–**29** in good to excellent yields. As depicted in Table 3 a wide variety of 2,3,6-trisubstituted dihydropiperidinylmolybdenum complexes can be constructed using this chemistry.

A number of copper-modified Grignard reagents add at the 6-position of the scaffold in very good yields (Table 3). Of importance, those reactions carried out with chiral, nonracemic starting materials **19**, **23**, and **28** did not show any epimerization of the final products (Table 3, entries 1, 7, and 12).[27] The total synthesis of the various natural products described later in this manuscript provided full confirmation of the reactivity pattern shown in Table 3. Thus, after four steps from scaffold **2** a large number of trisubstituted piperidine precursors can be obtained, where R^1, R^2, and R^3 are introduced independently from each other and in a fully regio- and stereocontrolled fashion.

Stereodivergent Demetalations of the Scaffold. One virtue of organometallic enantiomeric scaffolding is the ability to use organometallic reaction fundamentals to affect a divergent stereochemical outcome of a reaction from the same starting

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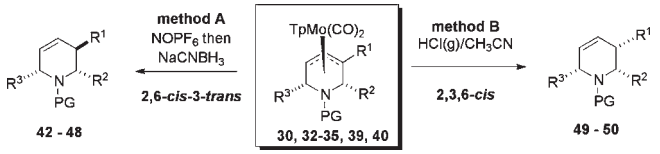
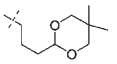
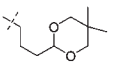
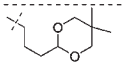
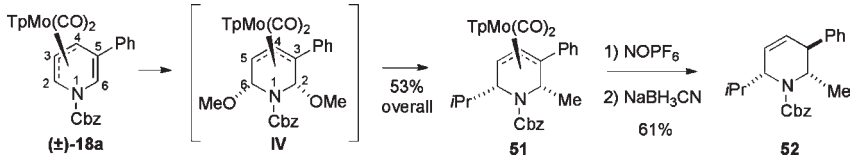
Table 4. Regiospecific and Stereodivergent Demetalations



entry	#	PG	R^1	R^2	R^3	method	#	yld[a] (dr)
1	**30**	(*S*)-CO_2CH(*n*-Pr)Ph	Me	$BnO(CH_2)_3$		A	**42**	54 (99.5:0.5)
2	**32**	Cbz	Et	$BnO(CH_2)_3$		A	**43**	53
3	**33**	Cbz	Et	$BnO(CH_2)_4$		A	**44**	57
4	**34**	Cbz	Et	$BnO(CH_2)_4$	*n*-hexyl	A	**45**	61
5	**35**	(*S*)-CO_2CH(*n*-Pr)Ph	Et	$BnO(CH_2)_4$	*n*-hexyl	A	**46**	56 (99.5:0.5)
6	**39**	Cbz	*n*-Pr	$BnO(CH_2)_3$	*n*-Pr	A	**47**	56
7	**40**	(*S*)-CO_2CH(*n*-Pr)Ph	*n*-Bu	$BnO(CH_2)_3$	*n*-pentyl	A	**48**	53 (99.5:0.5)
8	**32**	Cbz	Et	$BnO(CH_2)_3$		B	**49**	66
9	**40**	(*S*)-CO_2CH(*n*-Pr)Ph	*n*-Bu	$BnO(CH_2)_3$	*n*-pentyl	B	**50**	62 (99.5:0.5)

[a] Isolated yield.

Scheme 4. Sequential Functionalization of (±)-Tp(CO)$_2$(η^3)-Pyridinylmolybdenum 18



material. For example, it was previously demonstrated that 3-substituted η^3-3,4,5-pyranyl[12f] and -pyridinylmolybdenum complexes[12j] could be demetalated in a stereodivergent fashion relative to the 3-substituent. Demetalation using a CO/NO$^+$ ligand exchange followed by nucleophilic attack of hydride on the resulting cationic intermediate at the more substituted terminus of the π-complex and *anti* to the TpMo(CO)(NO)$^+$ moiety[35] (Method A) delivered one stereoisomer, while protodemetalation under acidic conditions[12k,13a] (Method B) placed hydrogen, also at the more substituted end of the η^3-allylmolybdenum, but *syn* to the TpMo unit. Using these same stereodivergent demetalation procedures the η^3-allylmolybdenum complexes **30**, **32**−**40** were easily converted to either 2,6-*cis*-3-*trans* or 2,3,6-*cis* trisubstituted dehydropiperidines. Reductive demetalation of 2,3,6-trisubstituted molybdenum complexes (**30**, **32**−**35**, **39**, **40**) in DME as the solvent gave 2,6-*cis*-3-*trans* **43**−**48** in 52−61% isolated yield, with complete regio-, stereo- and enantiocontrol (Table 4, entries 1−7). Alternatively, acidic protodemetalation of complexes **32** and **40** with HCl in CH_3CN afforded the unsaturated 2,3,6-*cis*-dehydropiperidines **49** and **50** in 42−66% isolated yields. The use of acetonitrile as the solvent moderates the acidity of the system and helps to minimize the formation of the more substituted olefin regioisomer.[12j]

The scope of the reductive demetalation protocol is fairly broad (Table 4, entries 1−7), although an acid-sensitive acetal was not well-tolerated during the acidic protodemetalation process; an ethylene glycol protected aldehyde (not shown) was hydrolyzed producing a moderate yield of the corresponding aldehyde. However, by substituting 2,2-dimethyl-1,3-diol for ethylene glycol for protection of the aldehyde, a more robust ketal was produced. In this case the expected protodemetalation product **49** was isolated in 66% yield from the acidic

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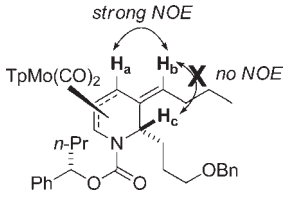
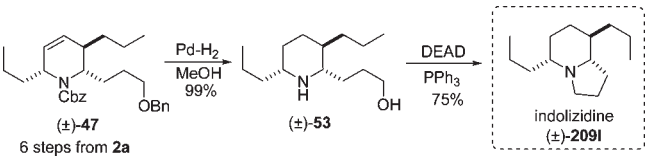


Figure 6. NOE experiment on compound (*E*)-**28**.

Scheme 5. Total Synthesis of Indolizidine (±)-209I



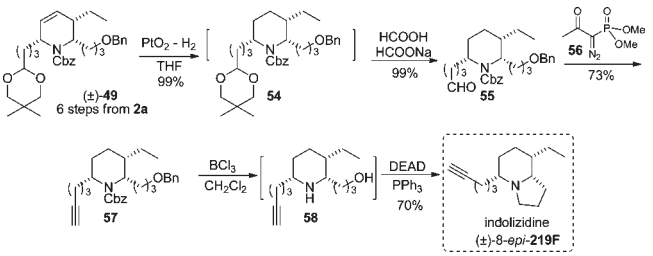
demetalation conditions (Table 4, entry 8). Using both protocols (reductive or protodemetalation), a series of 2,6-*cis*-3-*trans* and 2,3,6-*cis* dehydropiperidines was obtained in reasonable isolated yields (52−66%). Together, these two demetalation methods allow the sequential functionalizations depicted above to serve as a versatile strategy for the generation of a variety of trisubstituted 4,5-dehydropiperidines from the common scaffold **2**.

The trifunctionalization of the η^3-pyridinylmolybdenum scaffolds is not restricted to substituents attached at the 5-position of the scaffold through an sp^3-carbon. For example, bromine-induced oxidative dimethoxylation of the (±)-TpMo(CO)$_2$(5-phenyl-η^3-pyridinyl) complex **18** generates the intermediate **IV** shown in Scheme 4. Two subsequent methoxide ionization/carbanion addition sequences (TrPF$_6$ then MeMgBr; HBF$_4$ then CuBr·DMS/*i*-PrMgBr) provides the trifunctionalized dihydropyridinyl complex **51** in 53% overall yield. Activation of **51** with NOPF$_6$ followed by treatment with NaCNBH$_3$ stereospecifically delivers the 2,3,6-trisubstituted-4,5-dehydropiperidine **52** in 61% yield.

Total Synthesis of Indolizidine and Quinolizidine Alkaloids. The piperidine ring is embedded within the pharmacologically active indolizidine and quinolizidine families of alkaloid natural products, of which many hundreds of structurally diverse examples have been detected and identified from amphibian skin.[19b,36] To showcase the concept of organometallic scaffolding, syntheses of the indolizidine alkaloids (±)-209I,[15,37] (±)-8-*epi*-219F,[16b] and (−)-251N,[17] the quinolizidine alkaloid (−)-251AA,[18] and 6,7-dehydroindolizidine (−)-233E[19] were undertaken, all from the common scaffold **2** (Schemes 5−8). Two of the syntheses were carried out in the racemic series, and three used the high enantiopurity scaffold.

Alkaloids (−)-209I, (−)-219F, (−)-251N, (−)-251AA, and (−)-233E were first reported by Daly.[16c,19,36b,38] A total synthesis of (±)-209I was described by Rassat and co-workers where the 9-azabicyclo[3.3.1]nonane skeleton was derived from a symmetrical 1,5-octanediepoxide.[15] This racemic series approach allowed the formation of both indolizidine and quinolizidine families through a flexible installation of functional side chains. Asymmetric syntheses of (−)-209I were accomplished by Enders,[37b] Ma,[39] and Charette.[40] Enders approached the indolizidine skeleton from a chiral nonracemic pyrrolidine hydrazone, in which the 8-substituent was preinstalled. The Enders' strategy required preinstallation of a substituent in the starting material

Scheme 6. Demonstration of Stereodivergence: Synthesis of Indolizidine (±)-8-*epi*-219F



and is limited to construction of the indolizidine skeleton. Ma took advantage of a formal [4 + 2] cycloaddition of a chiral, nonracemic 3-chloro-1-substituted-amine with a substituted propiolic acid ester to form a substituted piperidine core. Charette approached (−)-209I via a novel Grob fragmentation of an aza-bicyclo[2.2.2]octene. Michael described a formal synthesis of (−)-209I in over 20 steps commencing with *tert*-butyl hexenoate.[37a] An asymmetric synthesis of (−)-219F was described by Toyooka and co-workers[16a,b] where the common precursor 2,6-disubstituted tetrahydropyridine was derived from amino adipic acid through 8 transformations. Toyooka also described total syntheses of (−)-251AA[18] and (−)-251N[17] using the same synthetic approach. No synthesis of indolizidine 233E has yet been reported based on a Scifinder search performed on November 29, 2010.

Using the organometallic scaffolding strategy, a total synthesis of indolizidine (±)-209I[15,37] was undertaken first. Compound **47**, described above (Table 4, entry 6), underwent a one-pot hydrogenation/hydrogenolysis that saturated the double bond and cleaved the benzylic protecting group from the primary alcohol. Compound **53**, obtained in near quantitative yield, possessed the same NMR signatures as the same compound obtained by Charette in his synthesis of (−)-209I.[40] Without further purification a classical Mitsunobu reaction was carried out,[41] providing the desired indolizidine (±)-209I in 75% yield.

In contrast to the generation of the 2,6-*cis*-3-*trans* dehydropiperidine substitution pattern used in the first scaffold-based synthesis, the second scaffolding sequence highlights the use of the stereodivergent demetalation tactic to construct the unnatural 2,3,6-*cis* dehydropiperidine from which indolizidine (±)-8-*epi*-219F[16b] was derived (Scheme 6). Compound **49**, which can be synthesized from scaffold **2a** in 6 steps, was catalytically hydrogenated to afford the trisubstituted piperidine **54** that was directly carried forward to aldehyde **55**. For removal of the robust 5,5-dimethyl-1,2-dioxane acetal, standard acid-catalyzed hydrolysis conditions were ineffective. Rather, cleavage of this acetal group was achieved by treatment with a buffered solution of formic acid. The formic acid serves as both a proton source for the catalysis as well as a trap for the 1,3-diol produced upon hydrolysis.[42] Application of these conditions to substrate **54** led quantitatively to aldehyde **55**.

Prior to generation of the indolizidine aldehyde **55** was converted into the corresponding terminal alkyne **57** in 73% yield using dimethyl (1-diazo-2-oxopropyl)phosphonate **56**.[43] After some exploration of debenzylation conditions,[44] the free alcohol intermediate **58** was obtained from **57** using boron trichloride. A Mitsunobu reaction transformed this intermediate to the intended indolizidine (±)-8-*epi*-219F in 70% yield.

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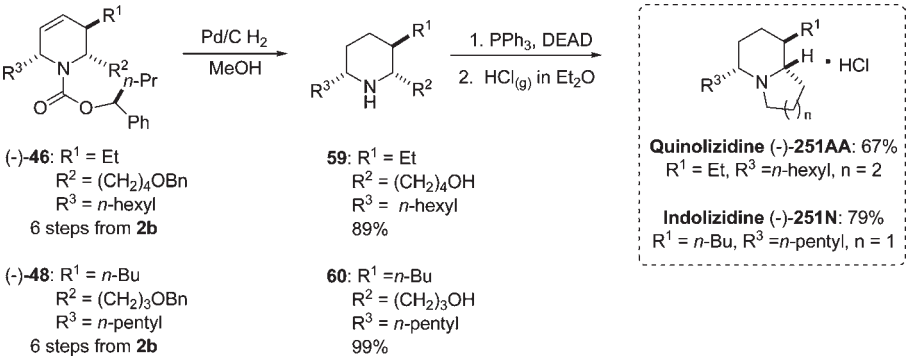
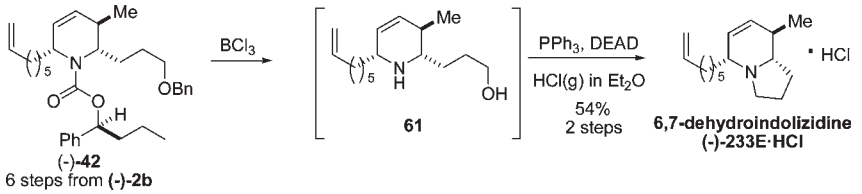
Scheme 7. Synthesis of Quinolizidine (−)-251AA·HCl and Indolizidine (−)-251N·HCl



Scheme 8. Synthesis of (−)-6,7-Dehydroindolizidine 233E



Sequences involving the chiral, nonracemic scaffolds for the synthesis of indolizidines and quinolizidines of high enantiopurity are shown in Scheme 7. The synthesis of indolizidine (−)-251AA[18] was achieved in 8 steps from scaffold **2b**. A one-pot hydrogenation/hydrogenolysis of compound **46** led to the isolation of compound (−)-**59** in 89% yield. A subsequent Mitsunobu reaction provided the expected quinolizidine (−)-251AA in 67% yield. The same sequence was used for a total synthesis of indolizidine (−)-251N,[17] starting from compound **48** (obtained in 6 steps from chiral, nonracemic complex **2b**) and proceeding through intermediate **60** (Scheme 7).

The diastereomeric excess of precursors (−)-**46** and (−)-**48** was determined by HPLC (>99.5:0.5 dr).[27] Since the molybdenum scaffolds described in this study showed no evidence of π-face racemization,[27] the quinolizidine (−)-251AA and indolizidine (−)-251N, produced by the hydrogenation/hydrogenolysis/Mitsunobu reaction sequence, are assumed to have an enantiomeric ratio of >99.5:0.5.

Finally, a total synthesis of 6,7-dehydroindolizidine (−)-233E[19] was carried out (Scheme 8). From the trisubstituted dehydropiperidine (−)-**42**, deprotection of the benzyl alcohol and the urethane in the presence of the two double bonds was achieved using BCl_3. A subsequent Mitsunobu reaction delivered 6,7-dehydroindolizidine (−)-233E in 54% isolated yield over the two steps. The diastereomeric ratio of the precursor (−)-**42** was >95.5:0.5 as assayed by HPLC. Therefore, just as described for quinolizidine (−)-251AA and indolizidine (−)-251N above, since no evidence of π-face racemization is found in the transformations described within,[27] 6,7-dehydroindolizidine (−)-233E, produced by the deprotection/Mitsunobu reaction sequence, is assumed to have an enantiomeric ratio of >99.5:0.5.

■ CONCLUSIONS

The efficient and scalable synthesis of the racemic TpMo(CO)$_2$(5-oxo-η^3-pyridinyl) scaffolds, (±)-**2a**, (±)-**2c**, and their chiral, nonracemic relatives, (−)-**2b** and (+)-**2b′**, allows the TpMo(CO)$_2$(5-oxo-η^3-pyridinyl) system to be used as a platform for a variety of versatile and efficient peripheral functionalizations. The nucleophilic addition of organocerium reagents to the ketone, followed by a highly regioselective ionization/nucleophilic addition/ionization sequence, led to the controlled functionalization of the 2- and 3-positions. A third functionalization at C-6 (treatment with HBF_4 followed by nucleophilic addition) leads to 2,6-*cis*-3-substituted piperidine precursors, which after stereodivergent demetalation gives access to either 2,6-*cis*-3-*trans* or 2,3,6-*cis* trisubstituted piperidines of high enantiopurity. This sequential functionalization of scaffold **2** was highlighted by the total synthesis of four naturally occurring alkaloids and one non-natural alkaloid.

The TpMo(CO)$_2$ unit shields one face of the π-ligand. Therefore, nucleophiles approach the organometallic scaffolds from the π-face opposite the TpMo(CO)$_2$ moiety leading to the dominant introduction of substituents around the scaffold periphery with *cis* relative stereochemistry. Thus, the 2- and 6-positions of the piperidine ring are easily adorned with a variety of substituents placed with *cis* relative stereochemistry.[12g,j,l,m] Two different stereodivergent demetalation protocols enabled the 3-substituent to be oriented either *cis* or *trans* to the *cis*-2,6-substitutent pair leading to *cis*-2,3,6-trisubstituted and 2,6-*cis*-3-*trans*-trisubstituted dehydropiperidines.[45] Finally, the use of organometallic enantiomeric scaffolds is currently under consideration for the generation of focused libraries in order to probe chemical space not easily addressed using traditional synthetic organic methods.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental details and characterization data for all compounds and copies of proton and carbon NMR spectra of all new compounds prepared.

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