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Enantiocontrolled Synthesis of 2,6-Disubstituted Piperidines by Desymmetrization of *meso*-η-(3,4,5)-Dihydropyridinylmolybdenum Complexes. Application to the Total Synthesis of (−)-Dihydropinidine and (−)-Andrachcinidine

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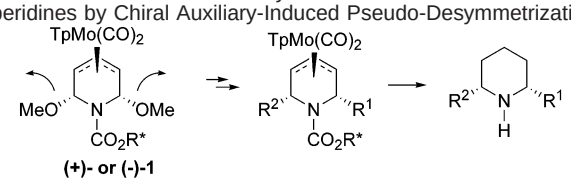
Enantiomerically pure iron and molybdenum π-complexes are powerful scaffolds for the enantiocontrolled construction of substituted carbo- and heterocycles.[1] Traditionally, the complexes are prepared either by resolution of racemic complexes or by face-selective π-complexation from enantiopure precursors.[2] Desymmetrization, despite being a powerful tool for the preparation of enantiomerically pure "organic" molecules,[3] has been explored only recently for organometallic π-complexes using hydride abstraction.[4] While interesting, the practicality of the reported *enantioselective* hydride abstraction approaches was limited by moderate enantioselectivities and the lengthy steps required to prepare the stoichiometric chiral, nonracemic hydride abstraction reagents. Herein we report a conceptually different approach that uses a pseudo-desymmetrization involving a highly diastereoselective methoxide abstraction from (+)- or (−)-**1**[5] (Scheme 1), where R* = (+)- or (−)-*trans*-2-(α-cumyl)cyclohexyl (TCC).[6] Through a sequential, one-pot methoxide abstraction/nucleophilic addition/methoxide abstraction/nucleophilic addition, and then protodemetalation/N-deprotection, a simple and enantiocontrolled synthetic entry to a variety of 2,6-disubstituted piperidines is achieved. 2,6-Disubstituted piperidines have attracted much attention due to their interesting structures and potent biological activities.[7]

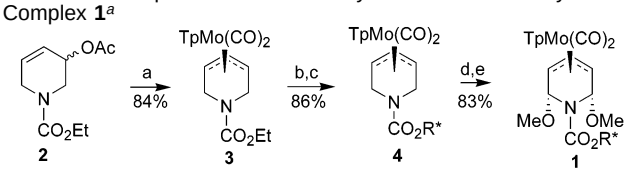
Chiral carbamate protected complexes **1** were prepared from the known (±)-ethyl 3-acetoxy-4,5-dehydro-1-piperidinecarboxylate **2**[8] in five simple steps (Scheme 2). Treatment of **2** with $Mo(CO)_3(DMF)_3$[9] followed by KTp[10] (Tp = hydridotrispyrazolylborate) gave *meso*-η^3-allylmolybdenum complex **3** in 84% yield. N-Deprotection of **3** with 4 equiv of TMSI at reflux in CH_2Cl_2 afforded the free amine in 94% yield. Reprotection with the chloroformate derived from either (+)- or (−)-TCC[6] in the presence of Et_3N and catalytic DMAP provided the urethane complexes (+)- or (−)-**4** in 91% yield. Conversion of **4** to the pseudo-*meso* complex **1** was trivially accomplished by a two-stage process: hydride abstraction with Ph_3CPF_6 followed by deprotonation of the formed η^4-diene cation with Et_3N to generate an η^3-pyridinyl complex (88%) and then conversion into (+)- or (−)-**1** in 96% yield following a previously described one-pot protocol (treatment with Br_2 then NaOMe at −78 °C).[11]

The sequential functionalization of (−)-**1** was carried out in the same manner as that of the analogous 2,6-dimethoxy-3-substituted dihydropyranyl[11] and -dihydropyridinyl complexes,[12] whose methoxide abstraction selectivity is imparted from the unsymmetrically substituted nature of the dihydropyranyl and dihydropyridinyl rings. In contrast, the methoxide abstraction selectivity for pseudo-symmetrical complexes **1** relies solely on the "desymmetrization" imparted by the chiral, nonracemic N-protecting group. In the event, methoxide abstraction from (−)-**1** with 1.0 equiv of Ph_3CPF_6, addition of MeMgBr, ionization of the remaining methoxide with

Scheme 1. Enantiocontrolled Synthesis of Disubstituted Piperidines by Chiral Auxiliary-Induced Pseudo-Desymmetrization

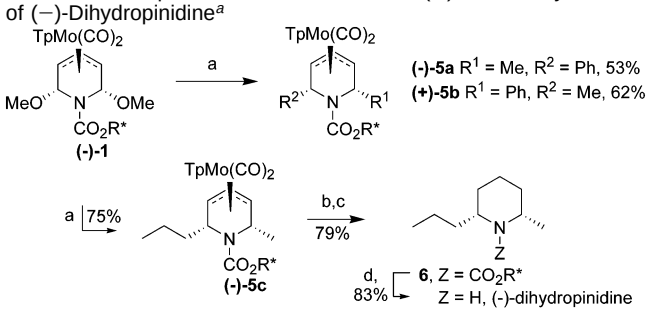


Scheme 2. Preparation of Pseudo-Symmetrical Dimethoxy Complex **1**[a]



[a] R* = (+)- or (−)-*trans*-2-(α-cumyl)cyclohexyl, TCC. (a) $Mo(CO)_3(DMF)_3$ then KTp, 84%. (b) TMSI, 94%. (c) (+)- or (−)-TCC chloroformate, Et_3N, DMAP, 91%. (d) Ph_3CPF_6 then Et_3N, 88%. (e) Br_2 then NaOMe, 96%.

Scheme 3. Sequential Functionalization of (−)-**1**; Total Synthesis of (−)-Dihydropinidine[a]



[a] R* = (−)-TCC. (a) Ph_3CPF_6 then R^1M; HBF_4 then R^2M. (b) HCl in EtOAc. (c) H_2, Pd/C, 79%. (d) KOH/EtOH, seal tube (150 °C), 83%.

HBF_4, and addition of PhMgBr (all steps without intermediate purification, 53% overall yield) provided the 2,6-disubstituted dihydropyridinylmolybdenum complex (−)-**5a** (Scheme 3). To measure the selectivity for the first methoxide abstraction from **1**, the diastereomeric molybdenum complex (+)-**5b** was prepared by reversing the order of nucleophiles added (PhMgBr then MeMgBr). With both diastereomers in hand, the selectivity of the first methoxide abstraction was estimated by ^1H NMR analysis of the crude products (−)-**5a** and (+)-**5b** to be at least 40/1.[13]

Support for the structure assignments of (−)-**5a** and (+)-**5b** was obtained by a total synthesis of (−)-dihydropinidine from (−)-**1**.[14] Complex (−)-**5c**, prepared in 75% overall yield from (−)-**1** in the same manner as that of **5a/b**, was subjected to protodemetalation (HCl) and hydrogenation (H_2, Pd/C) to afford the protected dihydropinidine **6** in 79% yield. Deprotection of **6** with KOH/EtOH in a sealed tube (150 °C) for 24 h provided (−)-dihydropinidine in

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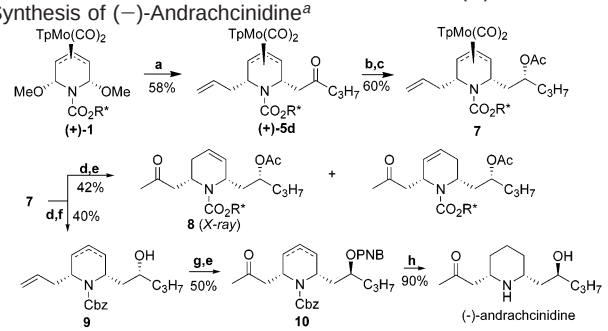
Scheme 4. Stereocontrolled Functionalization of (+)-**1**; Total Synthesis of (−)-Andrachcinidine[a]



[a] R* = (+)-TCC. (a) Ph_3CPF_6 then allylMgCl; HBF_4 then $CH_2{=}C(OLi)C_3H_7$, 58%. (b) K-Selectride, 64%. (c) Ac_2O, Et_3N, DMAP, 93%. (d) $NOPF_6$ then $NaCNBH_3$, 64%. (e) $PdCl_2$, CuCl, O_2, DMF/H_2O, 66%. (f) KOH/EtOH, seal tube (140 °C), then CbzCl, NaOH, 62%. (g) *p*-NO_2PhCO_2H, Ph_3P, DEAD, 76%. (h) KOH/MeOH then H_2, Pd/C, MeOH/EtOAc, 90%.

83% yield (Scheme 3). The optical rotation of its hydrochloride salt was consistent with that reported in the literature ($[\alpha]_D$ −10.5, c = 0.2 EtOH, lit.[15] $[\alpha]_D$ −11.6, c = 1.03 EtOH).

The synthetic power of this novel pseudo-desymmetrization method was demonstrated by a total synthesis of (−)-andrachcinidine,[16] an alkaloid isolated from *Andrachne aspera*. Sequential functionalization of (+)-**1** (Ph_3CPF_6 then allylMgCl; HBF_4 then $CH_2{=}C(OLi)C_3H_7$) afforded (+)-**5d** in 58% yield (Scheme 4). The selective reduction of (+)-**5d** with K-Selectride gave a single diastereomer of an alcohol (64%) that was acetylated (Ac_2O, Et_3N, and DMAP) to provide acetate **7** in 93% yield. The reductive demetalation of **7** with $NOPF_6$ at −40 °C followed by $NaCNBH_3$ at room temperature proceeded smoothly to give a mixture of two cyclohexene olefinic regioisomers (64%) that was subjected to a selective Wacker oxidation[17] of the allyl side chain to give ketone **8** and its olefin isomer in 66% yield. Unfortunately, an X-ray crystallographic analysis of crystalline **8** demonstrated that the selective reduction of (+)-**5d** with K-Selectride had produced the undesired alcohol stereochemistry.

The alcohol stereochemistry was adjusted, and the synthesis of andrachcinidine was completed using a modified reaction sequence (Scheme 4). As before, complex **7** was reductively demetalated to give a mixture of olefin regioisomers. Prior to the Wacker oxidation, the (+)-TCC auxiliary and the acetate were cleaved with KOH/EtOH in a seal tube (140 °C), and the amine was reprotected with CbzCl to give **9** (62% overall yield). The undesired alcohol stereochemistry was then inverted by a modified Mitsunobu reaction (76%),[18] and a subsequent Wacker oxidation proceeded exclusively at the allyl side chain and delivered the keto-olefin isomer mixture **10** in 66% yield. Finally, basic hydrolysis followed by hydrogenation led to cleavage of the N- and O-protecting groups and reduction of the olefinic double bond and afforded (−)-andrachcinidine in 90% yield from **10** (18% overall from molybdenum complex **7**). The spectroscopic data (^{1}H and ^{13}C NMR) of the synthetic product are in excellent agreement with those reported in the literature ($[\alpha]_D$ −20, c = 0.18 $CHCl_3$, lit. $[\alpha]_D$ −20, c = 1.6 $CHCl_3$).[16] This synthesis, together with the X-ray structure of **8**, confirmed the proposed structure of (−)-andrachcinidine.

In the related 2,6-dimethoxy-3-substituted dihydropyranyl and -dihydropyridinyl complexes studied earlier,[12] highly selective methoxide abstraction was rationalized by an interaction between the 3-substituent and the $TpMo(CO)_2$, with support from X-ray crystallographic studies. However, the diastereoselective methoxide abstraction described herein is distinctively different as the selectivity arises solely from the chiral auxiliary. Unfortunately, the structural origin of the highly selective methoxide abstraction from (+)- or (−)-**1** remains obscure. All attempts to obtain crystals of (+)- or (−)-**1**, or any alkoxide congeners suitable for X-ray crystallography, met with failure.

In summary, a novel and enantiocontrolled synthesis of 2,6-disubstituted piperidines using a diastereoselective methoxide abstraction of dimethoxy complexes with chiral protecting groups has been disclosed. While the method described should allow the enantiocontrolled synthesis of diverse 2,6-disubstituted piperidines, the synthetic potential was specifically demonstrated by the efficient synthesis of (−)-dihydropinidine and (−)-andrachcinidine.

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Supporting Information Available: A complete description of the synthesis and characterization data of all compounds prepared in this study and X-ray crystallography data of (−)-**8** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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