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Synthesis of a novel ethylene-bis(tetrahydroindenyl) ligand containing a functionalized four-carbon tether

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Abstract—In this work we present an efficient synthesis of a novel ethylene-bis(2-methyl-tetrahydroindenyl) ligand, **2b**, containing a tethered functional group. The tethered functional group may enable heterogenization of the homogeneous ligand on various solid supports. This strategy is the first attempt of incorporating a functional tether into a bridged metallocene ligand without disrupting the ethane bridge and represents a new approach to heterogenizing metallocene ligands. A practical synthesis was achieved by selective alkylation of the starting material and the Pauson–Khand cyclization. In addition, this strategy offers a new synthetic pathway for the preparation of the ethylene-bis(2-methyl-tetrahydroindenyl) ligand, **1b**.

Metallocenes are a subgroup of organometallic complexes, which are used for various catalytic reactions.[1] One particularly promising class of metallocene ligands are ethylene-bis(tetrahydroindenyl) and derivatives, e.g. **1a** and **1b**, (in Fig. 1). First developed by Brintzinger,[2] this chiral complex, whose chirality is derived from the ligand–metal linkage, proved to be effective for polymerization,[3] as well as for asymmetric hydrogenation catalysis.[4]

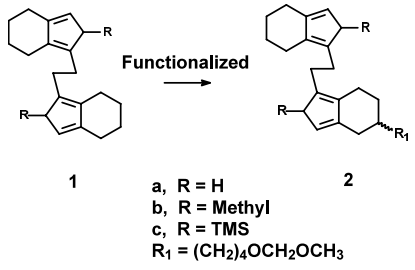

Figure 1. The homogeneous ethylene-bis(tetrahydroindenyl) ligand (**1**) and the functionalized ethylene-bis(tetrahydroindenyl) ligand (**2**). Configuration of the conjugated double bonds depends on the substituent, R.

The extraordinary effectiveness of metallocenes has lead to a considerable effort in developing a strategy for anchoring these complexes onto solid supports. While the ethylene-bis(tetrahydroindenyl) ligand has not yet been heterogenized, researchers have attempted to heterogenize similar cyclopentadienyl ligands resulting in catalysts with lower activity and selectivity.[5] In this work we sought to develop novel ethylene-bis(tetrahydroindenyl) ligands that contain a functional tether distant from the active catalytic site in order not to disrupt the ethane bridge. Herein, we report the first successful attempt at attaching a functionalized tether onto the ethylene-bis(2-methyl-tetrahydroindenyl) ligand, **2b**, through the cyclohexane ring, as shown in Figure 1. Our synthesis also represents a useful synthetic pathway for the preparation of the homogeneous ethylene-bis(2-methyl-tetrahydroindenyl) ligand, **1b**.

After reviewing the literature, we determined that the most effective strategy to attach a tethered functional group was to modify the synthesis presented by Halterman.[6] This approach utilizes a double alkylation of 1,5-hexadiyne, a Pauson–Khand cyclization to form the ethylene-bis(hydroindeneone) followed by a Shapiro elimination reaction. The five-step synthesis represents the most efficient synthetic pathway for preparing the ethylene-bis(tetrahydroindenyl) ligand. However, for our purposes it was necessary to modify this procedure in order to accommodate a carbon tether containing an alcohol group. Subsequent heterogenization could then occur at this site.

Keywords: ethylene-bis(tetrahydroindenyl); alkyne alkylation; cyclopentadiene; heterogenization.

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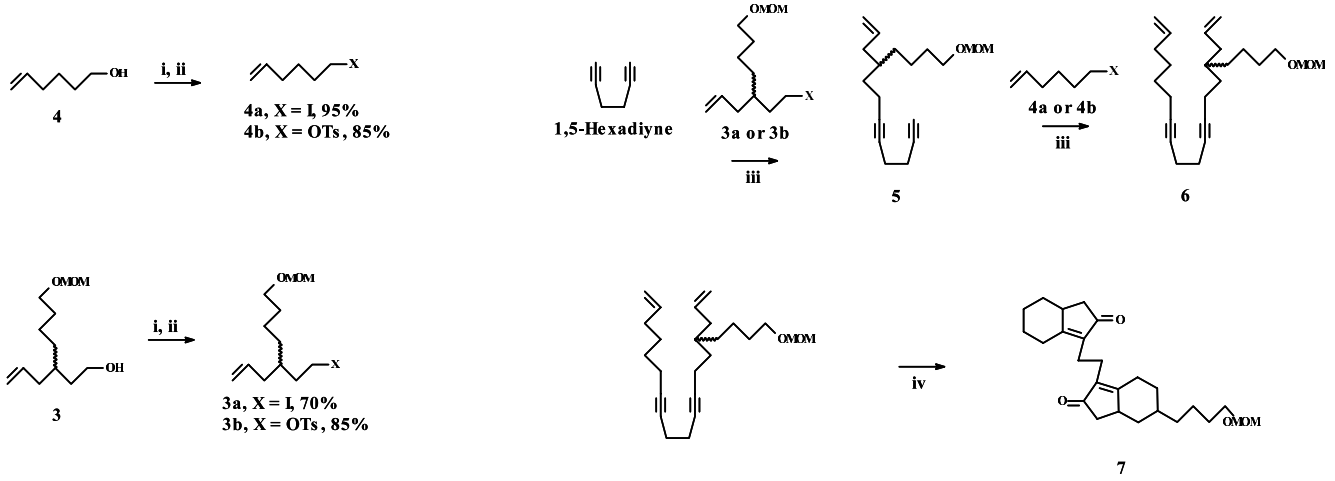
Our selective alkylation strategy is presented in Scheme 1. Before the alkylations were undertaken, it was necessary to generate alkyl-electrophiles by converting alcohols into the appropriate leaving group. 3-Allyl-7-methoxymethoxy-heptan-1-ol, **3**, and 6-hexen-1-ol, **4**, were converted to alkyl-iodides by reaction with imidazole (2 mol. equiv.), triphenyl phosphine (2 mol. equiv.), and I_2 (2 mol. equiv.) in ethyl ether and acetonitrile.[7] While the halogenation is straightforward and very favorable, the formation of hydriodic acid may cleave the MOM-alcohol protecting group, resulting in low yields of 4-(2-iodo-ethyl)-8-methoxymethoxy-oct-1-ene, **3a**. This did not appear to influence the 6-iodo-1-hexene, **4a**, even when the reaction was extended. In order to minimize the loss of the starting alcohol, alkyl-tosylates were also prepared. The alcohols were treated with pyridine (2 mol. equiv.) and tosylate chloride (2 mol. equiv.) in methylene chloride to obtain alkyl-tosylates, **3b** and **4b** in good yields.[8]

In an attempt to selectively alkylate a single terminal alkyne, we first synthesized 1-trimethylsilane-1,5-hexadiyne (pathway not shown).[9] The unprotected terminal alkyne was then alkylated via an S_N2 mechanism with **4a**.[10] A carbanion was first generated at −78°C by using *n*-butyllithium (1.1 mol. equiv.) with small amounts of HMPA to minimize lithium clustering. After 45 min, dilute **4a** was slowly added. The reaction was then allowed to warm up to room temperature over 4 h. Next, the alkyne-protecting group was removed using TBAF.[11] Unfortunately, all further attempts to alkylate dodec-11-ene-1,5-diyne with **3a** or **3b** failed.[12] Quenching the lithiated alkyne with deuterated water—as opposed to addition of the alkyl-halide—showed that nearly complete lithiation had occurred. As a result, the alkylation sequence was reversed. With the lack of available 1-trimethylsilane-1,5-hexadiyne, 1,5-hexadiyne was alkylated with **3a** or **3b**, as previously described, to obtain 9-allyl-13-methoxymethoxy-trideca-1,5-diyne, **5**. Alkylation with alkyl-iodide was more favorable with a 70% yield, compared to a 45% yield when alkyl-tosylates were used. Surprisingly, the double alkylation products were only observed when alkyl-iodide was used for the alkylation with yields less then 20%. Using the same alkylation procedure, compound **5** was alkylated with **4a** or **4b** to form 15-allyl-19-methoxymethoxy-nonadec-1-ene-7,11-diyne, **6**. This provided the desired asymmetric enyne. Success with reversing the alkylation sequence indicates either a mild steric or electronic limitation on the alkyne alkylations.

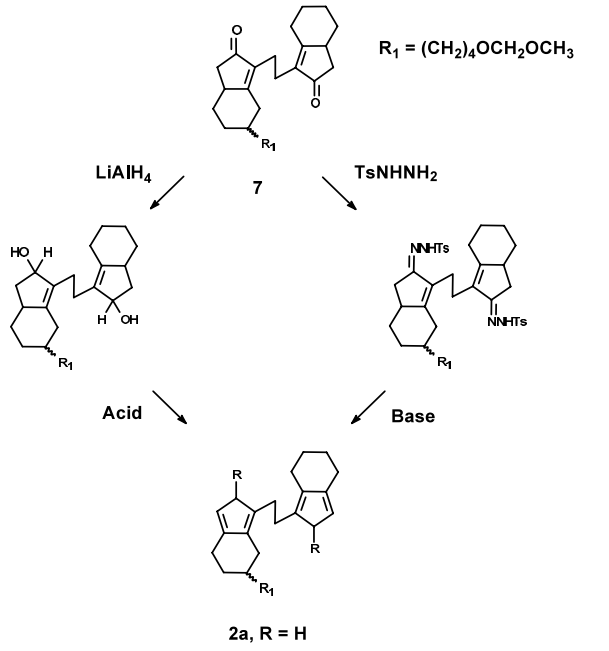
With our enyne, **6**, the double Pauson–Khand cyclization reaction was used to synthesize the branched ethylene-bis(hydroindeneone), as shown in Scheme 1.[6] Dicobalt octacarbonyl (2.2 mol equiv.) complexes with alkyne at ambient temperature to form a stable metal-alkyne bond. When the bubbling ceased, the reaction mixture was heated under reflux overnight to give **7** in 80% yield.[13] Although literature showed some steric limitations of the reaction,[14] the lack of any significant by-products and yields greater than 75%, led us to conclude that the tethered functional group did not result in steric inhibition with the reaction.

Reduction of the hydroindeneone, **7**, to a hydroindenyl, **2a**, can be carried out by forming a tosylhydrazone (2.2 mol equiv. *p*-toluenesulfonyl hydrozide) followed by the Shapiro elimination[6,15] (5.0 mol equiv. *s*-butyllithium) or by reducing the enone to an alcohol with $LiAlH_4$ (2.2 mol. equiv.) followed by treating it with a mild acid,[16] as shown in Scheme 2. Reduction with $LiAlH_4$ offered higher yields (>90% compared to <50% for reaction with tosylhydrazide), shorter reaction times, lower reaction temperatures and simpler work-ups. While both approaches were successful, the instability of the ethylene-bis(tetrahydroindenyl), **1a** and **2a**, prevented us from obtaining quantitative analytical data.[17]

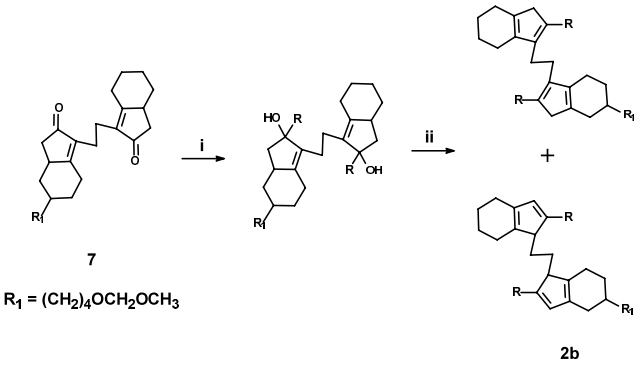
Either trimethylsilane,[18] or a methyl group,[19] can be attached to cyclopentadienyl to help stabilize tetrahydroindenyl, **2a**. Since **2b** is more stable and easier to prepare as well as to separate, we chose methyl addition. As shown in Scheme 3, methyllithium was slowly



Scheme 1. *Reagents and conditions*: (i) I_2, TPP, imidazole, (4/1) EE and acetonitrile, rt; (ii) TsCl, Me_2Cl_2, 0°C; (iii) 1. *n*-BuLi, −78°C, THF, 2. HMPA, 3. Electrophile+THF, 4. rt, 8 h; (iv) Co_2CO_8, acetonitrile, reflux 16 h.



Scheme 2. Formation of the ethylene-bis(tetrahydroindenyl) ligand.



Scheme 3. Reduction of the hydroindeneone by stabilizing the cyclopenta-dienyl to form two cycloalkene isomers. *Reagents and conditions*: (i) MeLi, EE, 0°C; (ii) H^+ or spontaneous.

added to **7** in ethyl ether at 0°C. The reaction was kept in an ice bath for 1 h and was then allowed to warm up to ambient temperature over 2 h. During the reaction, spontaneous dehydration was observed, forming the desired tethered ethylene-bis(2-methyl-tetrahydroindenyl), **2b**. Several cyclopentadienyl isomers[20] were observed in 55% yield and an overall yield of 15%.[21]

An analogous method can be applied to the synthesis of the ethylene-bis(2-methyl-tetrahydroindenyl) ligand, **1b**. Hydroindeneone was easily prepared using a double alkylation of 1,5-hexadyine with 6-iodo-1-hexene, **4a**, followed by the double Pauson–Khand cyclization.[22] Reduction of the hydroindeneone with methyllithium was followed by spontaneous dehydration. Two cyclopentadienyl isomers of **1b** were observed with an overall yield of 65%.[23] The hydroindeneone intermediate was also converted into the TMS-stabilized ethylene-bis(2-trimethylsilane-tetrahydroindenyl), **1c**, by reacting with $LiAlH_4$ followed by Amberlyst 15 to yield ethylene-bis(tetrahydroindenyl), **1a**. Next, **1a** was lithiated with *n*-butyllithium at 0°C and after 12 h quenched with chlorotrimethylsilane to afford **1c**.

It is noteworthy that the alcohol-protecting group (MOM) has not yet been removed. A strong base will be used to attach the metal to the ligand, which will most likely react with an unprotected alcohol. Therefore, it was decided to remove the alcohol-protecting group after the attachment of the metal. Several strategies for removing the MOM protecting group will be investigated.[11]

In conclusion, we have presented a practical and efficient synthesis for incorporating a tethered functional group into the ethylene-bis(2-methyl-tetrahydroindenyl), **2b**, ligand in 15% overall yield. The addition of the tethered group may enable anchoring the homogeneous organometallic ligand onto various heterogeneous supports. The five-step synthesis benefits from steric or electronic limitations by inhibiting the double alkylation of 1,5-hexadiyne using a alkyl-electrophile with minimal steric bulk, which selectively alkylates a single terminal alkyne in good yields. Selective alkylation of 1,5-hexadiyne also demonstrates the ability to incorporate a tethered functional group in the ethylene-bis(tetrahydroindenyl) synthesis without increasing the complexity of the synthesis and eliminates the need for alkyne protecting groups. Lastly, the presented synthesis is also a novel and efficient synthesis for the preparation of the untethered ethylene-bis(2-methyl-tetrahydroindenyl), **1b**.

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21. 5 - (4 - Methoxymethoxy-butyl)-2-methyl-1-[2-(2-methyl-4,5,6,7-tetrahydro-1*H*-inden-1-yl)-ethyl]-4,5,6,7-tetrahydro-1*H*-indene, 10% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) isomer protons for the desired isomer seen at 5.85 ppm. MS m/z (appi, ion trap) 410.2^+ (frag., Int.) 378.3 (100), 276.5 (12), 262.5 (27), 230.6 (14), 160.8 (34), 158.8 (10), 146.9 (36), 144.8 (11). UV ads. 315, 326 and 346 nm peaks adsorption.
22. 1,2,-Ethylene-bis(9-bicyclo [4.3.0]-non-1(9)-en-8-one), 80% isolated yield as a off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.8$ (t, 2H), 2.5 (d, 4H), 2.3–2.4 (b. s, 3), 2.23 (d, 1H), 2.12 (d, 2H), 1.75–2.05 (m, 8H), 1.4–1.55 (q, 2H), 1.1–1.35 (m, 2H), 95–1.1 (m, 2H). ^{13}C NMR: 208, 178, 136, 41, 40, 35, 28, 27, 21. MS m/z (appi, ion trap): 298.4^+ (frag., Int.): 280.4 (40), 263.5 (15), 262.5 (100), 260.4 (18), 1663.7 (12), 142.8 (17), 132.8 (30), 130.8 (51).
23. 1,2-Ethylene-bis(10-methyl bicyclo [5.3.0] dec-7,9 diene), 50% isolated yield as yellow crystals. ^{1}H NMR ($CDCl_3$): $\delta = 5.95$ (s, 2H), 5.9 (s, 2H), 2.95–3.15 (m, 4H), 2.6–2.75 (d, 4H), 2.1 (s, 16H), 1.85–1.95 (d, 4H), 1.6–1.75 (s, 16H), 1.05–1.2 (t, 12H). ^{13}C NMR: 152.6, 152.8, 143.4, 143.6, 135.7, 135.6, 111.9, 111.7, 111.5, 111.2, 44.4, 44.2, 44, 39, 39.5, 27.4, 27.2, 27, 23.3, 22.8, 22.7, 22.6, 22.5, 22.3, 22.1. MS m/z (appi, ion trap) 294.4^+ (frag., Int.) 278.3 (25), 236.4 (35), 196.6 (23), 184.7 (28), 170.8 (29), 161.8 (23), 160.7 (100), 158.7 (66), 147.6 (38), 146.8 (63), 144.8 (29), 134.9 (43), 130.9 (48), 118.9 (69), 105 (44).