Lanthanide-Catalyzed Hydroamination of Hindered Alkenes in Synthesis: Rapid Access to 10,11-Dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptene-5,10-imines

Gary A. Molander* and Eric D. Dowdy

Department of Chemistry and Biochemistry, University of Colorado at Boulder, Boulder, Colorado 80309-0215

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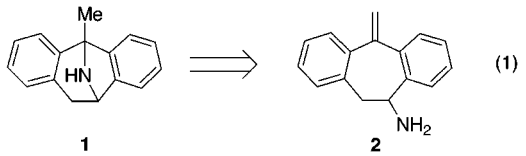
Introduction

Lanthanide reagents mediate a wide range of powerful organic transformations not possible utilizing more traditional methods.[1] Unique catalytic reactivity is also exhibited by the metallocene complexes of the lanthanide and group 3 metals. Lacking valence d electrons used by late transition metals for oxidative addition/reductive elimination,[2] the high reactivity of the metallocenes arises from olefin insertion and σ-bond metathesis reactions.[3] Long investigated as olefin polymerization catalysts,[4] these complexes have recently been utilized for small-molecule synthesis.[5] By combining olefin insertion reactions with a variety of intra- and intermolecular trapping steps, cyclization/hydrogenolysis, cyclization/hydrosilylation, and hydroamination reactions have been accomplished.[5] The catalytic complexes exhibit predictable chemoselectivity in polyfunctional substrates: protic groups such as amines are metalated first with subsequent olefin insertion if a strategically located and sterically accessible alkene is present.[6] In polyolefinic substrates lacking an amine, the catalysts will insert alkenes with predictable preference for the less hindered functional unit. The greatest strength of the method is the potential of the complex to insert multiple alkenes before the functionalization step. In this manner complex polycyclic products can be generated from simple substrates in a rapid fashion.[7]

The organolanthanide-catalyzed intramolecular hydroamination reaction is a powerful entry into a variety of heterocyclic systems.[8] Easily prepared aminoalkene substrates are cyclized under essentially neutral conditions with modest catalyst loading. Although the initial studies of this reaction focused on monosubstituted alkenes (because of the hindered nature of the catalysts), this requirement has been relaxed through rational modification of the catalyst structure.[9] A particularly interesting target for this technology is the tetracyclic amine MK-801.[10] The dibenzocycloalkyl motif is present in a variety of biologically active agents,[11] with MK-801 displaying potent anticonvulsant and neuroprotective properties.[12] The quaternary methyl group located α to the amine suggests a simple hydroamination retrosynthesis (eq 1). The 1,1-diaryl substitution of the alkene presented a significant steric challenge to catalysis, but the entropic advantage afforded by the close proximity of the reactive partners was anticipated to offset this difficulty.



1 **2** (1)

Previously reported approaches to the synthesis of MK-801 include a thermal, transannular addition of a hydroxylamine to an exocyclic alkene to form the nitrogen bridge.[10a] Although very efficient (96%), this reaction requires vigorous heating (refluxing xylenes or decane) and requires an additional step to remove the hydroxyl group from the amine. Another known approach to this ring system is the LDA-mediated addition of a secondary amine to an exocyclic alkene.[10c] Although this reaction proceeds at room temperature, the requirement that the amine be secondary hampers the generality of this process, allowing only the production of *N*-substituted derivatives of MK-801. We anticipated that the lanthanide-catalyzed intramolecular hydroamination reaction would avoid each of these problems because it is known to proceed under mild conditions and to operate efficiently on a wide variety of aminoolefin substrates.[8]

Results and Discussion

The cyclization substrate **2** is structurally similar to commercially available dibenzosuberone **3**, requiring only the installation of the alkene and primary amine functional groups (Scheme 1). Wittig olefination of **3** proceeds rapidly and in high yield to give alkene **4**.[13] The polar

* To whom correspondence should be addressed at the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323.

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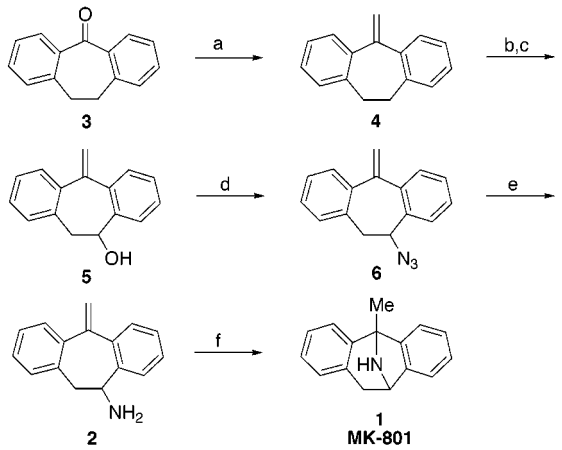
Scheme 1[a]



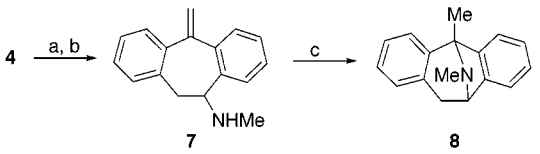
[a] Key: (a) Ph_3PMeBr, KO*t*-Bu, 98%;(b) NBS, AIBN, CCl_4; (c) H_2O, THF, 62% (two steps); (d) $(PhO)_2P(O)N_3$, DEAD, Ph_3P, 75%; (e) $LiAlH_4$, 88%; (f) 1% $[Cp^{TMS}{}_2NdMe]_2$, C_6D_6, 40 °C, 2 h, 98%.

functionality was created by benzylic bromination mediated by NBS with thermal initiation using AIBN.[14] The bromide prepared was quite labile, and could be isolated in only modest purity and yield after chromatography. NMR analysis of the crude material obtained by simply filtering the succinimide from the mixture and concentrating the filtrate revealed the presence of the bromide in good yield. An improved yield was realized by hydrolyzing the crude bromide directly, providing **5** in 62% yield (two steps).[15] The alcohol was converted to the amine (**2**) via the azide by Mitsunobu inversion with diphenylphosphoryl azide[16] and subsequent LAH reduction. This sequence was superior to a Mitsunobu reaction with phthalimide followed by deprotection owing to higher yields and greater ease of purification.

The conversion of the tricyclic aminoalkene to MK-801 proved to be quite facile when exposed to an appropriate lanthanide catalyst. $[Cp^{TMS}{}_2NdMe]_2$[17] was chosen as the precatalyst for this reaction as it possesses both good reactivity toward hindered alkenes and ease of preparation. The reaction was carried out simply by combining the substrate with $[Cp^{TMS}{}_2NdMe]_2$ in C_6D_6 under a nitrogen atmosphere. The solution was transferred to a sealed NMR tube to allow in situ monitoring of the progress of the reaction. As little as 1 mol % $[Cp^{TMS}{}_2NdMe]_2$ was sufficient to transform the substrate rapidly under mild heating. The product was isolated by filtering the crude reaction mixture through Florisil to remove the catalyst. The crude oil was purified by Kugelrohr distillation, giving a 98% yield of material that was spectroscopically identical to material described in the literature, and was found to be analytically pure by combustion analysis. Although this is a simple transformation, the high purity of the product is evidence of the remarkable selectivity of the catalyst. Neither intermolecular oligomerization nor olefin polymerization reactions were observed at all, and the amination was completely selective for the hindered end of the alkene. This selectivity is likely aided by the close proximity of the reactive functional groups of **2**.

N-Substituted derivatives were also rapidly accessed by this protocol (Scheme 2). In this case substrate

Scheme 2[a]



[a] Key: (a) NBS, AIBN, CCl_4; (b) 40% aqueous $MeNH_2$, THF, 20% (two steps); (c) 6% $[Cp^{TMS}{}_2NdMe]_2$, C_6D_6, 50 °C, 2 h, 94%.

preparation was shortened by direct conversion of the bromide used in Scheme 1 to an amine by treatment with aqueous methylamine in THF. Careful flash chromatography of the crude reaction mixture yielded 20% of pure **7** along with a similarly sized fraction of impure material. Exposure of this compound to the cyclization conditions provided *N*-methyl-MK-801 (**8**) in good yield. The facile nature of this transformation is remarkable in light of the highly hindered nature of both reactive partners.

Conclusions

Intramolecular hydroamination reactions of hindered aminoolefins are catalyzed by sterically open lanthanide metallocene catalysts. The ease of preparation and relatively high air stability simplify the use of $[Cp^{TMS}{}_2NdMe]_2$ as a hydroamination catalyst.[18] The cyclizations proceed under mild conditions to give heterocyclic products in high yield. Combined with a short substrate synthesis, these reactions provide rapid entry to the nitrogen-bridged dibenzocycloalkane series of pharmaceutically active chemicals typified by MK-801. *N*-Substituted derivatives are accessible by this method as well, thereby increasing the versatility of the synthetic method.

Experimental Section

Reagents. CCl_4 was distilled from CaH_2. Et_2O, THF, and C_6D_6 were distilled from sodium benzophenone ketyl. NBS was recrystallized from hot H_2O immediately prior to use and dried thoroughly in vacuo. $[Cp^{TMS}{}_2NdMe]_2$ was prepared by a literature procedure[17] and handled in a nitrogen-filled glovebox. All other reagents were used as received.

5-Methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (4). A flame-dried flask was charged with 2.72 g (23 mmol) of KO*t*-Bu suspended in 35 mL of dry Et_2O under Ar. Next, methyltriphenylphosphonium bromide (8.22 g, 23 mmol) was added in one lot, and the yellow mixture was stirred at ambient temperature for 30 min. The mixture was cooled to 0 °C, and **3** (4.16 g, 20 mmol) was added in small portions. After being warmed to room temperature, the mixture was stirred for 1 h before being diluted with 100 mL of pentane. A small amount of water was added to quench the excess reagent, and the mixture was filtered through a plug of silica gel. The silica was rinsed with additional pentane, and the filtrate was concentrated by rotary evaporation. The residue was purified by Kugelrohr distillation to yield 4.05 g (19.6 mmol, 98%) of the title compound as a colorless oil that crystallized on standing: mp 66−67 °C; ot 85 °C, 0.01 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.34 (m, 2H), 7.22−7.15 (m, 4H), 7.13−7.11 (m, 2H), 5.42 (s, 2H), 3.15 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 141.1, 138.3, 128.9, 128.1, 127.6, 126.2, 117.5, 33.2; IR ($CHCl_3$) 3061.2, 3015.8, 1616.0 cm^{-1}; HRMS calcd for $C_{16}H_{14}^+$ 206.1096, found 206.1113;

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LRMS (EI+) *m/z* 206 (100), 205 (83), 178 (18), 128 (12), 91 (21). Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 92.89; H, 7.19.

5-Methylene-10-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene (5). A solution of **4** (0.155 g, 0.75 mmol), NBS (0.186 g, 1.04 mmol), and AIBN (0.005 g) in 20 mL of CCl_4 was heated to reflux for 2 h. At that time GC analysis of an aliquot indicated the complete consumption of **4**. The mixture was cooled, filtered, and concentrated. The residue was dissolved in 4 mL of 25% H_2O in THF and stirred at room temperature for 48 h. The solution was then poured onto CH_2Cl_2 and washed with saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by flash chromatography on SiO_2 followed by Kugelrohr distillation to yield the title compound as a colorless oil (0.104 g, 0.47 mmol, 62%) that crystallized very slowly upon standing: ot 115 °C, 0.01 mmHg; R_f 0.35 (25% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 1H), 7.39−7.37 (m, 1H), 7.32−7.24 (m, 2H), 7.23−7.18 (m, 4H), 5.52 (d, J = 1.6 Hz, 1H), 5.36 (d, J = 1.6 Hz, 1H), 5.10 (td, J = 8.3, 2.8 Hz, 1H), 3.45 (dd, J = 14.5, 2.8 Hz, 1H), 3.20 (dd, J = 14.5, 7.9 Hz, 1H), 1.88 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 142.7, 139.6, 138.7, 133.4, 130.1, 129.4, 128.5, 128.2, 127.8, 127.7, 127.5, 126.9, 117.8, 70.7, 40.6; IR (neat) 3349.7, 3062.5, 1616.3 cm^{-1}; HRMS calcd for $C_{16}H_{14}O^+$ 222.1045, found 222.1037; LRMS (EI+) *m/z* 222 (35), 204 (36), 178 (100). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.78; H, 6.51.

10-Azido-5-methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (6). Triphenylphosphine (0.263 g, 1.0 mmol) was dissolved in dry THF, and the solution was treated with diethyl azodicarboxylate (0.175 g, 1.0 mmol) in THF. Next, diphenylphosphoryl azide (0.276 g, 1.0 mmol) was added dropwise followed by a THF solution of **5** (0.186 g, 0.84 mmol). After 1 h the mixture was concentrated in vacuo and purified by flash chromatography to yield the title compound (0.155 g, 0.63 mmol, 75%) as a white solid: mp 62−64 °C; R_f 0.45 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1H), 7.37−7.35 (m, 1H), 7.33−7.26 (m, 3H), 7.25−7.20 (m, 3H), 5.54 (d, J = 1.6 Hz, 1H), 5.39 (d, J = 1.6 Hz, 1H), 4.90 (dd, J = 8.3, 2.8 Hz, 1H), 3.47 (dd, J = 14.7, 3.0 Hz, 1H), 3.25 (dd, J = 14.7, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 142.1, 139.8, 134.8, 133.4, 129.6, 129.3, 129.0, 128.4, 128.3, 127.9, 127.6, 127.2, 118.4, 62.4, 38.2; IR ($CHCl_3$) 3024.4, 2099.7, 1617.9 cm^{-1}; HRMS calcd for $C_{16}H_{13}N_3^+$ 247.1109, found 247.1113; LRMS (EI+) *m/z* 247 (1), 218 (100), 205 (35). Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.21; H, 5.59; N, 16.52.

10-Amino-5-methylene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]-cycloheptene (2). Lithium aluminum hydride (0.118 g, 3.1 mmol) was suspended in 20 mL of dry Et_2O before the azide (0.380 g, 1.54 mmol) dissolved in 20 mL of Et_2O was added dropwise. The mixture boiled spontaneously during this addition, and was stirred for an additional 30 min. TLC analysis of an aliquot indicated the reaction was complete. The mixture was cooled to 0 °C and quenched by the dropwise addition of 10% aqueous NaOH until H_2 evolution ceased. The mixture was next filtered through Celite, and the filtrate was concentrated by distillation at atmospheric pressure. The residue was purified by Kugelrohr distillation at reduced pressure to yield the title compound (0.287 g, 1.30 mmol, 84%) as a colorless oil: ot 105 °C, 0.01 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (m, 4H), 7.23−7.16 (m, 4H), 5.46 (d, J = 1.6 Hz, 1H), 5.37 (d, J = 1.6 Hz, 1H), 4.44 (dd, J = 8.0, 3.0 Hz, 1H), 3.46 (dd, J = 14.7, 3.0 Hz, 1H), 3.02 (dd, J = 14.7, 8.0 Hz, 1H), 1.45 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 142.2, 142.0, 139.0, 134.7, 130.4, 128.5, 128.2, 128.1, 127.7, 127.6, 127.0, 126.6, 117.8, 52.4, 41.3; IR (neat) 3367.3, 3295.6, 3022.1, 1614.2 cm^{-1}; HRMS calcd for $C_{16}H_{15}N^+$ 221.1204, found 221.1201; LRMS (EI+) *m/z* 221 (63), 204 (100), 203 (92), 178 (85). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.84; H, 7.21; N, 6.20.

5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10-imine (MK-801) (1). In a nitrogen-filled glovebox $[Cp^{TMS}_2NdMe]_2$ (0.001 g, 0.9 mol %) was weighed into a vial and dissolved in 0.5 mL of C_6D_6. Next, 0.057 g (0.258 mmol) of **5** was added, and the light blue solution was transferred into a tube equipped with a Teflon-valved top using another 0.5 mL of C_6D_6 to rinse the vial. The mixture was then removed from the glovebox and heated to 40 °C, and the progress of the reaction was monitored by GC sampling of small aliquots. After 2 h the starting material was completely consumed. The solution was filtered through Florisil with Et_2O to remove the catalyst, and the filtrate was concentrated in vacuo. The residue was purified by Kugelrohr distillation to yield 0.056 g (0.253 mmol, 98%) of the title compound as a colorless oil: ot 100 °C, 0.01 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.24 (m, 2H), 7.10−7.03 (m, 5H), 6.93−6.91 (m, 1H), 4.69 (d, J = 5.6 Hz, 1H), 3.44 (dd, J = 16.7, 5.8 Hz, 1H), 2.72 (d, J = 16.8 Hz, 1H), 2.53 (br s, 1H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 144.7, 144.4, 132.3, 130.2, 128.1, 126.9, 126.6, 125.7, 121.6, 121.4, 118.6, 64.1, 58.4, 34.4, 20.2; IR (neat) 3210.2, 3016.1, 1600.5 cm^{-1}; HRMS calcd for $C_{16}H_{14}N^+$ (M − H)$^+$ 220.1126, found 220.1142; LRMS (EI+) *m/z* 221 (100), 220 (93), 206 (33), 178 (74). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.61; H, 7.05; N, 6.23.

10-Methylamino-5-methylene-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptene (7). A solution of **4** (1.031 g, 5.0 mmol), NBS (1.068 g, 6.0 mmol), and AIBN (0.005 g) in 20 mL of CCl_4 was heated to reflux for 2 h. At that time GC analysis of an aliquot indicated the complete consumption of **4**. The mixture was cooled, filtered, and concentrated. The residue was dissolved in 4 mL of THF; 2 mL of 40% aqueous $MeNH_2$ was added, and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with Et_2O and extracted (2×) with 10% HCl. The acidic extracts were washed with Et_2O before being made basic with NaOH. The aqueous layer was then extracted (2×) with CH_2Cl_2. After drying with Na_2SO_4, concentration of the solution afforded the crude material as a yellow oil. Purification by flash chromatography on SiO_2 using 25% EtOAc and 5% Et_3N in hexanes yielded two fractions: 0.233 g (0.99 mmol, 20%) of analytically pure material and an additional 0.25 g of 90% pure material. The pure fraction was further purified by Kugelrohr distillation to yield the title compound as a pale yellow oil: ot 120 °C, 0.05 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (m, 1H), 7.38−7.30 (m, 2H), 7.30−7.24 (m, 1H), 7.23−7.21 (m, 3H), 7.20−7.18 (m, 1H), 5.49 (d, J = 1.6 Hz, 1H), 5.45 (d, J = 1.6 Hz, 1H), 4.11 (dd, J = 8.1, 2.8 Hz, 1H), 3.40 (dd, J = 15.9, 2.8 Hz, 1H), 3.24 (dd, J = 15.9, 8.1 Hz, 1H), 2.49 (s, 3H), 1.40 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 140.3, 140.2, 139.9, 135.0, 130.3, 128.2, 128.1, 127.8, 127.7, 127.7, 127.0, 126.4, 117.6, 60.7, 38.6, 34.3; IR (neat) 3333.7, 3060.8, 3021.1, 1614.1 cm^{-1}; HRMS calcd for $C_{17}H_{17}N^+$ 235.1361, found 235.1375; LRMS (EI+) *m/z* 235 (100), 220 (44), 204 (98), 178 (48). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.47; H, 7.45; N, 6.07.

***N*,5-Dimethyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5,10-imine (8)**. The reaction was carried out in the same manner as for the preparation of **1** using 50 mg (0.212 mmol) of **7** and 6 mg (6.5 mol %) of $[Cp^{TMS}_2NdMe]_2$. The reaction was found to be complete after 2 h at 40 °C by NMR and GC analysis of a small aliquot. Analogous workup and purification yielded the title compound (47 mg, 0.200 mmol, 94%) as a colorless oil: ot 115 °C, 0.05 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.26 (m, 1H), 7.24−7.22 (m, 1H), 7.11−7.05 (m, 4H), 7.05−7.01 (m, 1H), 6.90−6.88 (m, 1H), 4.35 (d, J = 5.5 Hz, 1H), 3.34 (dd, J = 17.3, 5.5 Hz, 1H), 2.51 (d, J = 17.3 Hz, 1H), 2.36 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 142.7, 140.9, 132.3, 129.6, 126.9, 126.8, 126.6, 126.2, 123.5, 121.6, 118.9, 65.8, 62.9, 32.4, 28.5, 17.4; IR (neat) 3022.5, 1613.4 cm^{-1}; HRMS calcd for $C_{17}H_{16}N^+$ (M − H)$^+$ 234.1283, found 234.1266; LRMS (EI+) *m/z* 235 (100), 220 (13), 204 (12), 178 (29). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.56; H, 7.44; N, 5.95.

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