C−H Bond Activation of Hydrocarbon Segments in Complex Organic Molecules: Total Synthesis of the Antimitotic Rhazinilam

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C−H bond activation represents a fundamental chemical process of broad synthetic consequence.[1] To harness the full potential of these intriguing processes, the C−H activation step must be accompanied by a functionalization event, such as β-hydride elimination (dehydrogenation)[2] or atom group transfer (oxygen,[3] carbene,[4] and boron[5]). The possibility of programmable site selectivity of these transformations would provide entirely new opportunities to the synthetic community.[6] Despite significant advances in this area, most transition metal complexes capable of C−H bond activation are intolerant to functional groups and have a strong preference for the activation of aryl C−H bonds.[7] By assuming the possibility of overcoming such boundaries, novel and unique strategies for the assembly of complex organic molecules can be envisioned. We wish to communicate our investigations where such constraints were overcome and selective C−H functionalization (dehydrogenation) was achieved as the key step in the complete synthesis of the natural product rhazinilam (Figure 1).

After a stimulating discussion with Professor Erik J. Sorensen, the antitumor agent rhazinilam, a member of the *Aspidosperma* class of alkaloids, was selected as our first target.[8] The assembly of rhazinilam would be drastically simplified by selective activation of diethyl intermediate **1** (Figure 1). The quaternary stereogenic center, a central element of the molecule, would then be constructed via selective functionalization of the prochiral ethyl groups. This proposal posed a daunting challenge, considering the multiple functionalities present in **1**.

Our approach builds on the opportunity afforded by the proximity of the amino group to the ethyl groups, a favorable scenario for directed C−H activation.[9] According to this outline, selected ligands would be attached to intermediate **1** via the formation of a Schiff base linkage, followed by a metal complexation. Molecular model analysis showed that a carefully designed system was needed for the selective delivery of an activated metal complex to the ethyl group in question.

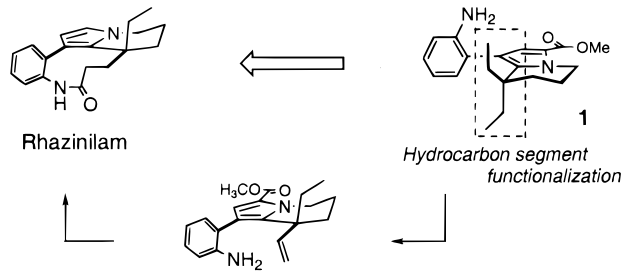
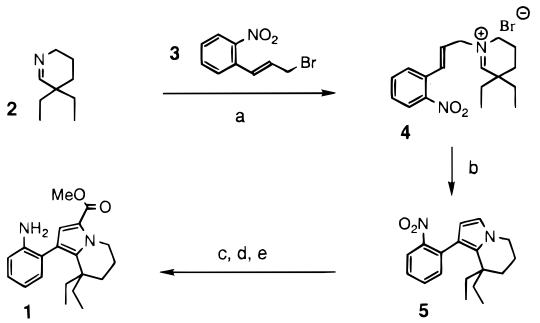


Figure 1. Selective C−H functionalization of diethyl alkane segment defines strategy for rhazinilam assembly.

Scheme 1[a]



[a] Conditions: (a) DMF, 100 °C, 90%; (b) Ag_2CO_3 (2 equiv), toluene, reflux, 70%; (c) CCl_3COCl; (d) NaOMe, MeOH; (e) H_2 (1 atm), Pd/C, 88% for steps c−e.

In the first phase of the investigation, intermediate **1** was synthesized in an efficient sequence as depicted in Scheme 1. Iminium salt **4** was generated from readily available imine **2**[10] and *o*-nitrocinnamyl bromide **3**. Heating of **4** in the presence of silver carbonate accomplished both cyclization and aromatization yielding pyrrole intermediate **5** in 70% yield.[11] The methyl carboxylate group was then installed as a temporary protection to stabilize the electrophile-sensitive pyrrole ring, followed by reduction of the nitro group to furnish amine **1**.

The initial exploratory stage, involving a variety of metals and ligands, directed our focus toward cationic platinum(II) complexes which have previously been shown to activate methane.[12] Also, sp^2-hybridized nitrogen atoms are suitable ligands for stable and active platinum complexes in the contex of C−H bond activation.[13] Thus, dimethyl platinum complex **7** (Figure 2) was constructed via Schiff base preparation, followed by treatment with $[Me_2Pt(\mu\text{-}SMe_2)]_2$[14] (Supporting Information). The generation of a platinum cation was then to be achieved via the action of a weakly coordinating acid. A detailed correlation between the structure (X-ray crystallography) and reactivity of the following systems (see below) provided the critical insights which guided our explorations.

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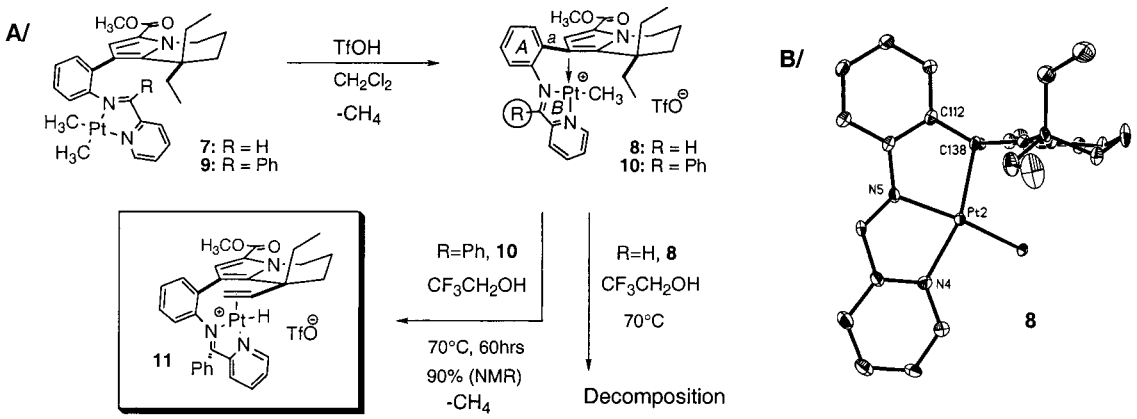
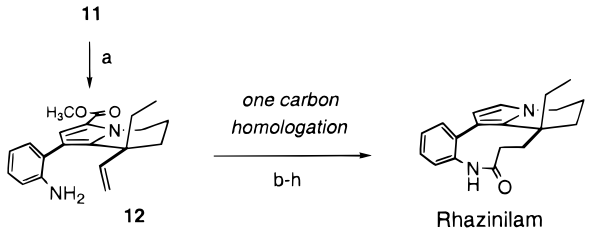


Figure 2. (A) Selective C−H bond activation of highly functionalized intermediate **1** via strategically placed platinum complex. (B) X-ray structure of complex **8** (triflate anion removed for clarity). Selected bond lengths: Pt(2)−C(138) 2.165(8) Å; Pt(2)−N(5) 2.007(7) Å; Pt(2)−N(5) 2.033(7) Å.

Addition of triflic acid to complex **7** led to the rapid formation of a new intermediate with concomitant loss of methane. Interestingly, complex **8**, possessing unusual coordination bonding between the platinum metal and the pyrrole moiety was formed (Figure 2B).[15] Note that bond "a" is bent out of the plane of the pyrrole ring, suggesting sp^3-like character of the pyrrole carbon. Heating of complex **8** in trifluoroethanol led to decomposition providing intractable mixtures. To liberate the platinum cation from the pyrrole ring and to facilitate its rotation toward the ethyl group, the stability or formation of intermediate **8** had to be undermined. It had previously been demonstrated that cationic platinum complexes require a weakly coordinated ligand (e.g., H_2O, pentafluoropyridine) which can readily depart and vacate a coordination site for an alkane.[16] Mindful of such prerequisites, the installation of a bulky R group was proposed to disfavor coplanarity of phenyl ring *A* and platinum complex *B* due to steric congestion and, in turn, weaken pyrrole complexation to the platinum metal in complex **8** (Figure 2). Thus, phenyl-substituted complex **9** was synthesized from readily available phenylpyridyl ketone and exposed to triflic acid (Supporting Information). Although analogous complex **10** was still formed, as established by an X-ray structure analysis,[17] its reactivity profile proved to be profoundly different. *Remarkably, thermolysis of complex **10** provided platinum hydride **11** as a single product in excellent yield (>90%) as determined by proton NMR spectroscopy. Indeed, activation of the desired ethyl group took place with concomitant loss of methane, followed by β-H-elimination affording alkene−hydride platinum(II) complex **11**.*

The platinum metal was subsequently removed via treatment with aqueous potassium cyanide,[18] followed by hydrolysis of the resulting Schiff base in the presence of hydroxylamine. Isolation and characterization of alkene **12** provided solid evidence for this sequence (Scheme 2, 60% yield for a four-step sequence **9**→**12**). To complete the total synthesis of rhazinilam, a one-carbon extension of the vinyl group and the subsequent macrocycle closure was then carried out in a standard fashion. Namely, transformation of the alkene double bond of **12** to an aldehyde was followed by Horner-Emmons reaction, catalytic hydrogenation, *tert*-butyl ester and Boc deprotection, and finally a macrolactam formation.[19]

Scheme 2[a]



[a] (a) KCN (0.5 M), CH_2Cl_2, H_2O; NH_2OH, MeOH, 60% for four steps from **9**; (b) Boc_2O, DMAP, 76%; (c) OsO_4, $NaIO_4$; (d) $Ph_3P{=}CHCO_2tBu$; (e) H_2, Pd/C, 70% for steps c−e; (f) TFA, CH_2Cl_2, 75%; (g) PyBOP, HOBT, iPr_2NEt; (h) NaOH (aq), MeOH then HCl (aq), 80% for g and h.

In summary, the total synthesis of the antitumor agent rhazinilam was achieved through a novel strategy centered on selective C−H bond activation. Dehydrogenation of the ethyl group, mediated by a platinum complex, was accomplished in the presence of a variety of functional groups including an ester, pyrrole and arene rings. Introduction of new C−H activation metal catalysts to the realm of functionalized substrates opens an exciting frontier in the assembly of complex organic molecules.

Acknowledgment. We thank Professor E. J. Sorensen, Dr. L. J. Williams and Vitas Votier Chmelar for intellectual contributions. Columbia University and The Camille and Henry Dreyfus Foundation are acknowledged for financial support of this work. We gratefully acknowledge Dr. Brian M. Bridgewater, David Churchill, and Professor Ged Parkin (X-ray work), Dr. Y. Itagaki (MS), and Dr. J. B. Schwarz (manuscript preparation).

Supporting Information Available: Experimental details for **9**−**12**. Crystallographic data for **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Figure 2 shows only one of two independent molecules found in the ORTEP diagram. The second molecule is structurally similar to that shown in Figure 2, with the exception that the platinum interaction with the pyrrole possesses more η^2 character (Supporting Information). See also: (a) Brunkan, N. M.; White, P. S.; Gagne, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 11002. (b) Kocovsky, P.; Malkov, A. V.; Vyskocil, S.; Lloyd−Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425−1433. (c) Meyers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 6682.

(16) See ref 12.

(17) The X-ray structure of **10** will be disclosed elsewhere.

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