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Total Synthesis of (−)-Rhazinilam: Asymmetric C−H Bond Activation via the Use of a Chiral Auxiliary

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Abstract: The antitumor agent (−)-rhazinilam was synthesized in three major steps, namely the pyrrole synthesis, selective C−H bond activation, and direct macrolactam formation. The key step involved asymmetric C−H bond functionalization (dehydrogenation) of the diethyl group segment in intermediate **6**. This was achieved by the attachment of chiral platinum complexes to the proximal nitrogen atom. A high degree of selectivity (60−75% ee) was achieved via the use of oxazolinyl ketone chiral auxiliaries.

Introduction

The introduction of functional groups via C−H bond activation has significant synthetic potential owing to the ubiquitous nature of such bonds in organic substances. However, the low reactivity of unactivated C−H bonds poses a considerable challenge with regard to the selective execution of functionalization reactions. Thus, the central tenet of synthetic chemistry, achieving control over the reactivity and selectivity profile of reagents and catalysts, resurfaces with pressing clarity in this context. Although significant progress has been made, C−H bond functionalization represents a major unsolved problem in synthetic chemistry.[1] Hitherto, organic and organometallic chemistry has not succeeded in providing generally applicable guidelines for practitioners of organic synthesis to employ these reactions in routine synthetic tasks.[2]

With the exception of intramolecular metal−carbene chemistry,[3] most transition metal complexes capable of C−H bond activation are sensitive to functional groups and have a strong preference for aryl and other activated C−H bonds.[4] We proposed to overcome these limitations via *coordination-directed C−H bond activation*.[5] Following this strategy, a suitable heteroatomic function would be utilized to direct an activated metal complex to a specific hydrocarbon segment of the substrate in such a way as to prevent interference by other functional groups. We have recently demonstrated the feasibility of this approach in the context of a racemic synthesis of the antitumor agent rhazinilam.[6] In this report, we describe the asymmetric synthesis of (−)-rhazinilam founded on asymmetric C−H bond functionalization (dehydrogenation) through the use of a chiral auxiliary. The synthesis of (−)-rhazinilam was achieved in three major steps: first, pyrrole annulation to construct the diethyl pyrrole intermediate; second, asymmetric dehydrogenation of the pro(R) ethyl group; and finally, macrolactam formation via direct carbonylation (Figure 1).

Results and Discussion

Platinum-Mediated C−H Bond Functionalization: The Racemic Sequence. In the first phase of the investigation, intermediate **6** was synthesized in a short sequence as depicted in Scheme 1. Iminium salt **4** was generated from readily available imine **2**[7] 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.[8] The methyl carboxylate group was then installed

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(3) (a) Taber, D. F.; Stribia, S.-E. *Chem. Eur. J*. **1998**, *4*, 990−992. (b) For a recent example of intramolecular metal-mediated nitrene insertion see: Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc*. **2001**, *123*, 6935−6936.

(4) Murai, S. *Activation of Unreactive Bonds and Organic Synthesis*; Springer: Berlin, Germany, 1999.

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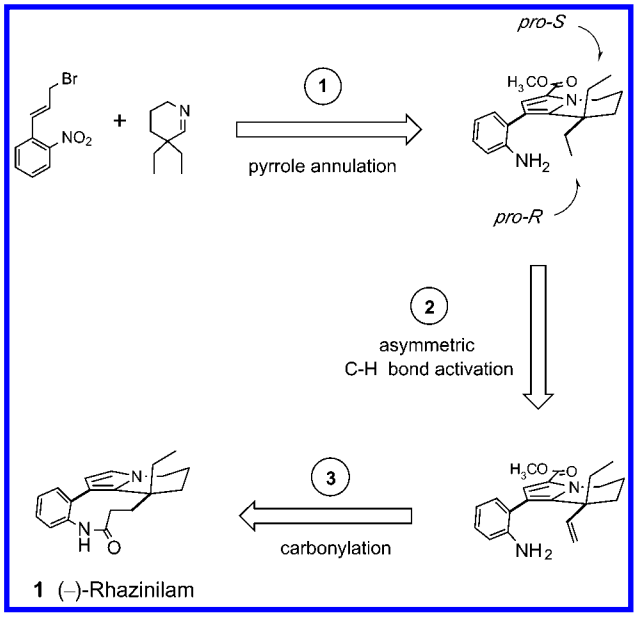
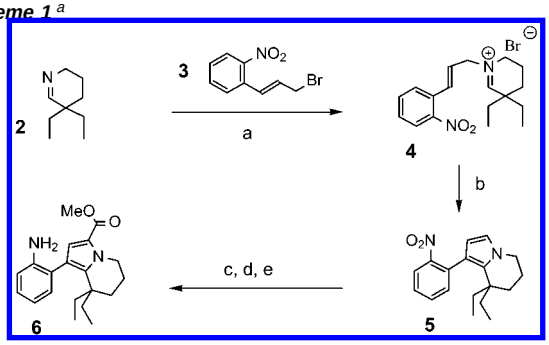


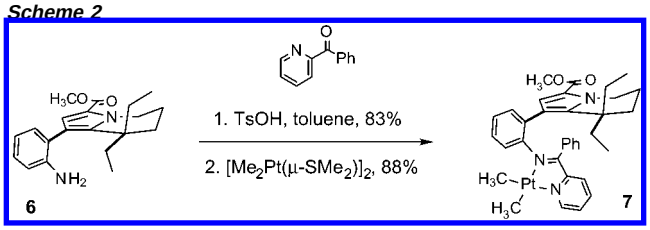
Figure 1. (−)-Rhazinilam was assembled in three major steps. The central step involved asymmetric dehydrogenation of the diethyl group segment.

Scheme 1 [a]



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

Scheme 2



as a temporary protection to stabilize the electrophile-sensitive pyrrole ring, followed by reduction of the nitro group to furnish amine **6**.

For the racemic synthesis, the pivotal platinum complex **7** was prepared from aniline **6** by sequential treatment with 2-benzoylpyridine (Schiff base preparation) and dimethylplatinum reagent $[Me_2Pt(\mu\text{-}SMe_2)]_2$ (Scheme 2). Addition of 1 equiv of triflic acid to **7** resulted in rapid liberation of methane and formation of complex **8**, which was fully characterized including an X-ray structure (Figure 2B). The unusual η^1-complexation mode between the platinum metal and the pyrrole ring (carbon 4) should be noted. In fact, pyrrole C4 exists as a distorted tetrahedron suggesting sp^3-hybridization of this center. The distortion of aryl rings by electrophilic platinum metals is precedented,[9] and by analogy to these reports, complex **8** should be kinetically labile. In such a system, decomplexation of the pyrrole ring from the platinum metal and the generation of a transient and reactive methylplatinum species should be feasible. Indeed, this proved to be the case. Thermolysis of complex **8** in CF_3CH_2OH[10] or CH_2Cl_2 afforded alkene−hydride **9** in high yield (90% by ^1H NMR). The presence of the phenyl substituent on the Schiff base ligand was crucial as the corresponding aldehyde-derived Schiff base yielded only traces of the desired product, favoring decomposition. Addition of Bu_4NCl to **9** in dichloromethane led to quantitative formation of **10** wherein the platinum metal is σ-bonded to the methylene carbon of the ethyl group (Figure 2). This observation may suggest that the initial C−H bond activation took place at the methylene carbon. Decomplexation of the platinum by aqueous KCN followed by removal of the Schiff base provided racemic alkene **11**. The entire sequence from protonation of **7**, through C−H activation and functionalization, decomplexation, and finally transamination to furnish **11** occurred in 60% overall yield. It is worth noting that all of the platinum complexes were prepared by using standard techniques and appeared quite stable to air and moisture, allowing easy manipulation of the compounds.

Asymmetric C−H Bond Activation: The Total Synthesis of (−)-Rhazinilam. Examples of asymmetric C−H bond activation and functionalization are rare since most efforts to date have focused on solving the chemo- and regioselective issues of these reactions.[11,12] Having developed a highly selective C−H bond functionalization process in the case discussed herein, we then became interested in the possibility of differentiating the two *enantiotopic* ethyl groups via the introduction of a chiral ligand. The platinum chemistry proved to be robust and insensitive to air and moisture, and therefore seemed likely to accommodate a broader range of ligands. Analysis of the X-ray structure of **8** suggested that in order to maximize interaction between the diethyl segment of the substrate and the chiral auxiliary, the platinum complex should be desymmetrized by placing an R group above or below (not outside) the complex framework (Figure 2 and Figure 3). Taking these design directives into account, as well as practical issues related to accessibility of the ligands, we set out to explore oxazolinyl ketones as chiral auxiliaries (Table 1).[13]

Oxazoline Schiff base complexes, prepared according to the method developed for pyridine complex **7**, were submitted to the C−H functionalization sequence including treatment with 1 equiv of TfOH and gentle heating (Supporting Information).

(9) (a) Falvello, L. R.; Forniés, J.; Navarro, R.; Sicilia, V.; Tomás, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 891−893. (b) Brunkan, N. M.; White, P. S.; Gagne, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 11002−11003. (c) Kocovsky, P.; Malkov, A. V.; Vyskocil, S.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425−1433. (d) Albrecht, M.; Gossage, R. A.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1999**, *121*, 11898−11899. (e) Kaminskaia, N. V.; Johnson, T. W.; Kostic, N. M. *J. Am. Chem. Soc.* **1999**, *121*, 8663−8664.

(10) Johansson, L.; Ryan, O. B.; Tilset, M. *J. Am. Chem. Soc.* **1999**, *121*, 1974−1975.

(11) (a) Sokolov, V. I.; Troitskaya, L. L.; Reutov, O. A. *J. Organomet. Chem.* **1979**, *182*, 537−546. (b) Ma, Y.; Bergman, R. G. *Organometallics* **1994**, *13*, 2548−2550 (correction: *Organometallics* **1994**, *13*, 4648). (c) Keyes, M. C.; Young, V. G., Jr.; Tolman, W. B. *Organometallics* **1996**, *15*, 4133−4140. (d) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425−426. (e) Mobley, T. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 3253−3254. (f) Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, 55−56. (g) Punniyamurthy, T.; Katsuki, T. *Tetrahedron* **1999**, *55*, 9439−9454. (h) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. *Chem. Commun.* **1999**, 2377−2378.

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(13) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360.

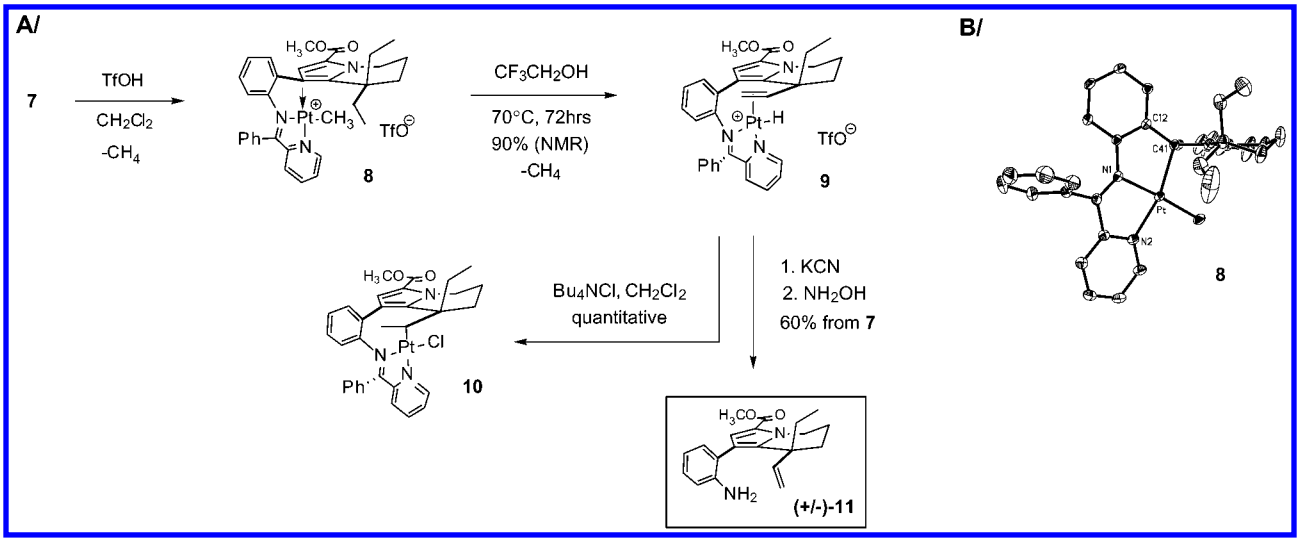


Figure 2. The racemic sequence. (A) Selective functionalization (dehydrogenation) of one ethyl group was accomplished in the presence of many functional groups via coordination-directed C−H bond activation. (B) X-ray structure of complex **8** (triflate anion removed for clarity).

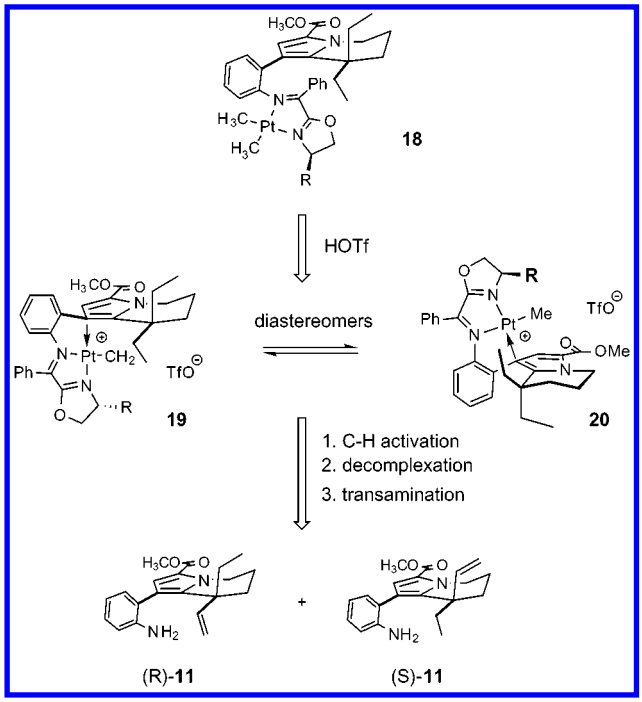


Figure 3. The asymmetric sequence. The proposed model explains the sense and magnitude of asymmetric induction. The bulkier R group affords greater enantiomeric excess of alkene **11**. The final ratio of enantiomers **11** differs from the ratio of diastereomers **19**/**20**.

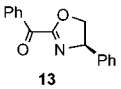
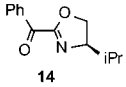
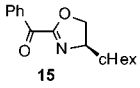
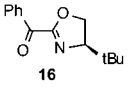
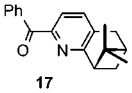
Decomplexation of the platinum metal yielded a mixture of Schiff base diastereomers (cf. **12**, Table 1) that was analyzed by HPLC to determine starting material conversion and the diasteromeric ratio of products (for experimental details see Supporting Information). As evident from Table 1, reaction temperature and bulkiness of the ligand affected both yield and selectivity of the functionalization reaction. Two major trends became apparent: first, higher temperatures improved yields, however at the expense of diastereoselectivity; second, bulkier ligands afforded better selectivity. For instance, the cyclohexyl oxazoline was superior to the phenyl-substituted ligand (7.5:1 vs 6:1 (*R*/*S*) at 60 °C, 72 h). The best selectivity was observed with the bulky oxazoline **16** derived from *tert*-butylglycinol, which afforded a single diastereomer. Unfortunately in this case, complex preparation and purification was problematic providing only low yields of the corresponding crude complex (<10% conversion). In addition to oxazoline ligands, chiral pyridyl ketone **17**[14] was prepared and studied; however, both the chemical yield and selectivity obtained were inferior to those of the oxazoline ligands. The Schiff base diastereomers were separated on a preparative scale by HPLC, and the Schiff base ligand was removed quantitatively (for ease of purification, hydroxylamine was used to cleave the Schiff base) to afford alkene **11** in high optical purity (96% ee, determined by chiral HPLC). The absolute stereochemical assignment was confirmed by conversion of (−)-**11** to (−)-rhazinilam.

By a procedure developed for achiral complex **7**, treatment of the oxazoline complex (cf. **18**, Figure 3) with TfOH yielded a mixture of diastereomers **19** and **20** in a ratio greater than one in all studied cases. This suggests a measurable interaction between the R group of the ligand and the rest of the molecule, most likely the diethyl segment. The C−H functionalization sequence then yielded a mixture of enantiomers **11**, in a ratio that differs from that of **19**/**20**. This observation suggests two mechanistic scenarios: first, that decomplexation of the platinum from the pyrrole ring in **19** and **20** generates a species wherein free rotation around the biaryl C−C bond occurs (the rate of rotation is faster than the rate of C−H functionalization); second, that each diastereomer reacts with a different rate (the rate of rotation is slower that the rate of C−H functionalization). The former mechanism is supported by the observation that both ratios (**19**/**20** and (−)-**11**/(+)-**11**) remained constant (and different from one another!) during the course of the reaction (^{1}H NMR measurements at 24, 48, and 72 h).

In the last stage of the synthesis, conversion of alkene **11** to rhazinilam required one-carbon homologation of the alkene moiety, macrolactam formation, and methyl ester deprotection. To avoid the multistep sequence reported by us previously, we have contemplated direct hydroamidation of **11**. This plan was reduced to practice, and as a result, the optically pure alkene (−)-**11** was converted to (−)-rhazinilam in two steps (Scheme 3). The macrolactam formation, achieved in one step (58% yield)

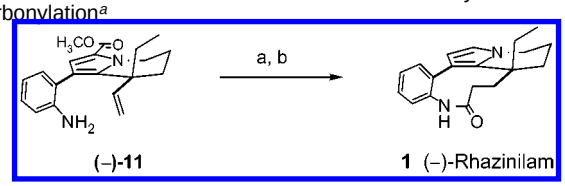
(14) Malkov, A. V.; Bella, M.; Langer, V.; Kocovsky, P. *Org. Lett.* **2000**, *2*, 3047−3049.

Table 1. Diastereoselective Directed C−H Bond Functionalization Studies

entry	LIGAND	T(°C)	ds ratio[a]	conversion (%)[b]	isolated yields (%)
1	 **13**	60	6 : 1	20	15
		65	4 : 1	60	35
		70	3 : 1	63	40
2	 **14**	60	5.5 : 1	16	10
		65	4 : 1	60	36
		70	3 : 1	65	40
3	 **15**	60	7.5 : 1	30	20
		65	5.5 : 1	58	35
		70	4.4 : 1	66	42
4	 **16**	60	>20 : 1	<10[c]	
5	 **17**	70	1.1 : 1		

[a] Determined by ^{1}H NMR (platinum hydride, not shown), and HPLC (Schiff base **12**). [b] Determined by HPLC. [c] Low conversion is due to the low yield of the complexation step. The crude mixture was submitted to the reaction sequence since the corresponding complex could not be purified; cHex = cyclohexyl; reaction and purification conditions are detailed in the Supporting Information.

Scheme 3. Direct Macrolactam Formation via Catalytic Carbonylation[a]



[a] Reaction conditions: (a) 10% Pd−C (5 mol %), dppb, HCOOH, DME, CO (10 atm), 150 °C, 58%; (b) NaOH(aq), MeOH then HCl(aq), 50 °C, 90%.

in the presence of Pd−C (5 mol %), dppb (1,4-bis(diphenylphosphino)butane), formic acid, and carbon monoxide,[15] followed by deprotection of the methyl ester, furnished optically pure (−)-rhazinilam.

Conclusion

In summary, the total asymmetric synthesis of rhazinilam was accomplished in three major steps, including the pyrrole synthesis, selective C−H bond activation, and direct macrolactam formation. This strategy centered on selective dehydrogenation of the ethyl group in a complex substrate containing multiple functional groups including an ester, pyrrole, and arene rings. Furthermore, asymmetric control over this transformation was achieved through the use of a chiral auxiliary, as 62−76% enantiomeric excess was achieved with the cyclohexyloxazoline ligand. This work illustrates the concept of directed C−H bond functionalization and its applicability to asymmetric processes.

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Supporting Information Available: Experimental procedures for compounds **1**−**17**, experimental details for C−H bond activation, product separation, and characterization, and X-ray structure of complex **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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