C–C Bond Formation via C–H Bond Activation: Synthesis of the Core of Teleocidin B4

Research by B.D. Dangel, K. Godula, S.W. Youn, B. Sezen, and D. Sames, J. Am. Chem. Soc. ***2002**, 124, 11856*

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Condensation of the Research

Purpose of the Study

To develop new synthetic strategies for complex molecule synthesis by considering nontraditional retrosynthetic bond disconnections only accessible by using coordination-directed C–H bond activation and subsequent C–C bond formation

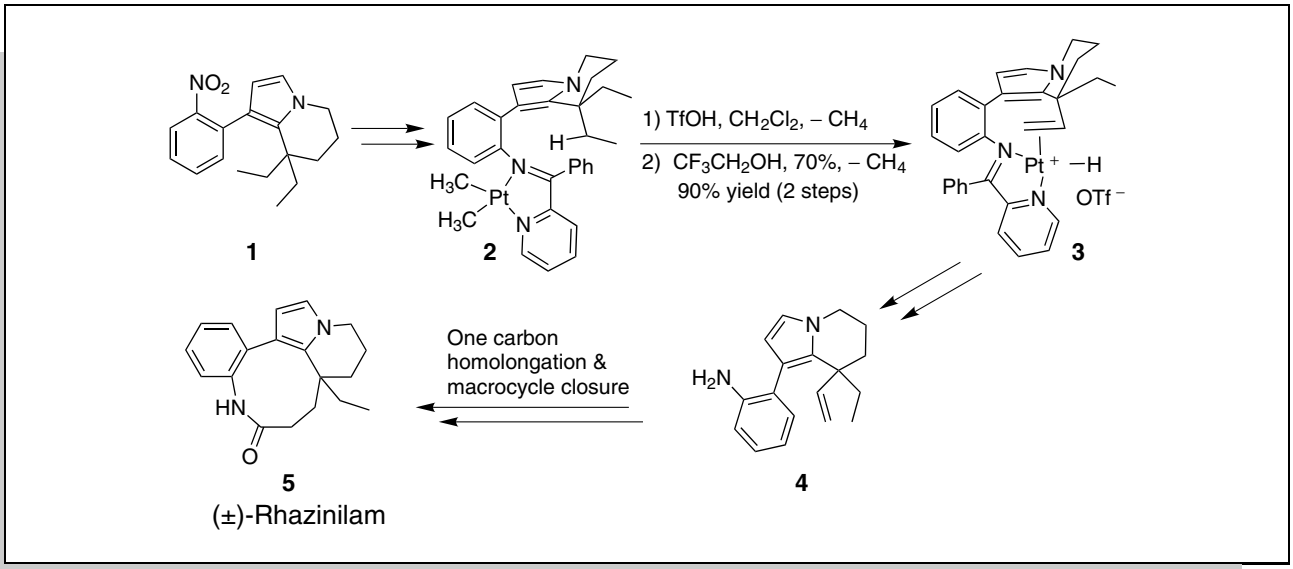
Background

In recent years, the activation of C–H bonds has emerged as an exciting new field in organic chemistry.[1] Simple C–H bonds, while inert to most traditional organic reagents, have been directly activated by various transition metals such as rhodium,[2] palladium,[3] manganese,[4] and ruthenium.[5] The applications of such transformations are seemingly limitless. However, given the similar bond dissociation energies and pK_a's of most C–H bonds, the chemoselective activation of specific C–H bonds has proven to be a difficult challenge. In spite of this, several research groups have begun to report success in controlling this reaction, even using it in complex molecule synthesis.

In 2000, Johnson and Sames reported the total synthesis of (±)-rhazinilam (**5**) using a platinum-mediated, coordination-directed C–H bond activation as the crucial step.[6] They constructed a pocket containing a Schiff base and a pyridine moiety within the rhazinilam precursor for binding a metal. After screening multiple metals, a stoichiometric amount of $[Me_2Pt(\mu\text{-}SMe_2)]_2$ was used to form the desired complex (**2**), which upon protination with triflic acid produced the desired olefin (**4**) via a C–H bond activation/β-hydride elimination sequence (Scheme 1).

CHEMTRACTS—ORGANIC CHEMISTRY **16:**249–253 (2003)

CCC 1431-9268



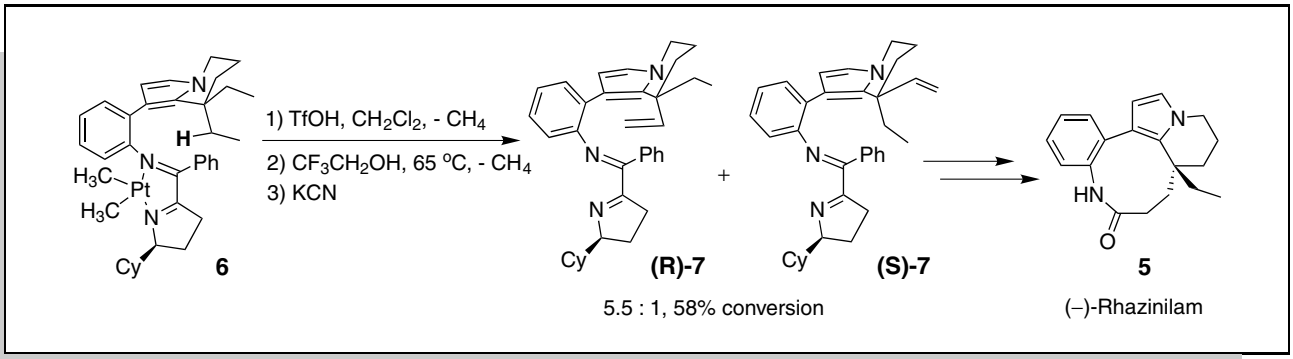
Scheme 1. Coordination-directed C–H bond activation as a route to (±)-rhazinilam.

In a full paper, Sames and co-workers described a similar sequence of reactions for the enantioselctive synthesis of (−)-rhazinilam using a Schiff base/chiral oxazoline scaffold, thus causing diastereoselective C–H activation/β-hydride elimination of the Pro-(R) ethyl group in the (−)-rhazinilam precursor.[7] This was followed by the removal of the metal and chiral auxiliary. After two more steps, the authors accomplished the total synthesis of (−)-rhazinilam in an 8% overall yield (Scheme 2).

In an attempt to further develop this field of coordination-directed C–H bond activation, Sames and co-workers have recently accomplished the racemic synthesis of the core of teleocidin B4. In this synthesis, two of the four major ring-forming steps are accomplished via C–H bond activation/functionalization reactions.

What Researchers Accomplished

The core structure of teleocidin B4 (**8**) contains two chiral quaternary carbons whose formation represents a formidable synthetic challenge.

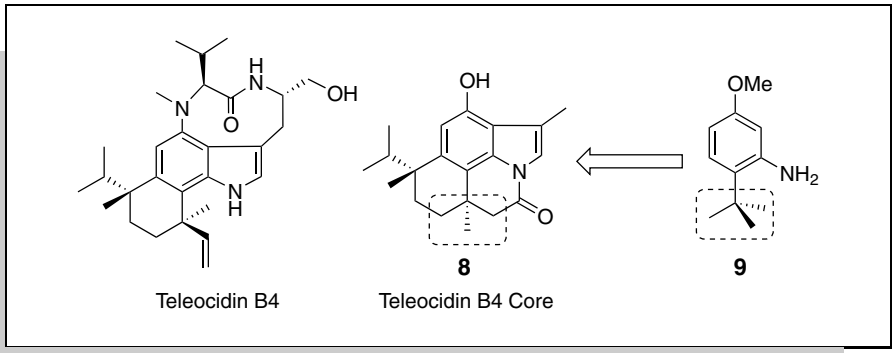


Scheme 2. Diasterioselective C–H bond activation in the synthesis of (−)-rhazinilam.

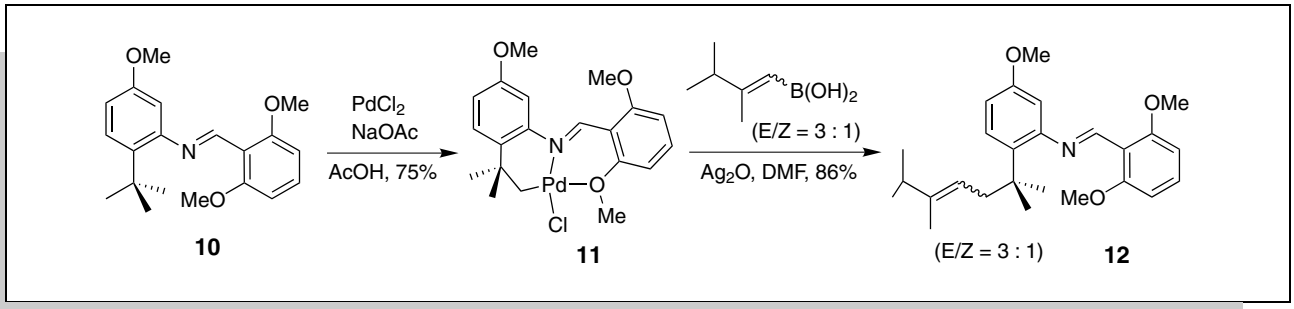
While traditional coupling protocols such as those developed by Suzuki and Stille could have been employed in this synthesis, Sames and co-workers set out to use coordination-directed C–H bond activation to perform the desired carbon–carbon couplings. The key step in their approach is the selective C–H bond activation of two methyl groups of an *ortho-tert*-butyl analine (**9**) (Scheme 3).

The authors began their synthesis by forming the Schiff base of **9** with 2,5-dimethoxybenzaldehyde. This imine (**10**) served as a suitable ligand for binding a stoichiometric amount of palladium. In the presence of the weak base NaOAc, the first C–H bond activation of the *tert*-butyl group was achieved. The resultant palladacycle (**11**) was amenable to silica gel chromatography and was characterized by NMR. The palladacycle (**11**) underwent an unprecedented transmetalation with a vinyl boronic acid to yield the desired alkylation product (**12**) in a good yield (Scheme 4).[8]

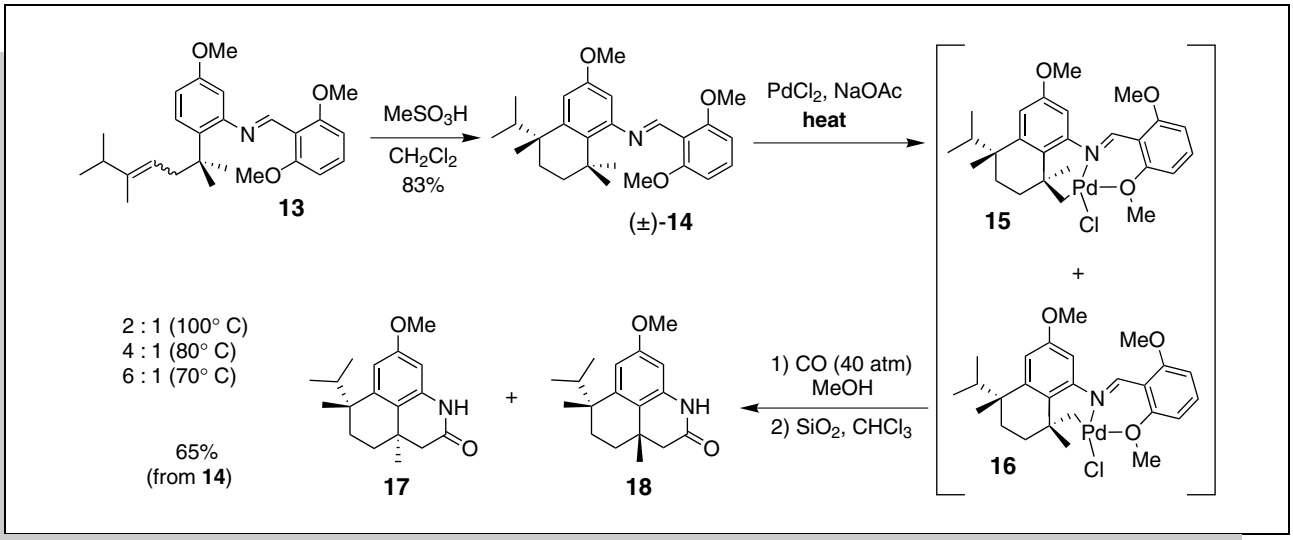
Following this alkylation, Sames and co-workers used Friedel-Crafts chemistry to construct the saturated cyclohexane ring.[9] Next the Schiff base (**14**) was treated with $PdCl_2$ and NaOAc at elevated temperatures to form diastereomeric **15** and **16**. Without isolation, the mixture of **15** and **16** was carbonylated using 40 atm of CO (g) at room temperature. Treatment of the crude reaction mixture with silica gel cleaved the Schiff base and induced spontaneous lactamization. The tricyclic lactams, **17** and **18**, were obtained with diastereoselectivities ranging from 2:1 to 6:1 (Scheme 5).



Scheme 3. The double C–H bond activation of an *ortho-tert*-butyl group leads to the synthesis of the core ring structure of teleocidin B4.



Scheme 4. First C–H bond activation in the synthesis of the teleocidin B4 core.



Scheme 5. Second C–H bond activation in the synthesis of the teleocidin B4 core.

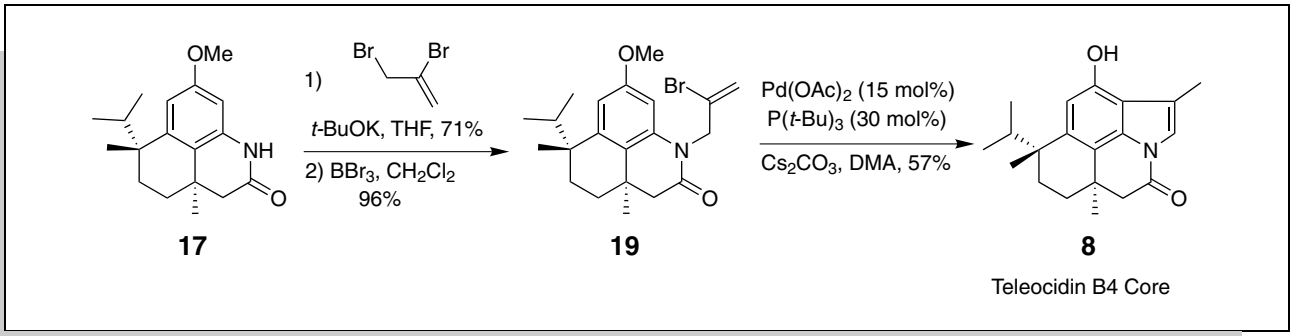
This diastereoselectivity was inversely proportional to the temperature of the palladacycle formation step, indicating that the origin of selectivity occurs during this initial metallation.

To complete the synthesis, the major isomer (**17**) was recrystallized from hexanes. The amide was then alkylated, and the phenol was deprotected using standard conditions. Finally, the fourth ring was constructed using a catalytic amount of palladium. This Heck reaction (also a formal C–H bond activating reaction) completed the synthesis of the teleocidin B4 core (Scheme 6).

Thus, two of the three methyl groups of a *tert*-butyl analine moiety were funtionalized via coordination-directed C–H bond activation/functionalization sequences.

Commentary on the Research

The total synthesis of the core ring structure of teleocidin B4 has been accomplished to show new and useful routes to complex molecules via



Scheme 6. Heck reaction completes the synthesis of the teleocidin B4 core.

coordination-directed C–H bond activation. The ability to direct the activation of a single saturated C–H bond for functionalization is important. By adding these coupling reactions to the synthetic chemist's arsenal, new starting materials may be considered in the arena of complex molecule synthesis. The only requirement for these methods is that a coordination cavity be attached to the precursor in order to control the regioselectivity of the subsequent C–H bond activation. One drawback to this method is the need for stoichiometric metal. This can be prohibitively expensive and can complicate purification of the organic product. However, it appears that the Sames group is on the verge of solving this problem, as well. In a recent publication, they performed a similar C–H bond activation/arylation of an *ortho-tert*-butyl analine using a catalytic amount of palladium.[10] Using these methods demonstrated by Sames and coworkers, multiple complex molecules will undoubtedly be synthesized in the near future.

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