

# C-H Functionalization in Natural Product Total Synthesis

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## ABSTRACT

The number of synthetic reactions capable of activating normally inert C-H bonds has escalated in recent years. These C-H functionalization reactions have been the benefactors of significant advances in both catalytic and stoichiometric transition metal chemistry. While many of the methodologies are still far from maturation, their impact on the total syntheses of complex natural products has nevertheless been significant. Syntheses utilizing these methods will be discussed.

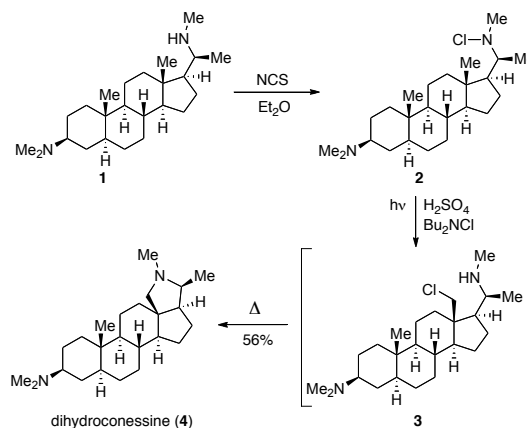
Although the field of total synthesis has made great advances since its humble beginnings in 1828, it is still far from being a mature or applied science. Ideally the synthesis of a complex molecule—either natural or designed—should be achieved in a minimum number of chemical transformations, in high overall yield, and with little chemical waste. In order to reach such lofty goals, significant attention has been focused in the area of C-H functionalization, whereby normally inert C-H bonds can be activated for a chemical transformation.<sup>1</sup> Since prefunctionalization of the substrate is unnecessary, both the number of steps and the use of wasteful reagents can be minimized. In addition, C-H bonds can normally be carried through a synthesis without incident, thereby diminishing the need for protecting groups. While such strategies have been used in total synthesis for over 50 years,<sup>3</sup> recent advances in organometallic chemistry have significantly expanded the synthetic utility of such processes. This review will highlight the use of various C-H functionalization methods in complex natural product total synthesis.

### The Origins of C-H Functionalization In Natural Product Total Synthesis

The synthetic steroid field was largely responsible for

many early developments in the area of hydrocarbon oxidation.<sup>2</sup> This area was largely focused on intramolecular radical abstraction chemistry and the rigid steroidal framework was an ideal platform for such endeavors. In 1958, the first reported example of unactivated sp<sup>3</sup> C-H oxidation in total synthesis was reported simultaneously by both the Corey and Arigoni labs in the context of an alkaloid synthesis (Scheme 1).<sup>3</sup> Utilizing the classic Hofmann-Löffler-Freytag reaction,<sup>4</sup> amine **1** could be converted into the alkaloid dihydroconessine (**4**) in only 2 steps. This time period also witnessed significant advances in remote C-H functionalization by the Barton laboratory and their introduction of the nitrite ester photolysis reaction (Scheme 2).<sup>5</sup>

**Scheme 1.** The First Example of Unactivated sp<sup>3</sup> C-H Functionalization in Natural Product Total Synthesis



(1) For recent reviews, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, 451, 417. (b) Bergman, R. G. *Nature* **2007**, 446, 391.

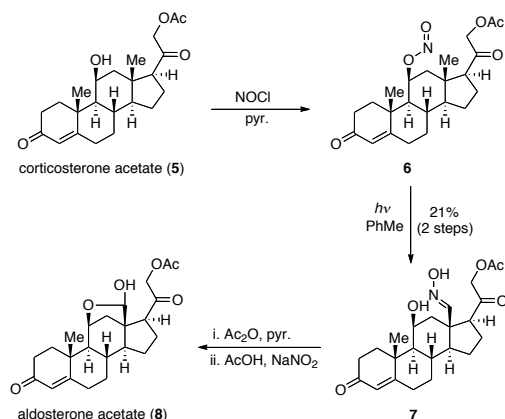
(2) Reese, P. B. *Steroids* **2001**, 66, 481.

(3) (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, 80, 2903. (b) Buchschacher, P.; Kalvoda, J.; Arigoni, D.; Jeger, O. *J. Am. Chem. Soc.* **1958**, 80, 2905. (c) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1959**, 81, 5209.

(4) (a) Hofmann, A. W. *Ber.* **1883**, 16, 558. (b) Löffler, K.; Freytag, C. *Ber.* **1909**, 42, 3427.

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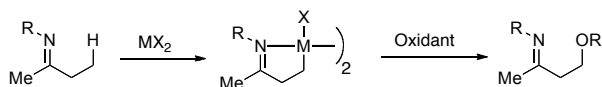
**Scheme 2.** Nitrite Ester Photolysis as a Key Development in Remote  $sp^3$  C-H Functionalization



**Heteroatom-Directed, Metal-Mediated  $sp^3$  C-H Functionalization**

Although a variety of metal-mediated C-H oxidations have been reported, few are capable of direct C-H oxidation of non-allylic or benzylic  $sp^3$  C-H bonds. Both the relative strength of such C-H bonds, combined with the large number of nearly equivalent positions has presented a significant challenge in this field. The most general solution to this problem—in a synthetic sense—has been the ability of Pd(II) and Pt(II) complexes to form metallocycles via nitrogen-directed C-H insertion followed by oxidation (Scheme 3).<sup>6</sup> Although known in a stoichiometric sense for decades,<sup>7</sup> many recent reports have rendered these reactions catalytic in metal salt thus increasing their value as a general synthetic tool.<sup>8</sup> Similarly, the bound metal center may also direct a C-H insertion/ $\beta$ -hydride elimination process, thus achieving functionalization by dehydrogenation. A particularly

**Scheme 3.** Directed Cyclometallation/Oxidation for the Functionalization of Unactivated  $sp^3$  C-H Bonds



(6) For recent reviews, see: (a) Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1683. (b) Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, *105*, 2471. (c) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.

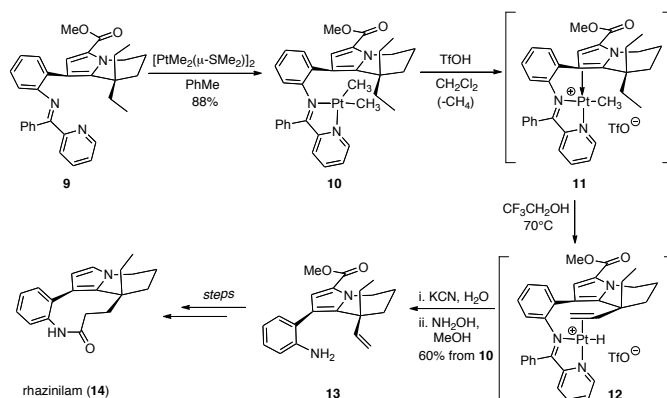
(7) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc. Chem. Comm.* **1978**, 1061.

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elegant demonstration of the aforementioned reaction type was reported by Sames and co-workers in the context of a total synthesis of rhazinilam (**14**) (Scheme 4).<sup>9</sup>

Pyrrole **9**, which contains two basic nitrogens capable of metal complexation, was transformed into Pt(II) complex **10**, which upon addition of TfOH formed complex **11** with concomitant loss of methane. Upon heating, complex **11** was found to undergo smooth C-H insertion (again with loss of methane) and subsequent  $\beta$ -hydride elimination to form alkene complex **12**. This entire process is selective in that only one of the two prochiral ethyl groups are oxidized. After removal of the bound metal hydrolysis of the imine, aniline **13** was obtained in 60% overall yield from **10**. Two steps then transformed **10** into the alkaloid rhazinilam (**14**).

**Scheme 4.** Selective C-H Functionalization by a Pt-Mediated Directed Dehydrogenation

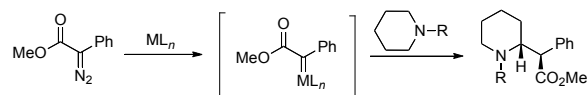


**Metal-Mediated Carbenoid and Nitrenoid  $sp^3$  C-H Functionalization**

The transition metal-mediated extrusion of dinitrogen from diazo compounds has become widely used for generating carbenes.<sup>10</sup> These highly reactive intermediates will readily insert into C-H bonds in both intra- and intermolecular manifolds (Scheme 5). Rh(II) and Cu(I) have been the most successful metals for such processes and both the high catalyst turnover and enantioselectivity that can be achieved currently make such methods particularly attractive in comparison with metal-mediated directed  $sp^3$  C-H oxidation (*vide supra*).

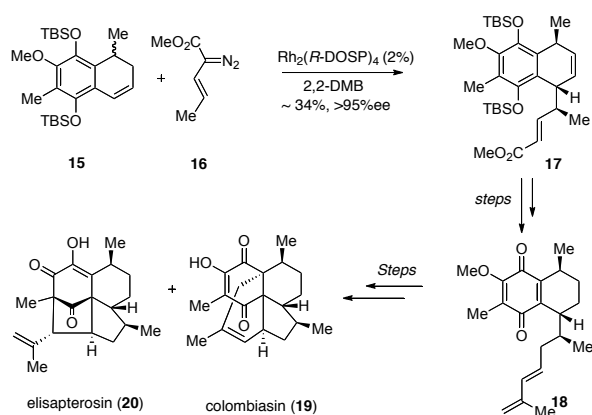
In addition, if the diazo component possesses an additional conjugated olefin (see structure **16**) and the substrate

**Scheme 5.** Pathway for the Metal-Mediated Decomposition of Diazo Compounds and Subsequent C-H Insertion



possesses allylic C-H bonds then a Cope rearrangement can occur following the C-H insertion step in a cascade process.<sup>10</sup> A stunning demonstration of this strategy was recently reported by the Davies laboratory *en route* to an asymmetric total synthesis of the Elisabethae diterpenes colombiasin (**19**) and elisapterosin (**20**, Scheme 6).<sup>11</sup> Treatment of racemic dihydronaphthalene **15** with diazoester **16** in the presence of the chiral rhodium catalyst  $\text{Rh}_2(\text{R-DOSP})_4$  afforded compound **17** in good enantiomeric excess. This powerful reaction forms all three key stereocenters common to this family of natural products in a single operation. Several straightforward steps then formed diene **18**, a compound which serves as a precursor to both **19** and **20**.

**Scheme 6.** Catalytic Asymmetric Tandem C-H Insertion/Cope Rearrangement in Terpene Synthesis



The synthetic utility of rhodium carbene insertion reactions in a complex setting was further demonstrated by Du Bois and co-workers in their landmark asymmetric synthesis of the marine alkaloid tetrodotoxin (**25**, Scheme 7).<sup>12</sup> The first strategic use of carbenoid insertion chemistry came in the conversion of diazo ketone **21** into cyclohexanone **22**, thereby forming the sole carbocyclic ring found in the natural product. This step occurred in both high yield as well as excellent regioselectivity despite the presence of multiple activateable C-H bonds. Ketone **22** was then elaborated to carbamate **23** in several steps. Treatment of this carbamate with catalytic  $\text{Rh}_2(\text{HNCOCF}_3)_4$  in the presence of an iodine(III) based oxidant furnished cyclic carbamate **24**, presumably through the intermediacy of a rhodium-bound nitrenoid. Compound **24** could then be advanced to the target (**25**).

(10) For recent reviews, see: (a) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Davies, H. M. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6422.

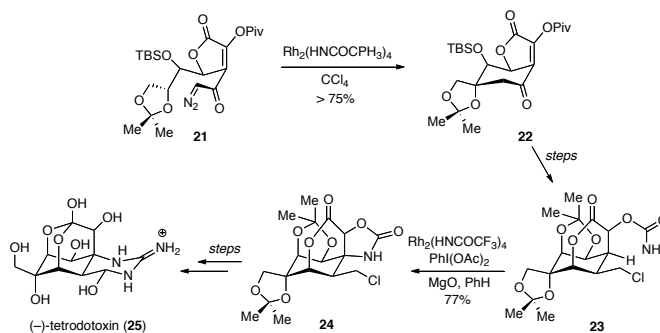
(11) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485.

(12) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.

(13) For a recent review, see Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(14) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119.

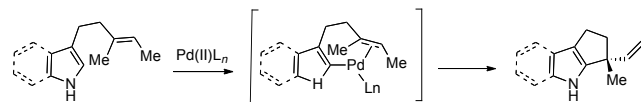
**Scheme 7.** Strategic Use of Carbenoid and Nitrenoid C-H Insertion Reactions *en Route* to Tetrodotoxin (**25**)



### Direct $\text{sp}^2$ C-H Functionalization of Electron Rich Aromatics via Metallation

The ability of electrophilic transition metal salts to metallate electron rich aromatic rings has opened a large door in the field of C-H functionalization (Scheme 8).<sup>13</sup> Originally demonstrated by Fujiwara in the late 1960's,<sup>14</sup> a large variety of aromatic and heterocyclic compounds have since been shown to react with a variety of metal complexes, most commonly derived from Palladium and platinum.<sup>13</sup> While a variety of stoichiometric processes are known, the development of catalytic variants has been much more difficult, although several impressive methodologies have recently been reported.<sup>15</sup>

**Scheme 8.** Arene Palladation as a general method for C-H Functionalization

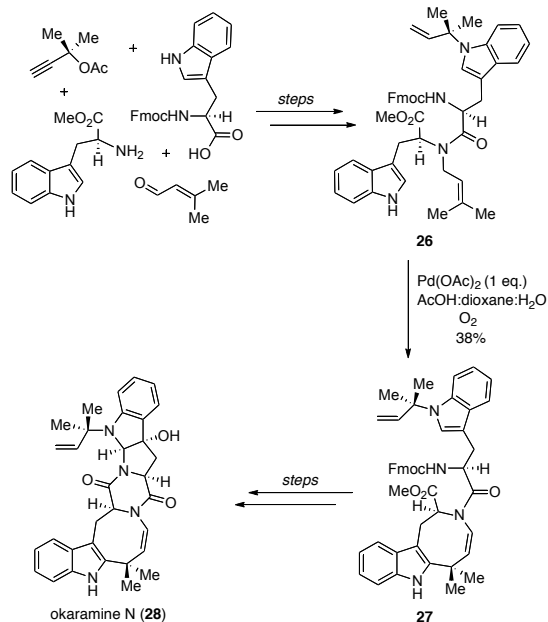


In the arena of total synthesis several noteworthy examples have recently been developed, both of which simplify the total synthesis. Recently Corey and co-workers reported a stoichiometric palladium-mediated C-H functionalization reaction in the context of an okaramine N (**28**) total synthesis (Scheme 9).<sup>16</sup> Treatment of amino acid derived indole **26** with  $\text{Pd}(\text{OAc})_2$  under an oxygen atmosphere first elicited indole C-2 palladation (see Scheme 8), followed by an intramolecular Heck-type cyclization to arrive at dihydroindoloazocine **27**. Several reactions then converted **27** into okaramine N (**28**).

(15) (a) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578.

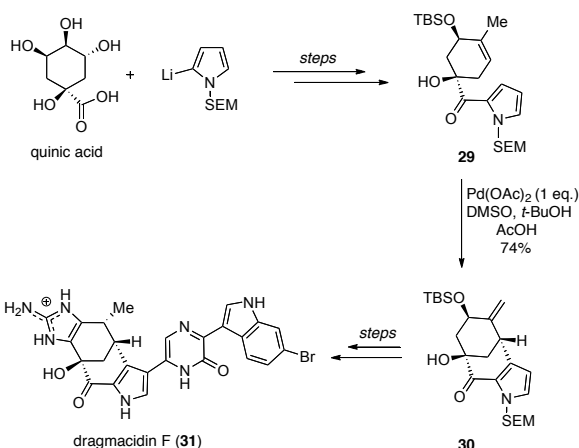
(16) (a) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.

**Scheme 9.** C-H Functionalization by a Palladium-Mediated Indole→Dihydroindoloazocine Cyclization



Other heterocyclic units have also been amenable to similar reaction manifolds. Stoltz and co-workers have recently reported a novel Pd(II)-mediated C-H functionalization/ Heck-cyclization of a pyrrole *en route* to the complex alkaloid drarmacidin F (**31**, Scheme 10).<sup>17</sup> Upon treatment with stoichiometric Pd(OAc)<sub>2</sub>, quinic acid derived acylpyrrole **29** underwent smooth cyclization to yield the complex tricyclic ring system of the natural product. With rapid and reliable access to **30**, the Stoltz group was able to complete the first total synthesis of this complex alkaloid.

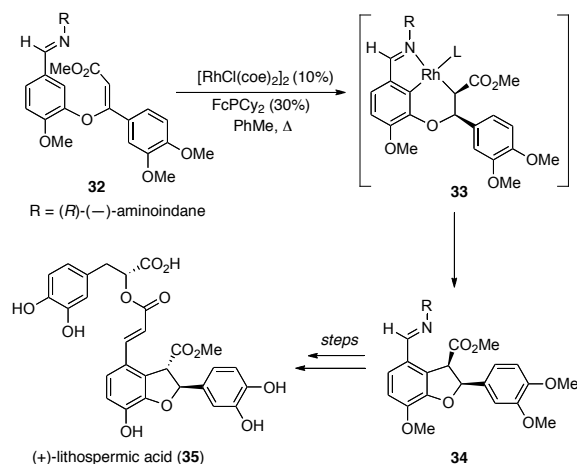
**Scheme 10.** Pyrrole C-H Functionalization as an Enabling Technology in the Synthesis of Drarmacidin F (**31**)



## Heteroatom-Directed Metal-Mediated $sp^2$ C-H Functionalization

The ability of neighboring heteroatoms to direct metal-catalyzed  $sp^2$  C-H functionalization of aromatic and olefinic C-H bonds has been demonstrated in a number of contexts.<sup>18</sup> Primarily utilizing complexes of ruthenium and rhodium, this general method for C-H functionalization has been demonstrated in both inter- and intramolecular manifolds. This powerfully simplifying transform was recently showcased in the total synthesis of (+)-lithospermic acid (**35**) by the Bergman and Ellman groups (Scheme 11).<sup>19</sup> Anisole **32** (which contains an imine moiety capable of metal chelation) underwent a facile C-H insertion reaction followed by cyclization to yield tricycle **34** after hydrolysis. Compound **34** could then be epimerized and converted into the natural product in a number of straightforward synthetic manipulations.

**Scheme 11.** Rhodium-Catalyzed  $sp^2$  C-H Functionalization in the Total Synthesis of (+)-Lithospermic Acid (**35**).



## Conclusion

C-H functionalization reactions have enormous potential to aid synthetic chemists in their ongoing pursuit of efficiency and waste reduction. As shown, the origins of this field do not necessarily lie with transition metal chemistry, yet its future most likely does. While many C-H functionalization reactions are still far from reaching their nearly limitless potential, their impact on the practice of total synthesis has already been substantial. Future developments in this arena will no doubt serve to greatly benefit chemists engaged in this area of research.

(17) (a) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552 (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *Synlett.* **2006**, 3081.

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