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Natural Product Synthesis via Palladium-Catalyzed Carbonylation

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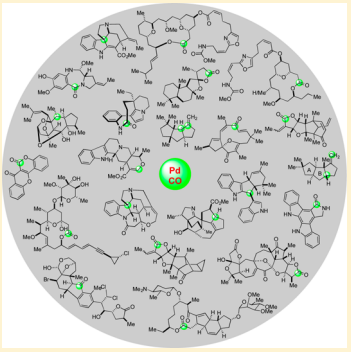
ABSTRACT: Carbon monoxide is an important one-carbon source and can be incorporated in complex molecules via various transition-metal-catalyzed carbonylation reactions. In particular, palladium-catalyzed carbonylation reactions have found broad application in total synthesis of natural products. Examples are presented in this Synopsis to highlight recent progress in this area, including our own work in macrolide and spirocyclic molecule synthesis. In these selected cases, carbon monoxide functions as a one-carbon linchpin to facilitate building structural complexity and improving synthetic efficiency.

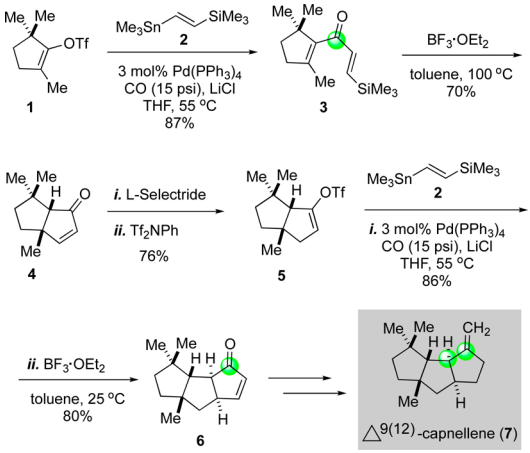


Carbon monoxide is a cheap and abundant one-carbon source in organic synthesis. It reacts with various transition metals to form highly reactive acyl-metallo species that can be intercepted to form multiple carbon−carbon and/or carbon−heteroatom bonds. In general, carbonyl-containing products such as ketones, esters, amides, and aldehydes are produced from these carbonylation reactions.[1] Among various transition-metal catalysts used in carbonylative transformations, palladium-based catalysts have played important roles.[2] Since Heck's seminal discoveries of palladium-catalyzed carbonylation of aryl and vinyl halides for the syntheses of esters, amides, acyl chlorides, and aldehydes (often referred as the Heck carbonylation) in 1974,[3] many versions of palladium-catalyzed carbonylation reactions have been developed and utilized in making fine chemicals, pharmaceutical molecules, and natural products. Herein, we highlight the use of palladium-catalyzed carbonylation reactions in facilitating total syntheses of complex natural products, including our recent contributions. This Synopsis is organized according to the following reaction types: the carbonylative Stille/Suzuki reaction, carbonylative lactone/lactam formation, the Semmelhack reaction, cascade palladium−ene cyclization/carbonylation, carbonylative C−H functionalization, carbonylative macrocyclization, and carbonylative spirolactonization.

CARBONYLATIVE STILLE/SUZUKI REACTION

Palladium-catalyzed carbonylative Stille[4] or Suzuki[5] reactions involve a viable three-component coupling of organotin/boron nucleophiles, organic electrophiles (halides, triflates, etc.), and carbon monoxide to rapidly synthesize unsymmetrical ketones. When both vinyl electrophiles and nucleophiles are used, divinyl ketones, important intermediates in organic synthesis, can be produced. A follow-up Nazarov cyclization could convert the resultant divinyl ketones to substituted cyclopentenones. Stille and co-workers used such an effective strategy in their total synthesis of $\Delta^{9(12)}$-capnellene (Scheme 1).[6] The palladium-catalyzed carbonylative coupling of triflate **1** and (trimethylsilyl)-vinylstannane **2** gave divinyl ketone **3**. Notably, this transformation requires the addition of 2−3 equiv of LiCl and high pressure of carbon monoxide. Lowering the reaction temperature resulted in the formation of a considerable quantity of the noncarbonylated coupling product. Divinyl ketone **3** underwent a silicon-directed Nazarov cyclization[7] to provide enone **4** in 70% yield. The second combination of the carbonylative coupling and silicon-directed Nazarov reaction afforded tricyclic enone **6** efficiently, which eventually led to $\Delta^{9(12)}$-capnellene after double-bond reduction and Wittig olefination.

Scheme 1. Stille Synthesis of $\Delta^{9(12)}$-Capnellene (1984)



In 2008, Chen and co-workers reported an elegant total synthesis of nakiterpiosin (Scheme 2).[8] One of the key steps in their synthesis involves an efficient carbonylative Stille reaction to unite two complex moieties **8** and **9**. Under the conditions of $Pd(PPh_3)_4$/CuCl in DMSO with 1 atm of carbon monoxide, the carbonylation product was produced in 62% yield. The CuCl

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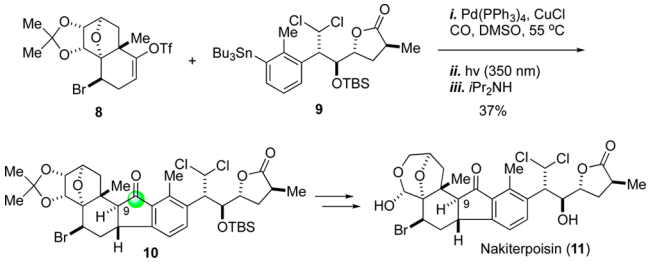
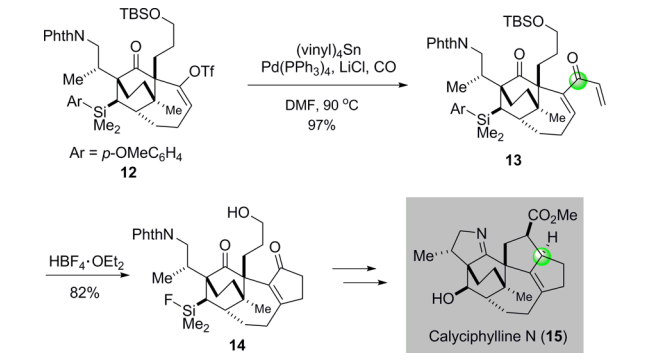
Scheme 2. Chen Synthesis of Nakiterpiosin (2008)



additive and DMSO solvent are critical for this transformation. The successful coupling of two highly acid- and base-sensitive parts **8** and **9** is a strong testimony of the generality, reliability, and efficacy of the carbonylative Stille reaction. The resultant aryl vinyl ketone was then subjected to a photo-Nazarov cyclization to produce cyclopentanone **10** in 60% yield after epimerization of the undesired C9-epimer. The total synthesis of nakiterpiosin was completed in four more steps.

Recently, Smith and co-workers employed a similar strategy to build the cyclopentene ring of the polycyclic natural product calyciphylline N.[9] As shown in Scheme 3, highly complex vinyl

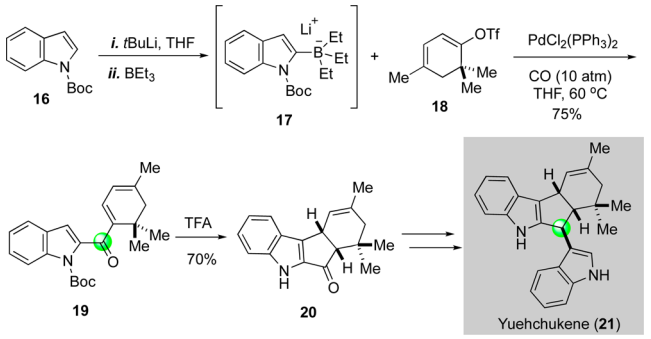
Scheme 3. Smith Synthesis of Calyciphylline (2014)



triflate **12** obtained by using an intramolecular Diels–Alder reaction to build the [2.2.2] bicyclic ring system was coupled with tetravinyltin under a carbon monoxide atmosphere using the conditions established by Stille to give divinyl ketone **13** in excellent yield. Nazarov cyclization of **13** with the aid of HBF_4 gave **14** in 82% yield, which was subsequently elaborated to complete the first total synthesis of calyciphylline N with an intramolecular aldol condensation on the newly generated ketone (derived from carbon monoxide) to close the other cyclopentane ring as one of the key steps.

A combination of carbonylative Suzuki coupling and Nazarov reaction was employed by Ishikura and co-workers[10] to synthesize the bis-indole alkaloid yuehchukene which was isolated as a racemic mixture and has shown impressive anti-implantation activity and high binding affinity to estradiol receptor (Scheme 4). A directed *ortho*-metalation of *N*-Boc-indole **16** followed by treatment with triethylborane gave the lithiated "ate" complex **17**, which was then coupled with vinyl triflate **18** and carbon monoxide without further purification under a catalytic amount of $PdCl_2(PPh_3)_2$ in THF. Notably, due to the tetracoordinated nature of "ate" complex **17**, no additional base is required to promote the transmetalation step. Subsequent treatment of the carbonylative coupling product with TFA promoted the Nazarov cyclization as well as Boc-deprotection to give **20** in 70% yield, which was further advanced to yuehchukene

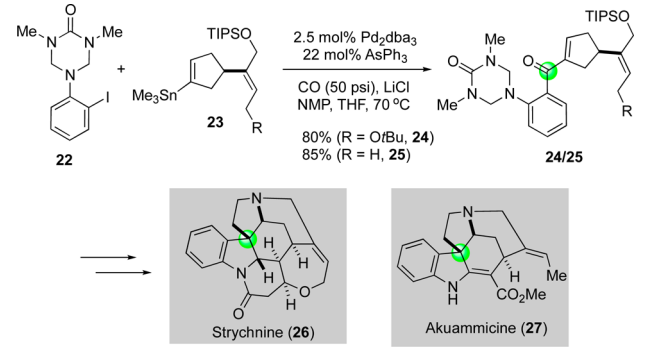
Scheme 4. Ishikura Synthesis of Yuehchukene (2000)



via a sequence of ketone reduction and Lewis acid promoted indole alkylation.

Another classical application of the carbonylative Stille coupling lies in the total syntheses of *Strychnos* alkaloids including akuammicine and strychnine by Overman and co-workers (Scheme 5).[11] In these cases, carbon monoxide was used

Scheme 5. Overman Synthesis of Strychnine and Akuammicine (1993)



as a linker to connect triazone-protected *o*-iodoaniline **22** and vinylstannane **23**. Again, lithium chloride and pressurized carbon monoxide were necessary for the carbonylation reaction. Additionally, triphenylarsine turned out to be the best ligand for this transformation. Carbonylation products **24** and **25** were then advanced to strychnine and akuammicine, respectively, with an aza-Cope-Mannich reaction[12] as the key transformation to form the desired pyrrolidine.

In these selected natural product syntheses via carbonylative Stille/Suzuki reactions, the desired unsymmetrical ketones were generated in one step from three components: an organotin/boron, an organic electrophile, and carbon monoxide. In comparison to conventional synthetic approaches, which mainly rely on acylation or Friedel–Crafts-type reaction, no carboxylate synthesis and the related functional group manipulations are required for the catalytic carbonylation process. The regioselectivity is predetermined by the positions of the stannane/boron and the halides/triflates on the coupling partners but not by the electronic properties of the substrates.

CARBONYLATIVE LACTONE/LACTAM FORMATION

In addition to the use of organotin/boron as nucleophiles to form unsymmetrical ketones, as reported in the original Heck carbonylation,[3] alcohols, amines, and hydride can be used as nucleophiles to trap the acylpalladium species derived from the reaction of organic electrophiles and carbon monoxide to form

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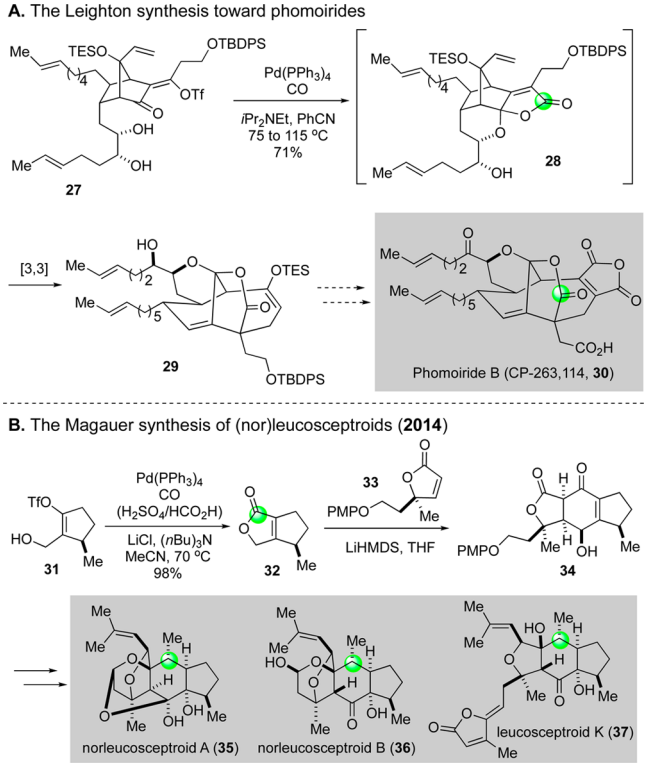
esters,[13] amides,[14] and aldehydes,[15] respectively. These cases can be viewed as a one-carbon homologation process and have been used frequently in total synthesis. If the alcohol or amine nucleophile is properly tethered in the same molecule with the newly generated acylpalladium species, a lactone or lactam could be produced.[16] In a synthetic study toward the phomoiride molecules, Leighton[17] and co-workers designed and executed a beautiful cascade sequence of hemiketal formation, carbonylative lactonization, and Cope rearrangement to convert **27** to **29** in only one step (Scheme 6A). Hugelshofer and Magauer used the

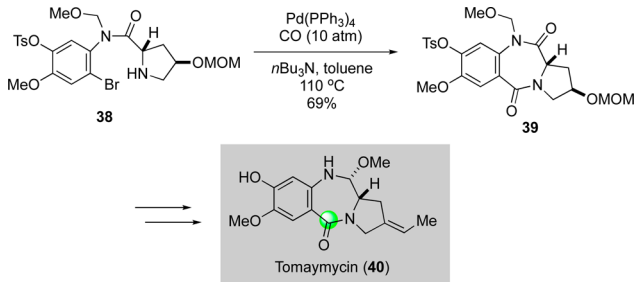
Scheme 6. Carbonylative Lactonization



palladium-catalyzed carbonylative lactonization to synthesize α,β-unsaturated lactone **32** in 98% yield from readily available vinyl triflate **31**. Notably, in this case, instead of using carbon monoxide from a cylinder, carbon monoxide was in situ generated by the reaction of formic acid with sulfuric acid using a connected reactor and formic acid functions as a carbon monoxide surrogate.[18] The α,β-unsaturated lactone **32** was then coupled with **33** through a Hauser−Kraus-type annulation to give tricyclic intermediate **34**, which was further advanced to several (nor)leucosceptroids (Scheme 6B).[19]

The palladium-catalyzed carbonylative lactamization has not been used as frequently as the corresponding lactonization in total synthesis of natural product. Mori, Ban, and co-workers developed a new synthesis of diazepam and the related 1,4-benzodiazepines by means of palladium-catalyzed carbonylative lactamization.[20] The application of this method was demonstrated in their total synthesis of tomaymycin (Scheme 7), prothracarcin, and anthramycin. A pressurized carbon monoxide atmosphere was required to suppress the competitive carbon−nitrogen.

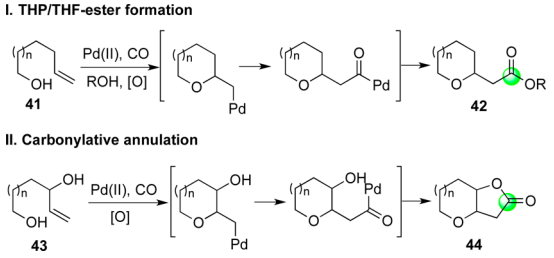
Scheme 7. Mori and Ban Synthesis of Tomaymycin (1986)



SEMMELHACK REACTION

Tetrahydropyran (THP) and tetrahydrofuran (THF) rings exist in many pharmaceutical molecules and natural products including macrolides. Among many methods to synthesize these structural motifs, the Semmelhack reaction[21] stands out due to its mild reaction conditions, broad substrate scope, and high synthetic efficiency (Scheme 8). The Semmelhack reaction

Scheme 8. Semmelhack Reaction



proceeds by an intramolecular addition of alcohol nucleophiles to π-alkene-palladium(II) complexes (oxypalladation) followed by carbon monoxide migratory insertion to the alkylpalladium-(II) intermediates and quenching the highly reactive acylpalladium species with another alcohol either intermolecularly or intramolecularly (annulation) to form THP/THF esters or THP/THF-fused lactone, respectively. Overall, at least two carbon−oxygen bonds and one carbon−carbon bond are constructed. Carbon monoxide is incorporated as the ester or lactone carbonyl group.

The application of both types of Semmelhack reactions has been magnificently demonstrated in many natural product total syntheses,[22] a few of which are highlighted in Schemes 9 and 10. In the Leighton[23] synthesis of leucascandrolide A, the standard Semmelhack reaction conditions were used to convert **45** to THP ester **46** in 75% yield and high stereoselectivity. The ester group was later converted to the desired THP-macrolide via the Yonemitsu-modified Yamaguchi protocol. In their formal synthesis of neopeltolide, She and co-workers[24] used the Semmelhack alkoxycarbonylation to produce THP-ester **50** from C_2-symmetric alcohol **49** derived from 1,3-propanediol via the Krische's iridium-catalyzed asymmetric carbonyl allylation.[25] In MacMillan's total synthesis of callipeltoside C,[26] the Semmelhack reaction was employed to build the central THP ring. Callipeltoside C, leucascandrolide A, and neopeltolide all have a THP-bridged macrolide, but callipeltoside C differs from the other two by having a hemiketal at C3. This higher oxidation level at C3 renders further challenges for total synthesis, which was overcome by choosing an alkynyl alcohol instead of alkenyl alcohol as the substrate for the Semmelhack reaction. Using the reaction conditions developed by Marshall[27] and co-workers,

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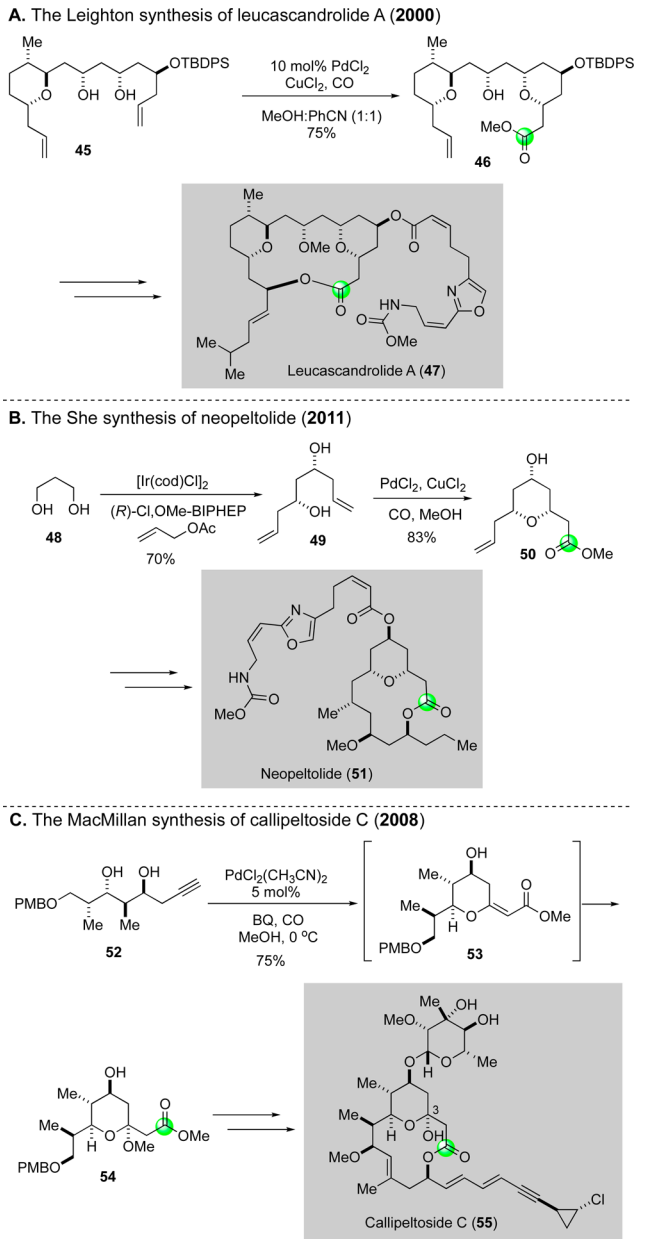
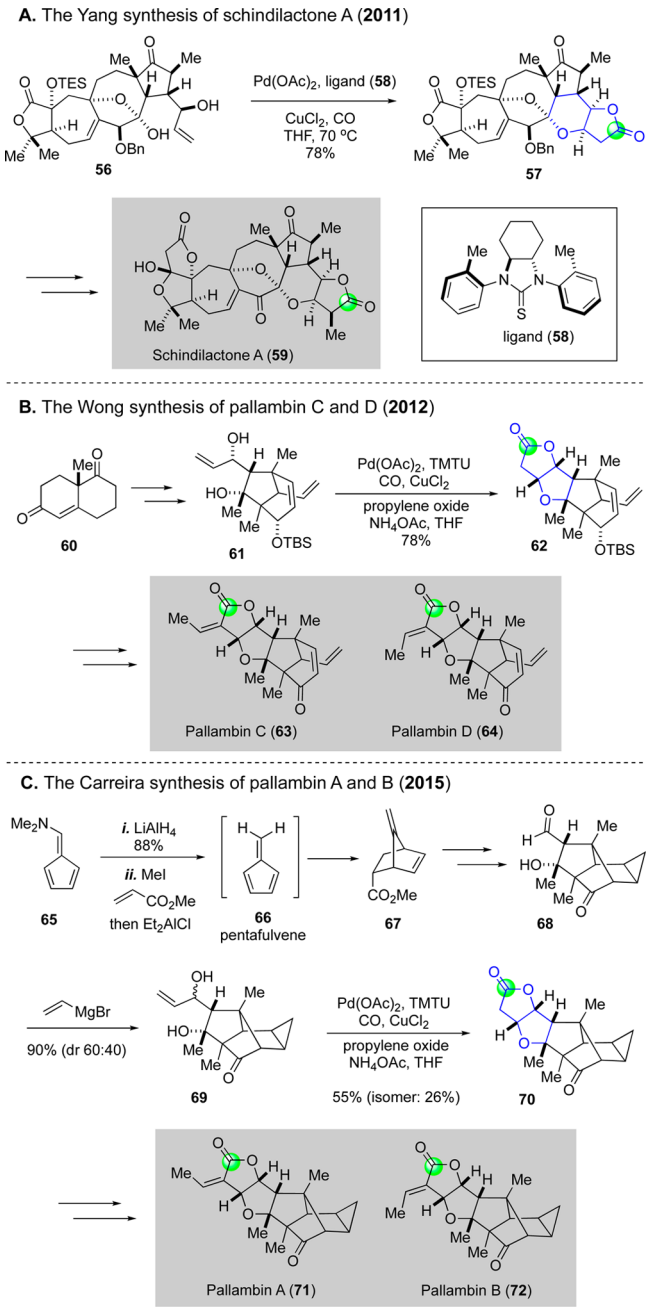
J. Org. Chem. 2017, 82, 2319−2328

Scheme 9. Semmelhack Reaction in Total Synthesis of THP–Macrolides



Scheme 10. Semmelhack Annulation in Total Synthesis of THP/THF-Fused Lactone



MacMillan and co-workers successfully converted alkynyl alcohol **52** to **54** in 75% yield with 95:5 anomeric diastereocontrol at the C3 carbon center. The use of an alkynyl group allowed a direct introduction of the C3 ketal presumably via a palladium-catalyzed ketal formation from the initial intramolecular alkoxycarbonylation product **53**. In these three cases, the Semmelhack reaction enables rapid construction of the THP ring in high stereoselectivity and yield. Carbon monoxide eventually ends as the carbonyl group of these biologically active and complex macrolides.

The intramolecular trapping of the acylpalladium complexes derived from intramolecular alkoxycarbonylation to form THP/THF-fused small-sized lactones (usually five-membered lactones) has been broadly used in facilitating complex natural product synthesis as well. This annulation process provides expedient access of bicyclic lactones, which are frequently found in many natural products and can also be converted to other structural skeletons readily. Strong testimonies to the utility of the Semmelhack carbonylative annulation reaction are highlighted in Scheme 10. In their first total synthesis of schindilactone A,[28] Yang and co-workers demonstrated an impressive use of the Semmelhack carbonylative annulation in a very challenging and sophisticated case (cf. **56** → **57**). Upon treatment of **56** under their palladium/thiourea[29] catalyst system in THF under a balloon pressure of carbon monoxide, polycyclic product **57** was produced in 78% yield. All of the functional groups of **56** including silyl ether, hemiketal, ketone, enones, and lactone are well tolerated under the reaction conditions. In 2012 and 2015, both the Wong group[30] and Carreira group[31] used the Semmelhack annulation to construct the bicyclic lactone ring system of the pallambins. Wong's synthesis of pallambins C and D started from the Wieland–Miescher ketone, and Carreira's

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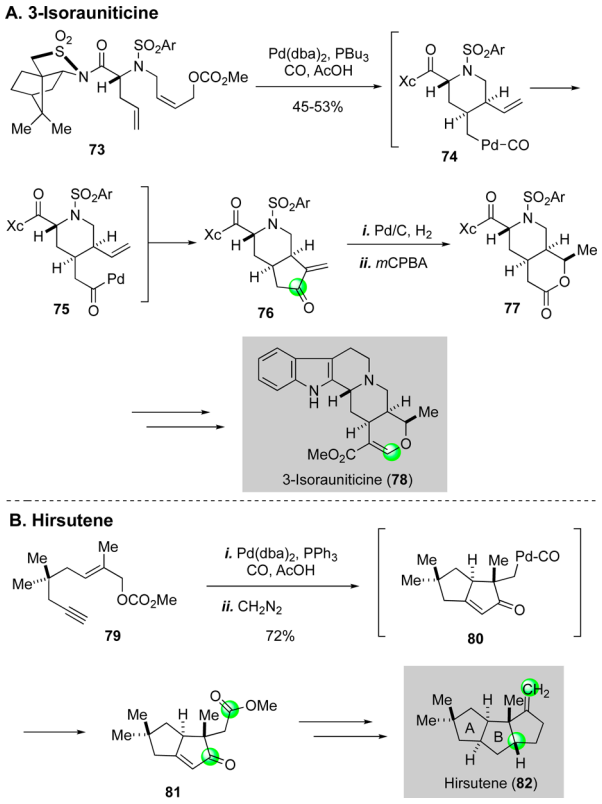
synthesis began with a Diels–Alder reaction of pentafulvene and methyl acrylate. Both of these syntheses used the modified carbonylative annulation reaction conditions developed by the Yang group.[32]

CASCADE PALLADIUM–ENE CYCLIZATION/CARBONYLATION

In a continuation of their interest in metallo–ene reactions, Oppolzer and co-workers pioneered a sequence of palladium-catalyzed intramolecular insertion of alkenes into π-allylpalladium and carbonylation reactions (formally considered as a cascade palladium–ene cyclization/carbonylation) to build fused bicyclic ring systems. This cascade process forms multiple (three or four) carbon–carbon bonds with insertion of one or two carbon monoxide molecules into the products as carbonyl functional groups for further transformations.[33] The utility of this cascade process has been demonstrated in their total syntheses of 3-isorauniticine[34] and hirsutene[35] (Scheme 11). For the 3-isorauniticine synthesis, the cascade process initiated with an intramolecular palladium–ene reaction upon treatment of allylic carbonate **73** with a catalytic amount of $Pd(dba)_2$ to generate alkyl palladium species **74**, which then underwent a sequence of carbon monoxide migratory insertion, double-bond insertion, and β-hydride elimination to produce bicyclic enone **76** in 45–53% yield accompanied by 25% of two diastereomers with stereochemistry variations at the newly formed ring junction. Enone **76** was then converted to lactone **77** via a stereoselective hydrogenation from the less hindered convex face and a regioselective Baeyer–Villiger oxidation with stereochemistry retention at the newly generated carbon center. Lactone **77**, already containing the key *cis*-6,6-fused ring system and three of the four stereocenters, was then advanced to 3-isorauniticine. Another magnificent application of the cascade palladium–ene cyclization/carbonylation was demonstrated in their hirsutene synthesis. The cascade process was used to rapidly build the A,B-ring system of hirsutene including the construction of one all-carbon quaternary center. In this case, the cascade process initiated with an insertion of the tethered alkyne into the π-allyl-palladium derived from carbonated **79** and two carbon monoxide molecules were incorporated, one in the ketone and the other one in the ester group. The reaction gave 72% yield of the cyclized products as an 85:15-mixture of diastereomers favoring the desired product. The minor product has opposite stereochemistry at the newly generated all-carbon quaternary center. Both the resulting enone and ester groups serve as convenient handles for further transformations to complete the total synthesis of hirsutene.

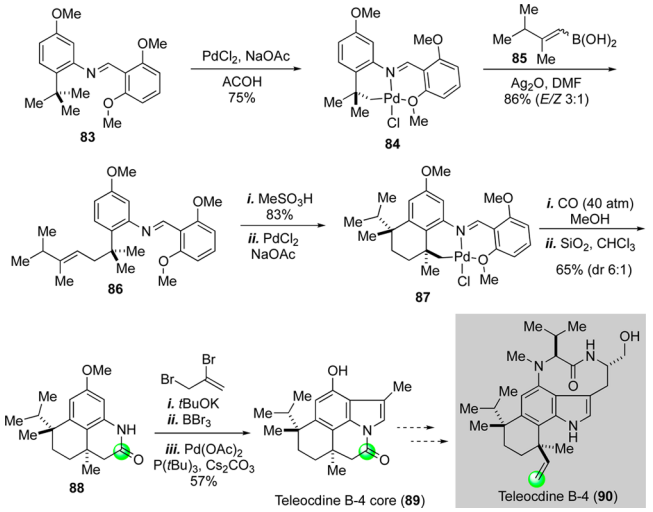
Scheme 11. Oppolzer Syntheses of 3-Isorauniticine (1991) and Hirsutene (1994)



CARBONYLATIVE C–H FUNCTIONALIZATION

C–H functionalization has become as a powerful tool in organic synthesis. The obvious advantage of direct C–H functionalization is that only one or even none of the coupling partners need to possess a prefunctionalized group; therefore, it could significantly enhance synthetic efficiency by removing the prefunctionalization as well as the related protection/deprotection steps. While a significant amount of palladium-catalyzed C–H functionalization methods have been developed, palladium-catalyzed carbonylative C–H functionalizations have been quite limited.[36] Their application in total synthesis is even more sporadic. The following three examples were selected to highlight the power of using palladium-catalyzed C–H carbonylation in total synthesis. One pioneering example came from the Sames group in their synthesis of the teleocidin B-4 core structure (Scheme 12).[37] A stoichiometric amount of $PdCl_2$ first reacted with **83** to afford pure palladacycle **84** in 75% yield via a directed C–H activation of one of the methyl C–H bonds. Upon treatment with **85** in the presence of Ag_2O, a carbon–carbon bond formation took place with palladacycle **84** to furnish **86** in 86% yield with 3:1 *E*/*Z* selectivity. After a Friedel–Crafts cyclization, the resultant product was treated with $PdCl_2$ again to form palladacycle **87**, which was converted to a methyl ester via addition of carbon monoxide and methanol. Removal of the

Scheme 12. Sames Synthesis of the Teleocidine B-4 Core (2002)



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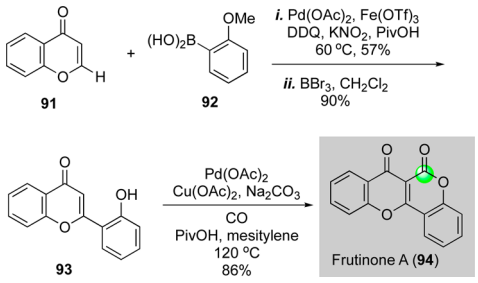
Schiff base followed by lactam formation gave **88** in 65% yield. Notably, the direct C−H palladation of one of the two methyl groups can be quite stereoselective. At lower reaction temperature (70 °C), a 6:1 ratio was obtained. This stereoselectivity suggested that the isopropyl group occupied the pseudoequatorial position in the favored transition state of the C−H palladation step and the *anti* pseudoequatorial methyl group, which is more accessible to the metal center was activated. Lactam **88** was then advanced to **89** via a palladium-catalyzed intramolecular alkenylation of the aromatic C−H bond to afford the core of teleocidin B-4. In principle, the carbon monoxide carbon could eventually become the terminal olefin carbon. While the first two C−H functionalizations require more than stoichiometric amounts of $PdCl_2$, this conceptually new synthesis is thought-provoking and inspiring.

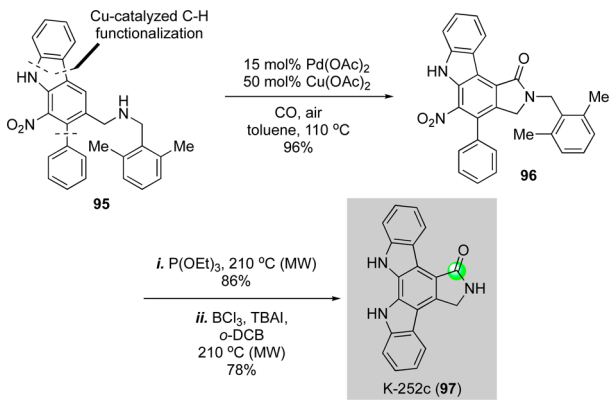
Another example is shown in Scheme 13. Hong[38] and coworkers demonstrated a sequential palladium-catalyzed intermolecular C−H arylation of chromone **91** and intramolecular C−H carbonylation of the resultant 2-phenolchromone **93** to complete a three-step total synthesis of frutinone A, a potent inhibitor of the CYP1A2 enzyme. This straightforward synthetic route allowed them to rapidly produce frutinone analogues for identifying new inhibitors of CYP1A2 enzyme for cancer prevention.

Scheme 13. Hong Synthesis of Frutinone A (2015)



Early 2016, the Gaunt group reported an elegant synthesis of K-252c (staurosporinone) by using the carbonylative C−H functionalization to construct the 5-membered lactam (Scheme 14, **95** → **96**).[39] To synthesize the C−H carbonylation precursor, they employed three impressive copper-catalyzed C−H functionalizations[40] to build the two aryl−aryl carbon−carbon bonds and one carbon−nitrogen bond.

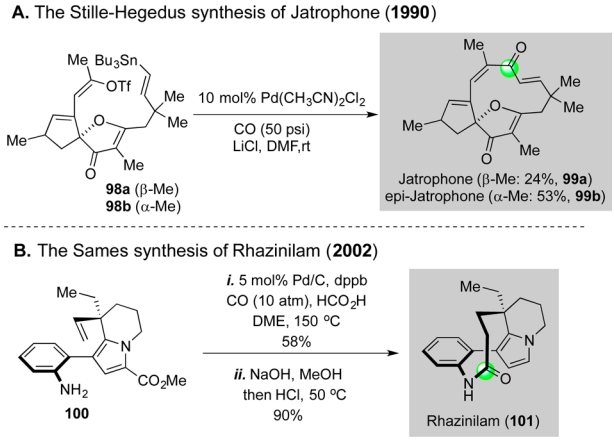
Scheme 14. Gaunt Synthesis of K-252c (2016)



CARBONYLATIVE MACROCYCLIZATION

Macrocycles have been frequently found in many important drug molecules and natural products. It has always been challenging to form macrocycles mainly due to the entropic disadvantage. Among the macrocycles, macrocyclic ketone, macrolactam, and macrolide are three privileged structures. The application of palladium-catalyzed carbonylation in building these macrocycles has been very limited.[41] One beautiful example of the application of carbonylative macrocyclization is from the Stille−Hegedus synthesis of jatrophone (Scheme 15A).[42] They used an intramolecular carbonylative Stille coupling to build the macrocyclic ketone of the target molecule under 50 psi of carbon monoxide with 10 mol % of $Pd(CH_3CN)_2Cl_2$. The reaction is quite sensitive to the stereochemistry of the carbon center bearing the methyl group. With a β-substituted methyl group, the reaction yield (24%) is lower than the one with a α-substituted methyl group (53%). This transformation is highly efficient and forms two carbon−carbon bonds and one macrocycle with the incorporation of the carbon monoxide as the final ketone group in one step. In the Sames synthesis of rhazinilam (Scheme 15B),[43] biaryl starting material **100** derived from a platinum-mediate dehydrogenation via a C−H activation process was converted to **101** via a Pd/C-catalyzed hydrocarbonylative lactamization process. The reaction probably proceeded by an olefin migratory insertion to the Pd−H bond. The resultant alkyl-palladium intermediate underwent carbonylation, and the acylpalladium species was then trapped by the intramolecularly tethered aniline to form the desired 9-membered lactam. Removal of the methyl carboxylate completed an elegant total synthesis of rhazinilam.

Scheme 15. Carbonylative Macrocyclization in Total Synthesis



Since starting at Purdue in 2012, we have been interested in developing new catalytic carbonylation methods, particularly those using carbon monoxide as a one-carbon linchpin to stitch simple starting materials into complex intermediates to streamline the total synthesis of important bioactive natural products. Inspired by the Semmelhack chemistry, we have developed an efficient palladium-catalyzed cascade alkoxycarbonylative macrolactonization to construct THP/THF-containing macrolactones with different ring sizes and substituents (Scheme 16).[44] This tandem catalytic transformation features mild reaction conditions and works for challenging tertiary alcohols. In comparison to other reported THP/THF-containing macrolactone syntheses, no carboxylate synthesis is required; therefore,

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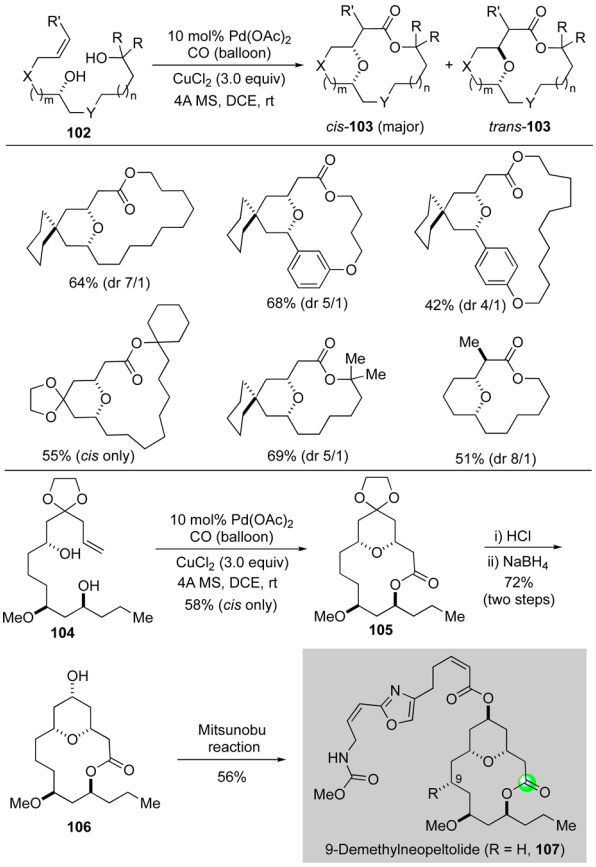
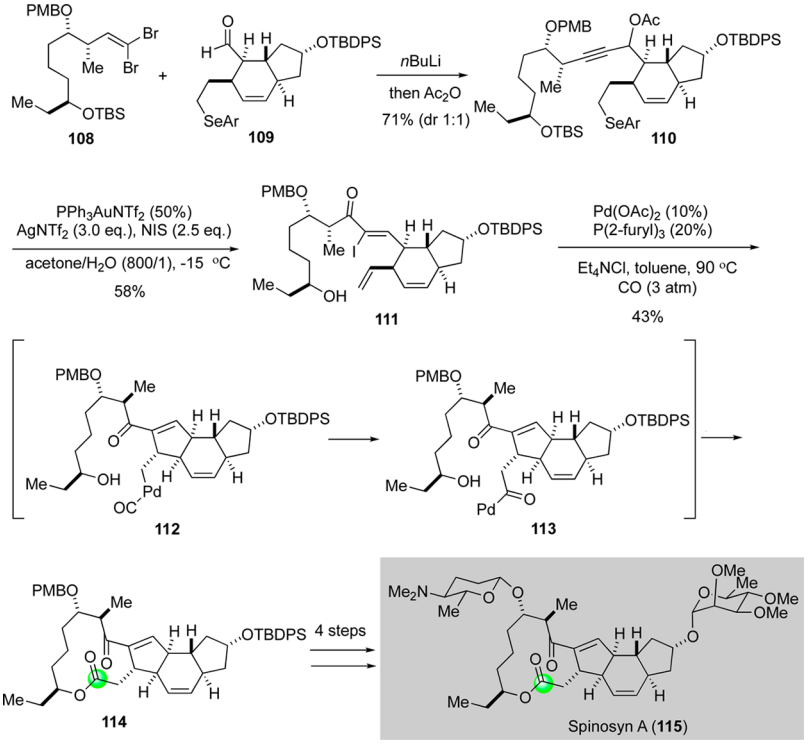
Scheme 16. Dai Synthesis of 9-Demethylneopeltolide (2014)



the corresponding masking and unmasking steps are avoided. The highly reactive acylpalladium intermediate was generated in situ and trapped by the tethered primary, secondary, or tertiary alcohols. The metal center may have acted as a template to bring the remote alcohol into proximity to facilitate the macrolactonization. Overall, this one-step transformation accomplishes the formation of two carbon−oxygen bonds, one carbon−carbon bond, and a bridged macrocyclic ring. Its application was further demonstrated by a total synthesis of the 9-demethylneopeltolide,[45] a potent anticancer analog of neopeltolide.[46] When $Pd(OAc)_2$ was used as catalyst and $CuCl_2$ as oxidant under a carbon monoxide balloon in 1,2-dichloroethane at room temperature, alkendiol **104** was converted to THP-bridged macrolactone **105** in 58% yield with excellent *cis* selectivity. Compound **105** was then converted to 9-demethylneopeltolide in three steps.

Very recently, we completed a total synthesis of spinosyn A using a palladium-catalyzed carbonylative Heck macrolactonization to form the 5,12-fused macrolactone in one step (Scheme 17).[47] Spinosyn A is the major component of spinosad, an important natural insecticide that is widely used in agriculture.[48] Our synthesis features a Corey−Fuchs-type 1,2-addition to unite dibromide **108** and aldehyde **109**. The latter was synthesized by using the MacMillan chiral amine-catalyzed intramolecular Diels−Alder reaction.[49] Acetate **110** then underwent a one-step, gold-catalyzed propargylic acetate rearrangement,[50] oxidative selenide elimination, and TBS removal to give α-iodoenone **111** in 58% yield. Upon treatment with 10 mol % of $Pd(OAc)_2$ and 20 mol % of $P(2\text{-furyl})_3$ under carbon monoxide (3 atm) in toluene at 90 °C, **111** was converted to tetracyclic intermediate **114** in 43% yield in one step. This cascade palladium-catalyzed carbonylative Heck macrolactonization began with a regular Heck-type double bond insertion. β-Hydride elimination of newly generated alkylpalladium species **112** to give a regular Heck reaction product was suppressed presumably due to lack of the empty coordinate site on the metal

Scheme 17. Dai Synthesis of Spinosyn A (2016)



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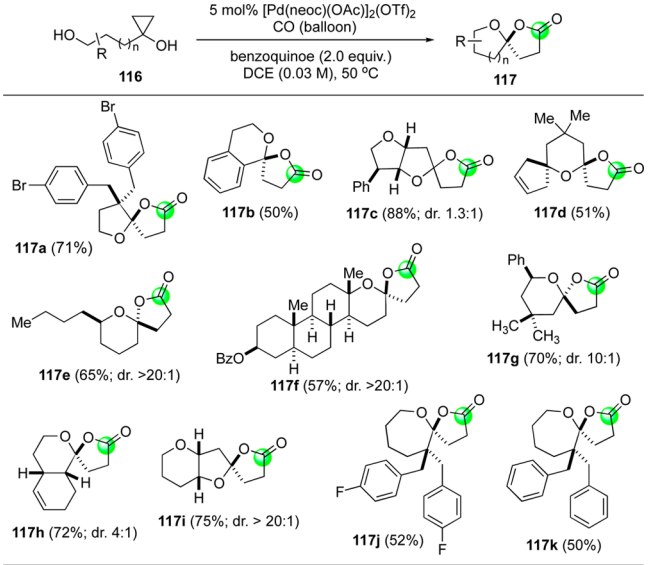
J. Org. Chem. 2017, 82, 2319−2328

center. Instead, a carbon monoxide migratory insertion took place to give acylpalladium **113**,[51] which was trapped by the remote secondary alcohol to form a 12-membered lactone. Overall, this efficient transformation constructed two carbon−carbon bonds and one carbon−oxygen bond and furnished a 5,12-fused macrolactone in only one operation. The carbonylation product was then advanced to spinosyn A with two deprotection steps and two glycosylation steps.

CARBONYLATIVE SPIROLACTONIZATION

The oxaspirolactone motif occurs prominently in many bioactive natural products. During our ongoing efforts to develop catalytic carbonylative macrolactonization methodologies to build complex, biologically active molecules and to exploit cyclopropanols in ring-opening cross-coupling reactions,[52] we have developed an efficient and general oxaspirolactone synthesis by using palladium-catalyzed cascade carbonylative spirolactonization of hydroxycyclopropanols (Scheme 18).[53] The use of

Scheme 18. Catalytic Carbonylative Oxaspirolactone Synthesis

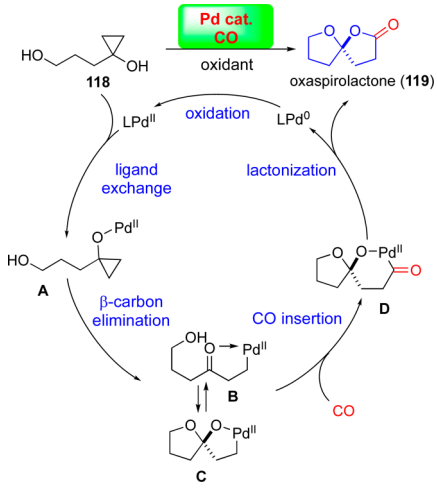


$[Pd(neoc)(OAc)]_2(OTf)_2$, a cationic dimeric palladium catalyst developed in the Waymouth laboratory,[54] is critical for this transformation. With 5 mol % of this catalyst and benzoquinone as oxidant, a variety of substrates can be converted to the corresponding oxaspirolactones including the spiro(4.4), -(5,4), and -(6,4) ring systems. In general, the stereoselectivity of the spiro(5.4) ring systems are excellent due to the anomeric effect.

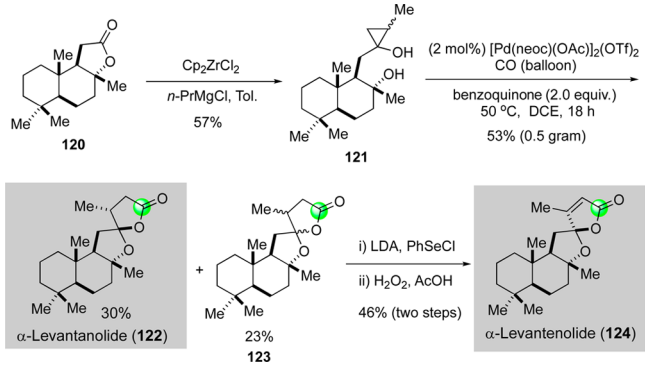
Mechanistically, as shown in Scheme 19, the proposed catalytic cycle involves a palladium(II)-catalyzed β-carbon elimination to provide a palladium homoenolate (cf. **A** → **B**). Intramolecular lactol formation followed by CO insertion and reductive elimination gave the spirolactone product and a Pd(0) complex. The latter was then oxidized back to Pd(II) complex for the next cycle. Some of the intermediates in the proposed catalytic cycle have been observed by ESI-MS studies.

We also demonstrated the potential application of this catalytic carbonylative spirolactonization method by two- and four-step total syntheses of C12 oxygenated labdanolic diterpene α-levantanolide and α-levantenolide (Scheme 20), respectively, from commercially available (3a*R*)-(+)-sclareolide (**120**). Compound **120** was converted to unsymmetrical cyclopropanol

Scheme 19. Proposed Mechanism for the Carbonylative Oxaspirolactone



Scheme 20. Dai Syntheses of α-Levantanolide and α-Levantenolide (2016)



121 as a 4:1 mixture of diastereomers in 57% yield using the Kulinkovich protocol.[55] The catalytic carbonylative spirolactonization occurred with high regioselectivity by cleaving the less substituted Walsh bond to afford a mixture of three diastereomeric oxaspirolactone products in 53% combined yield. The major diastereomer was identified as α-levantanolide (**122**). The mixture of **122** and **123** was then advanced to α-levantenolid (**124**) via a α-selenylation/oxidative elimination process.

SUMMARY

We have highlighted the application of a series of palladium-catalyzed carbonylation reactions in facilitating the total syntheses of complex natural products. When well planned, these carbonylation reactions can significantly increase structural complexity and enhance synthetic efficiency. However, in comparison to other commonly used palladium-catalyzed cross-coupling reactions,[56] the scope and potential of the palladium-catalyzed carbonylation reactions are still far from being fully explored, which will require collective effort to move the boundaries forward.

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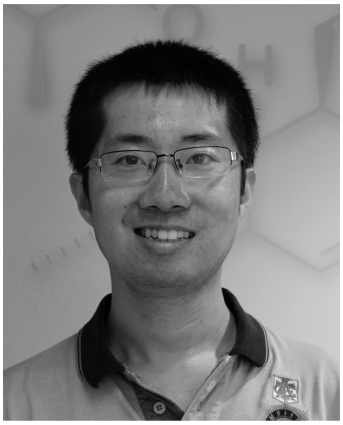
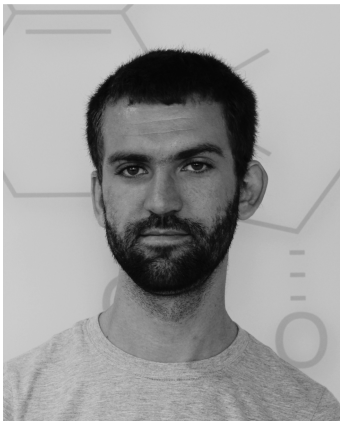
Notes

The authors declare no competing financial interest.

Biographies



Yu Bai was born in Tianjin, China, in 1983. He received his B.Sc. degree from Nankai University in 2006, where he conducted research in the laboratory of Professor Zhongwen Wang. He joined Professor Mingji Dai's group at Purdue University in 2012 and obtained his Ph.D. degree in August 2016. He is currently a postdoctoral research fellow in Professor Barry M. Trost's group at Stanford University.



Dexter C. Davis was born in Madison, WI, in 1989. He received his B.Sc. degree in chemistry from the University of Wisconsin—Eau Claire in 2012. He is currently a 5th year Ph.D. student in Professor Mingji Dai's group at Purdue University. His research focuses on new palladium-catalyzed carbonylation reaction development and total synthesis of natural products.

Mingji Dai grew up in Sichuan, China, and received his B.S. from Peking University in 2002. After two years of research with Professors Zhen Yang and Jiahua Chen at the same university, he went to New York in 2004 to pursue graduate study under the guidance of Professor Samuel J. Danishefsky and earned his Ph.D. degree in 2009. He then took a postdoctoral position in the laboratory of Professor Stuart L. Schreiber at Harvard University and the Broad Institute. In August 2012, he began his independent career as an assistant professor in the Chemistry Department of Purdue University. His lab currently focuses on developing new strategies and methodologies for the synthesis of complex natural products and other medicinally and biologically important molecules.

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