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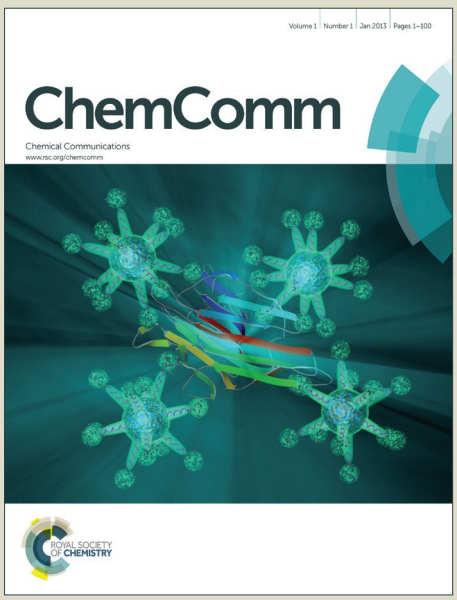

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Cascade Pd(II)-Catalyzed Wacker Lactonization-Heck Reaction: Rapid Assembly of Spiranoid Lactones

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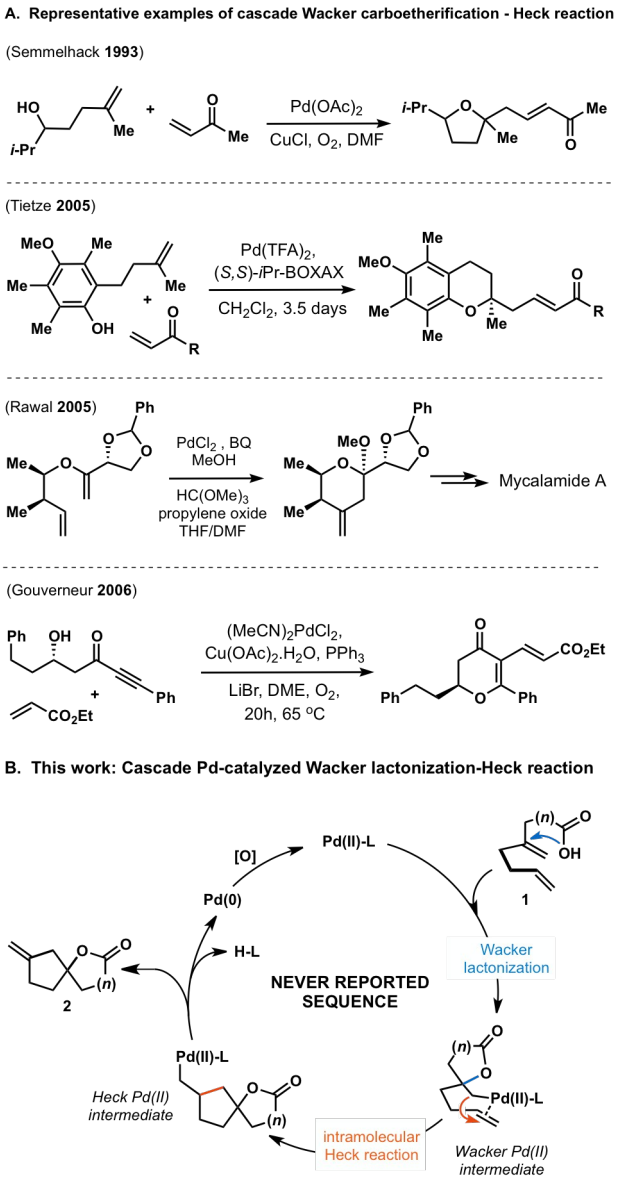
An unprecedented Pd-catalyzed cascade Wacker-Heck lactonization-cyclization sequence is reported. The process provides a facile approach to bi- and tricyclic spiranoid lactones in good yields. The reaction shows general substrate scope and a broad functional group tolerability. In addition, a rare 4-exo trig Heck-type cyclization is demonstrated.

Palladium-catalyzed cascade reactions are extensively used in synthesis of functionalized heterocycles.[1] Very often, these transformations involve a reactive alkyl-Pd intermediate, which can undergo further transformations prior to a terminal reductive process. Depending on the reactants and the reaction conditions, it is possible to trap these transient alkyl-Pd species with alkenes, via the Heck-type C-C bond formation reaction (as demonstrated for the first time by Semmelhack in 1993; Scheme 1A).[2] Pd(II)-catalyzed cascade reactions were profitably selected as a key step for the total synthesis of several natural products. For instance, in 2005, Tietze et al. reported the enantioselective synthesis of vitamin E relying on a domino Wacker-Heck sequence (Scheme 1A).[3] An alternative Wacker-Heck process was developed by Rawal et al. to design a key fragment necessary for the total synthesis of mycalamide A.[4] Later, in 2006, Gouverneur et al. reported a Pd(II)-catalyzed oxy-carbopalladation process allowing for the orchestrated union of hydroxy ynones with ethyl acrylates. With *β*-hydroxy ynones, this cascade Wacker-Heck process gave access to highly functionalized tri- and tetrasubstituted dihydro-pyranones.[5]

An examination of the above-mentioned, and many other synthetic protocols,[6] led us to the realization that vast majority of Wacker-Heck cascades reported to date, rely on the cyclization of alcohols. To the best of our knowledge, cascade



Scheme 1. Reported (A.) and projected (B.) Pd(II)-catalyzed Wacker-Heck oxidative heterocyclization cascades.

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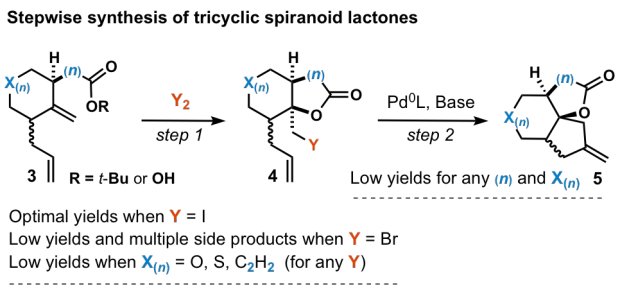
sequences initiating from Wacker lactonization and followed by the Heck-type C-C bond formation (**1** -> **2**; Scheme 1B), are yet to be reported. In light of these considerations, we envisioned that the development of such methodology would be highly desirable, as it would find broad applicability for the straightforward construction of complex spiro-lactones.

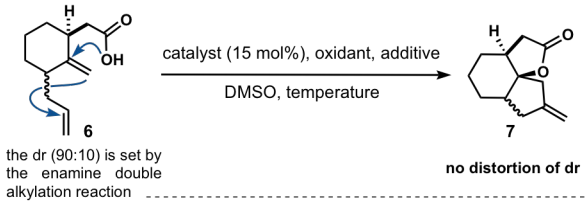
The group of compounds that attracted our attention was the family of spiranoid lactones that can be frequently observed as scaffold segments of various biochemical compounds of natural origin, and have been firmly established to demonstrate pharmacological activity.[7] Recently, we reported synthesis of tricyclic scaffolds via Y_2/M-L-mediated cyclization sequence [Y_2 represents I_2 or Br_2, with M-L being $Pd_2(OMe\text{-}dba)_3$–SIMes catalyst]. The stepwise strategy (Scheme 2) is based on the notion that, in the presence of I_2 or Br_2 and a metal–ligand system, the key cycloalkylmethylene precursor **3** generates lactone intermediate **4**, and further undergoes an intramolecular cyclization to form the corresponding tricyclic spiranoid lactones **5**.[8]

Our previously reported sequence was designed to allow simplified access (first collective protocol) to a wide range of tricyclic spirolactones. Even though it is clearly the shortest sequence reported to date, some of its characteristics are ought to be mended. With regards to the initial halolactonization step (Scheme 2), the optimal yields of the intermediate were achieved only by the means of iodine utilization. This reaction demonstrated low efficiency for substrates integrated with heteroatoms (X_n = O or S) or central ring structures comprised of cycloheptane core (X_n = C_2H_4). As far as the following Heck-type cyclization, typically, we have observed it to produce relatively low yields (40% range at best). Moreover, a side-product, originating from the reduction of the bicyclic iodolactones, was occasionally detected in the reaction mixture. Overall, the above-mentioned drawbacks imposed limitations, under which the corresponding tricyclic compounds were obtained in somewhat moderate yields. Thus, with the aim to enhance the efficacy of this strategy and bypass the limitations described above, we hypothesized that a direct assembly of spiranoid lactones should be established. To attain the desirable result, we conceptualized an unprecedented cascade sequence, employing Wacker lactonization followed by Heck C-C bond formation reaction.



Scheme 2. Limitation of previously reported stepwise approach.

Table 1. Conditions evaluation for cascade Wacker lactonization-Heck cyclization sequence.



# [a]	Catalyst	Oxidant (equiv.)	Additives (equiv.)	T °C	Yield %
1	$Pd(OAc)_2$	O_2	NaOAc (2.0)	80	44
2	$Pd(OAc)_2$	O_2	NaOAc (2.0) $Cu(OAc)_2$ (0.15)	80	20
3	$Pd(OAc)_2$	O_2	NaOAc (2.0) $Cu(OAc)_2$ (0.15) Pyridine (0.3)	80	26
4	$Pd(OAc)_2$	O_2	NaOAc (2.0) $Cu(OAc)_2$ (0.15) PPh_3 (0.3)	80	14
5	$Pd(OAc)_2$	O_2	Na_2CO_3 (2 eq.) $Cu(OAc)_2$ (0.15)	80	17
6	$Pd(TFA)_2$	O_2	Pyridine (0.4) MS 3Å	100	9 [b]
7	$Pd(OAc)_2$	O_2	AcOH (0.3) $Cu(OAc)_2$ (0.15)	80	46
8	$Pd(OAc)_2$	BQ (4.0)	NaOAc (2.0)	80	35
9	$Pd(OAc)_2$	Ag_2CO_3 (2.0)		100	23
10	$Pd(OAc)_2$	AgOAc (2.0)		80	72 [c]
11	$Pd(OAc)_2$	AgOAc (2.0)		100	75
12	$Pd(OAc)_2$	AgOAc (2.2)		100	88 (70) [d]
13	$PdCl_2$	AgOAc (2.2)		100	61
14	$Pd(MeCN)_2Cl_2$	AgOAc (2.2)		100	48
15	$Pd(dba)_2$	AgOAc (2.2)		100	48
16	$Pd(COD)_2Cl_2$	AgOAc (2.2)		100	52
17	$Pd(TFA)_2$	AgOAc (2.2)		100	57
18	$Pd_2(dba)_3$	AgOAc (2.2)		100	44

[a] All reactions were performed with 0.2 mmol of the substrate (GC yields). [b] Stoltz et al. (toluene was used as solvent; see ref. 9a). [c] Larock et al. (see ref. 9b). [d] Isolated yield, dr 90:10.

In order to test our hypothesis, the allylmethylene-cyclohexyl acetic acid **6**, which was prepared in 30% yield (overall for three steps; see SI) from cyclohexanone,[8] was selected as the model precursor (Table 1). Our initial studies (following the classical protocols, designed for Pd-catalyzed lactonization of carboxylic acids)[9] were carried out on a 0.2 mmol scale in the presence of $Pd(OAc)_2$ at temperatures ranging from 80 to 100 °C, using a variety of oxidizing reagents, bases, and other additives. We found that an efficient system for the desired transformation could be formed from the combination of $Pd(OAc)_2$ and AgOAc at 100 °C (entries 10 and 11, Table 1). The other Pd sources examined ($Pd(TFA)_2$, $PdCl_2$, $Pd(MeCN)_2Cl_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, and $Pd(COD)Cl_2$) led to the reduction of starting precursor **6** or gave low yields of the desired tricyclic spirolactone **7**. The use of DMSO as the solvent provided the optimal yield of product (See SI). It should be noted that, under the initial sets of conditions tested (entries 1-11), ^1H

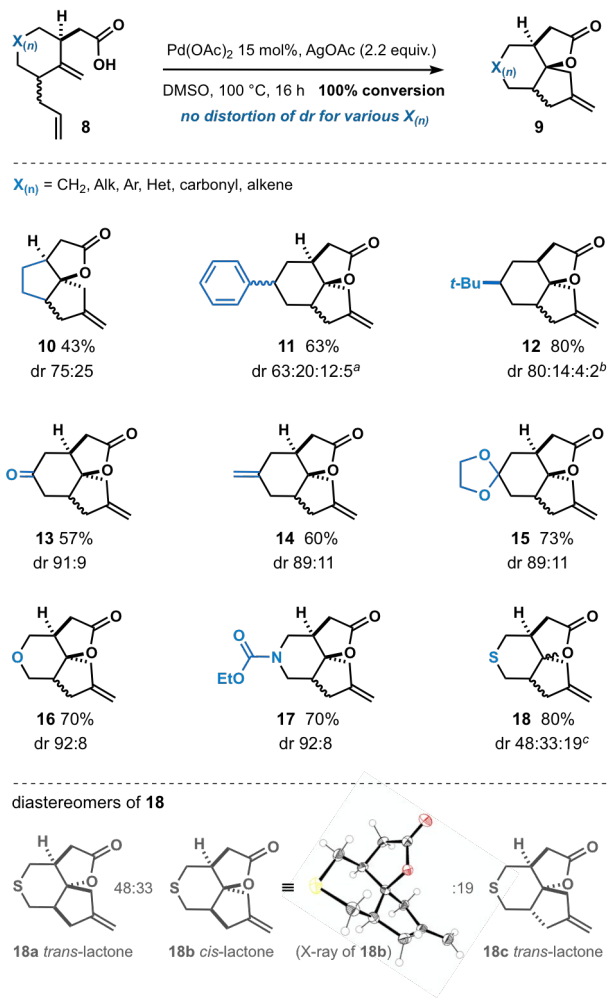
NMR analysis of the crude reaction mixtures showed incomplete conversion of **6**. The use of excess AgOAc (2.2 equiv.) proved to be necessary to achieve complete conversion (entry 12), and allowed for a convenient protocol to be developed.

Following the initial survey of oxidizing reagents and optimization of Pd sources, we next prepared a range of diene carboxylic acids.[8] The precursors so designed were then subjected to Pd-catalyzed cascade cyclization conditions to provide a range of tricyclic spirolactones in a regioselective manner and in good yields (Table 2). Under these conditions, heterocycles such as dioxoles, carbamates, THP, tetrahydro-thiopyranes, as well as various functional groups were tolerated. In view of the difficulties previously encountered,[9] the successful formation of heterocyclic lactones is particularly gratifying. The steric bulkiness of the *tert*-butyl group adjacent to the cyclohexyl ring had no influence on the reaction, and product **12** was isolated in 80% yield.[10] It should be noted that no distortion of the dr was detected for most of the transformations performed; the diastereomeric ratio of the final products was corresponding to those of the starting materials.

As an expansion of this study, we next explored the preparation of tricyclic angularly fused scaffolds of type-**20** (Table 3). This time, the functional modifications were performed on the side alkyl chains bearing acid and alkene moieties, leaving the central cyclohexyl ring topology unchanged (**19**). As expected, in the presence of $Pd(OAc)_2$ and AgOAc, cascade cyclizations of such precursors afforded the desired spirolactones **21**-**23** as single products and in good yields. For instance, *δ*-spiro lactone **21** can be constructed when the acid chain is being extended by one carbon [*n* = $(CH_2)_2$; Table 3]. Interestingly, during the cascade cyclization course of **24**, compound **23** was isolated as the only product. The structure of **23** was assigned on the basis of its ^1H and ^{13}C NMR spectra and the results of HRMS analysis. While in principle, the reactive intermediate **25** could undergo two possible *β*-H eliminations, giving rise to different targets (as shown below), it should be noted that no evidence for the presence of other terminations was detected under the optimized set of conditions. Presumably, the fast *β*-H elimination of intermediate **25** occurs from the less hindered methyl group (Table 3).[11]

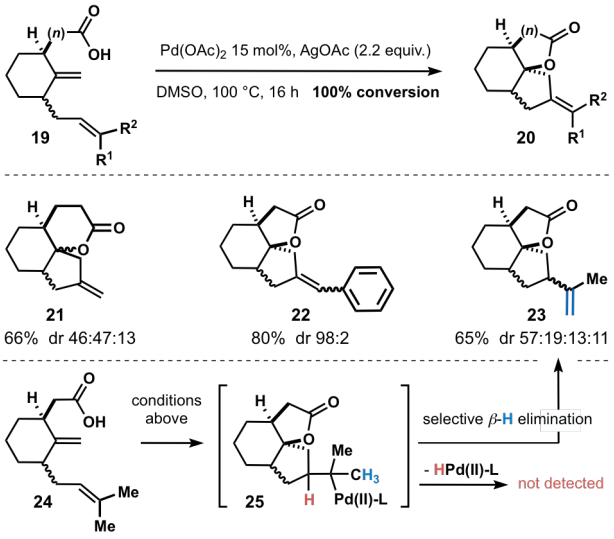
With suitable access to tricyclic lactones in hand, the cascade cyclization was then extended to the synthesis of bicyclic spirolactones using acyclic diene carboxylic acids as starting materials. We were pleased to find that reaction of **26** (general structure) afforded **27** and **28** in 82% and 76% yield, respectively (Scheme 3).

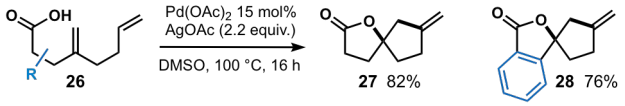
Table 2. Cascade cyclization: Functional modification of the cycloalkylmethylene unit



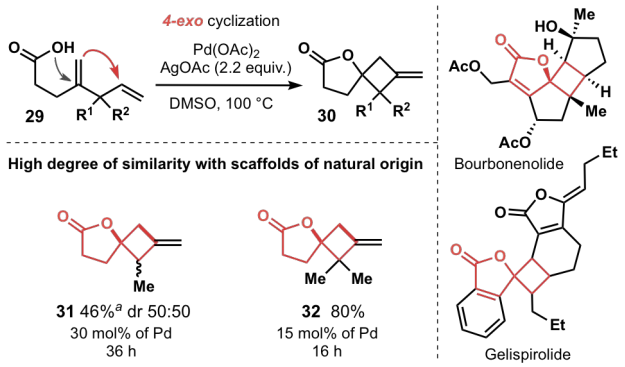
[a]3.0 equiv. of AgOAc were used. [b]The position of the *t*-Bu group is believed to be fixed as equatorial; thus, only four individual diastereomers were observed (ref. 10). [c]From the 82:18 dr of the starting material, it is deduced that **18a** and **18b** were afforded from the major diastereomer. The stereochemistry of **18a** and **18c** was assigned on the basis of their ^1H and ^{13}C NMR spectra. Whereas the crucial stereochemistry of the diastereomer **18b** was confirmed by X-ray analysis, the outcome of **18a** and **18c** resulted as an inseparable mixture (see SI section).

Table 3. Cascade cyclization: functional modification of the alkyl side chains





Scheme 3. Synthesis of bicyclic spirolactones via Wacker lactonization-Heck cyclization sequence.



Scheme 4. Pd-catalyzed cascade synthesis of oxaspiro-octanones: 4-exo-trig cyclization. [a]50% Conversion (ref. 15).

At this point, we became intrigued by the possibility of applying the established cascade protocol to acyclic 1,4-diene carboxylic acids **29** (Scheme 4). For this transformation, the mono- and bis-methylated methyleneheptenoic acids were prepared and subjected to Pd-catalyzed conditions. The cascades of both substrates were demonstrated to be highly regioselective, yielding two distinct 4-exo bicyclic frames, **31** and **32** (Scheme 4).[12] Even though both 4-exo and 5-endo cyclizations of **29** are possible,[12a,13] in practice, we have only detected exclusive regioselectivity to solely generate the rigid and rare 5/4 bicyclic scaffolds of type-**30**. To our delight, the dimethyloxaspirooctanone **32** was obtained in very good yield (80%) under the optimized conditions (Thorpe-Ingold effect).[14] The formation of **31**, on the other hand, was found to require a greater amount of catalyst; nevertheless, incomplete conversion was observed even after prolonged reaction time (36 h), and the starting material was recovered. The obtained 5/4 bicyclic frames are highly similar to scaffolds of natural products associated with the families of gelispirolides[15] and bourbonenolides[16] (representative examples are shown in Scheme 4). Thus, we believe our methodology will become a potential platform for future construction of these natural products and their structural analogues in a rapid and efficient manner.

In summary, we have developed an unprecedented cascade Wacker-type lactonization-Heck reaction for the formation of variously substituted bi- and tricyclic spiranoid lactones of different topology and stereochemical configurations. The transformation shows good functional group tolerability and broad substrate scope, overcoming the difficulties of previously reported studies. In addition, rarely reported palladium-catalyzed 4-exo-trig Heck-type cyclizations are demonstrated. We expect this methodology to find immediate application in the synthesis of biologically active natural products and their structural analogues.

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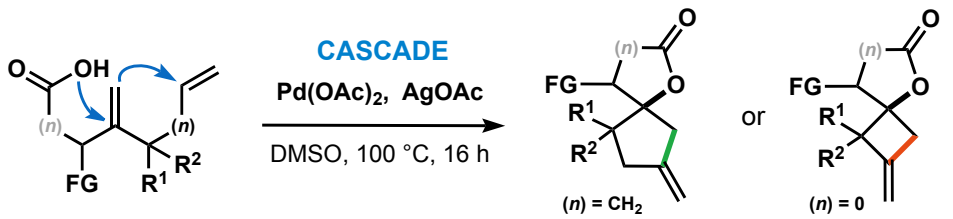

FG = Ar, Alk, Alkene, carbonyl, Het (O,S), dioxole, carbamate
R^1, R^2 = H or **Alk**

rare Pd-catalyzed 4-exo cyclization