Synthesis of chromanones: a novel palladium-catalyzed Wacker-type oxidative cyclization involving 1,5-hydride alkyl to palladium migration†

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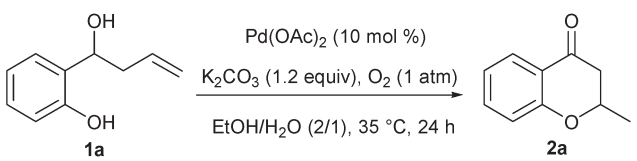
A series of 2-methylchromanone derivatives have been prepared by using a novel palladium-catalyzed Wacker-type oxidative cyclization, in which a 1,5-hydride alkyl to palladium migration and a direct chirality transfer were involved.

Chromanones are widely distributed in many natural products[1] and have many biologic activity such as anti-HIV-1 activity.[2] The construction of these compounds have attracted much attention in the synthetic community over the last few decades. Previously, the conventional methods for the building of chromanones mainly included: (a) oxo-Michael addition of *o*-tiglolylphenol,[3] (b) cyclization of the corresponding chromene with paraldehyde in the presence of special base,[2c] (c) intramolecular Friedel–Crafts reaction of 4-arylbutyric acid at high temperature (180 °C),[4] (d) selective reduction of chromone by calcium metal in liquid ammonia,[5] (e) oxidation of the corresponding alcohol,[6] and (f) gold catalyzed annulation of salicylaldehydes and aryl acetylenes at 150 °C for 36 h.[7] However, most of these reactions are limited by either complex starting materials or rigorous reaction conditions.

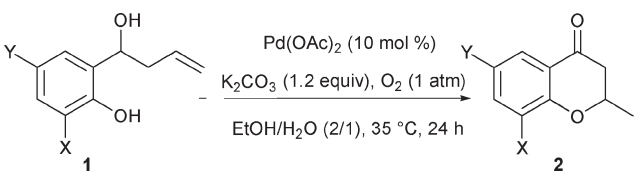
Palladium-catalyzed Wacker-type oxidative cyclization is one of the most important processes in the synthesis of heterocycles.[8] In this communication, we report a novel palladium(II) catalyzed Wacker-type oxidative cyclization to the synthesis of 2-methylchromanones **2** from easily obtained starting materials **1** (Scheme 1).[9] We also describe the preliminary mechanistic considerations for the reaction, which suggests this transformation *via* an unusual 1,5-hydride alkyl to palladium migration.

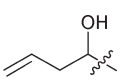
After the optimization of the reaction conditions (see ESI†), we were delighted to find that the treatment of **1a** with catalytic $Pd(OAc)_2$ (10 mol%) and potassium carbonate (1.2 equiv.) under an atmosphere of oxygen (1 atm)[10] in EtOH–H_2O (2 : 1) at 35 °C resulted in an oxidative cyclization and the generation of **2a** with a yield of 67% (Table 1, entry 1).‡ Under this mild condition, we examined the scope and the generality of the transformation. As can be seen from the results in Table 1, electron-donating groups on the phenyl ring of **1** favored the reaction and the corresponding chromanones **2** were obtained with good yields (entries 2–7) and weak electron-withdrawing groups had little influence on the cyclization (entries 8 and 9). On the other hand, a strong electron-withdrawing group on the phenyl ring retarded the reaction (entry 10), perhaps due to that the substituent group weakened the nucleophilicity of the hydroxyl. Even **1k**, which bears a C–Br bond and is sensitive to palladium catalyst, gave the desired product with moderate yield. Moreover, hydroxyl groups and carbon–carbon double bonds, which can be oxidized by palladium(II) complexes, survived in the reaction (entries 12 and 13).



Scheme 1 Wacker-type oxidative cyclization of **1a**.

Table 1 Palladium(II)-catalyzed Wacker-type cyclization[a]



Entry	Reagent	X	Y	Yield of **2**[b] (%)
1	**1a**	H	H	67
2	**1b**	H	MeO	80
3	**1c**	H	Me_3C	72
4	**1d**	H	Me	70
5	**1e**	MeO	H	76
6	**1f**	Me	H	83
7	**1g**	Me_3C	Me_3C	71
8	**1h**	Cl	H	70
9	**1i**	H	Cl	64
10	**1j**	H	MeCO	42
11	**1k**	H	Br	43
12	**1l**	H		65
13	**1m**	H		61

[a] *Reaction conditions*: 0.1 M of **1** in EtOH–H_2O (2 : 1). [b] Isolated yield.

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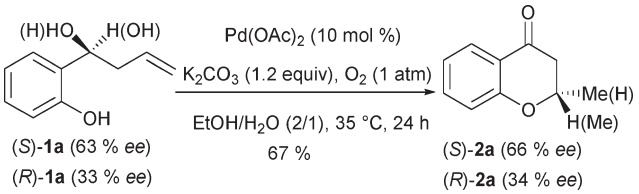
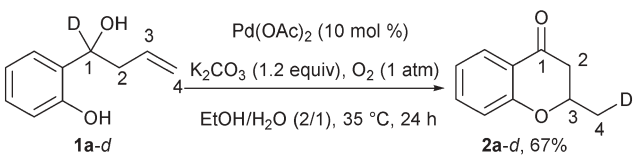
† Electronic supplementary information (ESI) available: Synthesis of substances, optimization of the reaction conditions, determination of the absolute stereochemistry and enantiomeric excess of **1a** and **2a**, proposed mechanism for pathway B and characterization data for the products. See DOI: 10.1039/b711613f



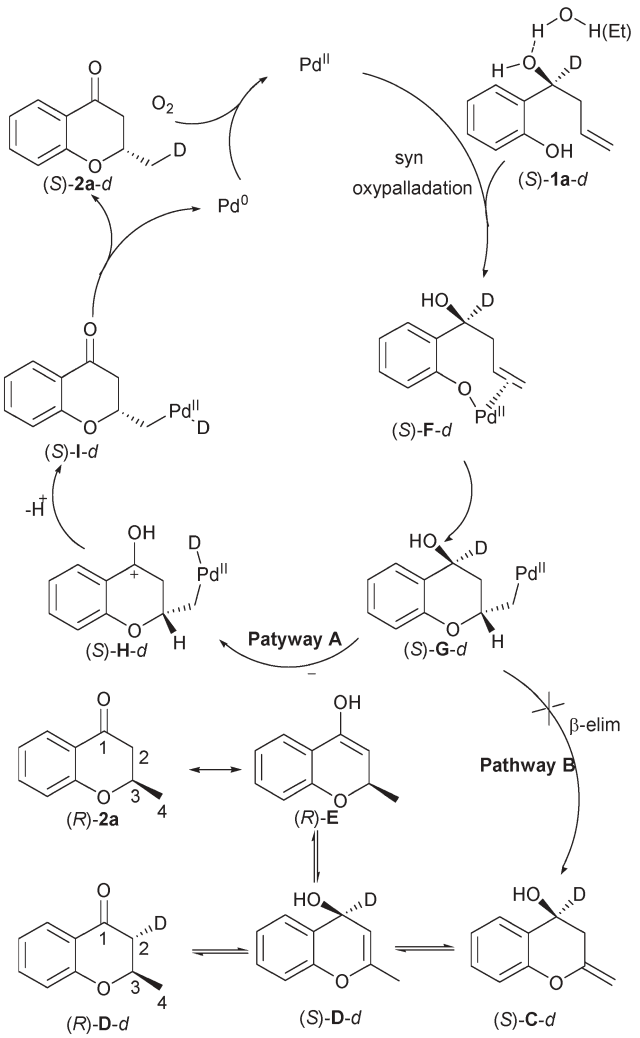
Scheme 2 Chirality transfer experiment of cyclization.

As the (+)- and (−)-chromanone derivatives have different anti-HIV activities,[2c] the asymmetric synthesis of 2-methylchromones become more valuable. We wonder whether enantioenriched **2a** could be obtained from enantioenriched **1a** directly through chirality transfer process.[11] We were delighted to find that enantioenriched (*S*)-**1a** or (*R*)-**1a** afforded enantioenriched (*S*)-**2a** or (*R*)-**2a**, respectively, under our conditions with excellent chirality transfer (Scheme 2). With this result in hand, it is reasonable to believe that enantioenriched chromanone derivatives can be realized under such mild conditions with enantioenriched starting materials.

Afterwards, the reaction mechanism was investigated. Initially, we envisioned the mechanism of this Wacker-type cyclization involving β-hydride elimination/hydropalladation sequences. To test this, a deuterium labeling experiment was designed and performed (Scheme 3).[12] To our surprise, when deuterium substrate **1a**-*d* was subjected to the standard reaction conditions, it was found that deuterium was transferred from C-1 in **1a**-*d* to C-4 in **2a**-*d* exclusively. This result can not be explained by the β-hydride elimination/hydropalladation sequences. A new mechanism was thus proposed on the basis of the deuterium labeling experiment. As shown in Scheme 4, (*S*)-**1a**-*d* was employed as an example to clarify the reaction process. We assumed that the hydrogen bond between hydroxyl of (*S*)-**1a**-*d* and solvent would inhibit the complexation of olefin with Pd(II) from the "hydroxyl-face" but form a complex with the opposite face to form (*S*)-**F**-*d*. When protic solvent was replaced with an aprotic solvent, experimentally, a trace amount of the corresponding product was obtained (see ESI†), which supported our assumption. Afterwards, the palladium–oxygen bond undergoing *syn*-oxypalladation in (*S*)-**F**-*d* affords (*S*)-**G**-*d*, which is well recognized by deuterium-labeling studies.[12a,b] Then (*S*)-**G**-*d* gives rise to the corresponding chromanone derivative *via* pathway A or B. If followed by β-hydride elimination as outlined in pathway B, either (*R*)-**2a** without deuterium or (*R*)-**2a**-*d* with deuterium at C-2, would be generated after several rearrangements (for details of the proposed mechanism for this pathway, see ESI†). Actually, these products was not observed in the reaction. Another process is feasible as described in pathway A. The palladium in (*S*)-**G**-*d* can come close to the *Si*-face deuterium at C-1 and catches this deuterium to form (*S*)-**H**-*d*. The resulting carbocation is efficiently



Scheme 3 Deuterium labelling experiment of Wacker-type cyclization.

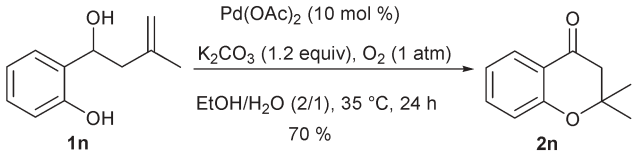


Scheme 4 Proposed mechanism for the Wacker-type cyclization of (*S*)-**1a**-*d* involving 1,5-palladium migration.

stabilized by the hydroxy group. Then the deprotonation of (*S*)-**H**-*d* produces (*S*)-**I**-*d*. Following reductive eliminations of deuterium and the alkyl group from palladium leads to (*S*)-**2a**-*d*. Overall, palladium at C-1 acts as a bridge which transfers a hydrogen atom from C-1 to C-4. In this transformation, the β-hydride elimination was suppressed absolutely by 1,5-hydride alkyl to palladium migration. To the best of our knowledge, this is the first time of a report of intramolecular 1,5-hydride alkyl to palladium migration. This mechanism is also in full agreement with the chirality transfer since the same configurations of C-1 in starting materials and C-3 in products implied an occurrence of *Si*-migration of the deuterium from C-1 to C-4 *via* a palladium bridge.

To further support this proposed mechanism, **1n** as a starting material without β-H was investigated as shown in Scheme 5. The cyclized product **2n** was obtained in 70% yield under the conditions. As **1n** has no β-H to eliminate, **2n** can not be obtained from pathway B. In contrast, its formation can be explained by pathway A. This result also supports the 1,5-hydride shift and excludes the β-H elimination process.

In conclusion, we have developed a palladium(II)-catalyzed Wacker-type oxidative cyclization for the synthesis of 2-methyl-chromanones from readily available starting materials under mild



Scheme 5 Cyclization of starting material **1n** without β-H.

conditions. A variety of chromanone derivatives were prepared with good yields by using this cyclization. In addition, deuterium labeling, chirality transfer and cyclization experiments using **1n** support the proposed mechanism which includes a novel 1,5-hydride alkyl to palladium migration. Work is currently being undertaken to better understand the migration and extend the scope of the reaction.

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Notes and references

‡ *Representative procedure* for Wacker-type cyclization: To a solution of **1a** (1 mmol, 164 mg) in 6.6 mL of EtOH and 3.3 mL of H_2O was added K_2CO_3 (1.2 mmol, 166 mg) and $Pd(OAc)_2$ (0.1 mmol, 22.4 mg). After the mixture was heated at 35 °C under an atmosphere of oxygen (1 atm) for 24 h, the ethanol was removed by reduced pressure and the residue was extracted three times with ethyl acetate. The combined organic extracts were dried using anhydrous Na_2SO_4 and evaporated under reduced pressure; the mixture was then purified by column chromatography over silica gel to afford product **2a** with high purity. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.88 (dd, J = 7.8 Hz, 1.5 Hz, 1 H), 7.50–7.44 (m, 1 H), 7.03–6.95 (m, 2 H), 4.63–4.56 (m, 1 H), 2.68 (d, J = 7.8 Hz, 2 H), 1.52 (d, J = 6.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 192.5, 161.7, 136.0, 127.0, 121.2, 120.9, 117.9, 74.3, 44.6, 21.0. IR (KBr film, cm^{-1}): ν = 2926, 1695, 1609, 1464, 1385, 1308, 1230, 1122, 1036, 949, 764, 569. HRMS: calc. $C_{10}H_{10}O_2$ (M^+): 162.0681, found: 162.0703.

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