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Efficient generation of an oxidopyrylium ylide using a Pd catalyst and its [5+2] cycloadditions with several dipolarophiles[†]

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An efficient method for the generation of an oxidopyrylium ylide from 6-acetoxy-6-acetoxymethyl-2*H*-pyran-3(6*H*)-one using a Pd catalyst and [5+2] cycloadditions of the resulting ylide are described. Among substituted styrene derivatives as dipolarophiles, electron-rich styrenes showed higher yield (up to 80%). The [5+2] cycloaddition reactions can also be applied to *exo*-methylene cyclic compounds, and an improved method for the synthesis of polygalolide intermediate has been demonstrated.

A number of natural products containing an 8-oxabicyclo[3.2.1]octane skeleton, such as englerins,¹ intricarene,² anthecularin,³ polygalolides,⁴ descurainin,⁵ and cartorimine,⁶ are biologically and medicinally important compounds (Fig. 1). In addition to being a common structural motif in numerous natural products, the [3.2.1]oxabicvclic ring system has also been shown to be a versatile intermediate for transformation to functionalized sevenmembered carbon skeletons.⁷ The [5+2] cycloaddition between oxidopyrylium ylides and alkenes is one of the best synthetic approaches to the 8-oxabicyclo[3.2.1]octane scaffold.⁸ In fact, these [5+2] cycloadditions were used for the construction of [3.2.1]oxabicyclic rings as the key step in the syntheses of englerins A and B,⁹ polygalolides A and B,¹⁰ descurainin,¹¹ and cartorimine¹¹ (Fig. 1).¹² Typically, oxidopyrylium ylides are generated from 2H-pyran-3(6H)-one derivatives by thermal, base-promoted, or acid-mediated elimination (Fig. 2, classical method).^{8,13,14} However, depending on the substitution pattern of the precursors such as 6-acetoxy-6-acetoxymethyl-2H-pyran-3(6H)-one (1), low yields of the cycloadducts can be problematic for the practical synthesis of the [3.2.1]oxabicyclic core. To overcome this issue, we hypothesized that Pd catalysis would enable efficient generation of the oxidopyrylium ylides through the formation of a π -allyl palladium species¹⁵ followed by deprotonation with a base (Fig. 2, a novel Pd-catalyzed method).



Fig. 1 The oxidopyrylium ylide [5+2] cycloadditions for syntheses of selected natural products containing an 8-oxabicyclo[3.2.1]octane skeleton.

Indeed, it has been known that [3+2] trimethylenemethane cycloaddition reactions are catalyzed by Pd(0) species effectively, in which 3-acetoxy-2-trimethylsilylmethyl-1-propene undergoes oxidative addition to form the π -allyl intermediate.^{16,17} Thus, we expected that π -allyl formation by a Pd catalyst may facilitate deprotonation by enhancing the acidity of the carbonyl α -proton. Furthermore, the catalytic generation under mild conditions would enable evaluation of the reactivity of dipolarophiles toward oxidopyrylium ylides based on their electronic properties. Herein, we report that the addition of a catalytic amount of [Pd(η^3 -C₃H₅)Cl]₂ in the presence of i-Pr₂NEt was found to be effective

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Fig. 2 Our novel Pd-catalyzed method vs. classical method.

for the efficient generation of an oxidopyrylium ylide from 2*H*-pyran-3(6*H*)-one **1**.

Initially, the reaction of 2*H*-pyran-3(6*H*)-one **1** with styrene (**2a**: 2.0 or 5.0 equiv.) as a model reaction was carried out in the presence of i-Pr₂NEt (1.0 equiv.) in CH₂Cl₂ (Table 1).¹⁸ In the absence of a Pd catalyst, low conversion (10–41%) of starting material **1** was observed even at 100 °C in toluene (entries 1–3). The addition of PdCl₂ (10 mol%) in CH₂Cl₂ (0.063 M) at 25 °C using 2.0 equiv. of **2a** resulted in 100% conversion of **1** in 16 h, and [5+2] cycloadducts **3a** were obtained in 24% NMR yield (*endo/exo* = 80:20) along with 15% NMR yield of by-product **4**, which corresponds to the dimer of the oxidopyrylium ylide (entry 4). PdCl₂/PPh₃ or Pd(PPh₃)₄ did not show satisfactory results in terms of the yield of the desired cycloaddition

Table 1 Optimization of reactions of 2H-pyran-3(6H)-one 1 with styrene

~ Dh-2a (2.0 or 5.0 equiv) i-Pr2NEt (1.0 equiv Pd-catalyst CH₂Cl₂ (0.063 M) endo-3a exo-3a Pd-Catalyst Temp Time Conv. Yield (%) of 3a (endo/exo)^{b,j} Entry (mol%) $(^{\circ}C)$ (h) (%)1 None 25 16 10 8 (81:19) 2 None 35 16 25 $16^{c}(82:18)$ 3 None 100 16 41 $36^{c}(78:22)$ 4^d $PdCl_2(10)$ $24^{c}(80:20)$ 25 16 100 5^d $PdCl_2/PPh_3$ (10) $27^{c}(79:21)$ 25 16 100 6^d 7^d 25 16 0 $Pd(PPh_3)_4$ (10) 100 $Pd_2(dba)_3(5)$ $16^{c}(84:16)$ 25 5 100 8 26 (81:19) $Pd_2(dba)_3(5)$ 25 3 100 $[Pd(al)Cl]_2^e(5)$ 9 72 68 (79:21) 25 100 $[Pd(al)Cl]_{2}^{e} (10)$ $[Pd(al)Cl]_{2}^{e} (5)$ 10 65 (80:20) 25 42 100 11 35 24100 60 (82:18) $\left[Pd(a) Cl \right]_{2}^{e}$ (10) 12 20 100 71 (81:19) 35

^{*a*} The reaction of 2*H*-pyran-3(6*H*)-one **1** (0.063 M) with styrene (5.0 equiv.) was carried out in the presence of i-Pr₂NEt (1.0 equiv.) in CH₂Cl₂. ^{*b*} Combined yield (isolated). The selectivity (*endolexo*) was determined by ¹H NMR analysis. ^{*c*} Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^{*d*} 2.0 equiv. of 2a. ^{*e*} [Pd(η^3 -C₃H₅)Cl]₂. ^{*f*} Yield of 4 (%); entry 2: trace, entry 4: 15%, entry 5: 25%, entry 7: 33%, entry 8: 29%, entry 9: trace, entry 10: 10%, entry 11: 8%, entry 12: 13%.

products (entries 5 and 6). The use of $Pd_2(dba)_3$ (5 mol%) shortened the reaction time to 5 h for 100% conversion, affording 16% (NMR yield) of cycloadducts **3a**, albeit with 33% (NMR yield) of dimer **4** (entry 7). The $Pd_2(dba)_3$ -catalyzed reaction in the presence of 5.0 equiv. of **2a** resulted in 26% yield of **3a** and 29% yield of **4** (entry 8). Finally, $[Pd(\eta^3-C_3H_5)Cl]_2$ was found to be the most suitable catalyst to obtain the highest yield of **3a** among the Pd catalysts tested (entries 9–12). After investigation of catalyst loading and reaction temperature, the conditions shown in entry 12 (10 mol% $[Pd(\eta^3-C_3H_5)Cl]_2$ at 35 °C) led to the best result [**3a**: 71% (isolated); **4**: 13% yield], which indicates that at least 84% of the corresponding oxidopyrylium ylide was generated.¹⁹

With the optimized conditions in hand, the substrate scope of several electron-deficient and electron-rich styrene derivatives was investigated (Scheme 1a). The reactions with styrenes **2b–2d** possessing electron-withdrawing substituents at the *para*-position resulted in lower yields (**3b–3d**: 53–69%) compared with that of styrene (71%), with the formation of dimer **4** in 12–16% yields. In contrast, electron-rich styrenes **2e–2i** afforded higher yields (**3e–3i**: 75–80%), especially in the case of *o*- or *p*-methoxy substituted styrenes, where the dimer formation was



Scheme 1 Pd-Catalyzed [5+2] cycloadditions of styrenes, vinyl ethers, and electron-deficient alkenes with the oxidopyrylium ylide generated from 2H-pyran-3(6H)-one **1**.

(2a)^a

minimized as expected (see the ESI⁺). To investigate the scope of electron-rich alkenes further, we selected *n*-propyl vinyl ether (5a) as a candidate for the dipolarophile. Although additional optimization of reaction conditions was required to suppress the production of dimer 4 (see the ESI[†] for details), the optimal yield (6a: 71%, endo only) was obtained using 0.2 equiv. of i-Pr₂NEt at a concentration of 0.13 M at 35 °C (Scheme 1b). Ethyl, cyclohexyl, and t-butyl vinyl ethers 5b-5d also provided only endo-cycloadducts 6b-6d in good yields (60-76%, Scheme 1b) under the same conditions. On the other hand, the Pd-catalyzed reactions with electron-deficient alkenes such as acrylic acid derivatives 7a and 7b and N-phenylmaleimide (7c) proceeded smoothly to give cycloadducts 8a-8c in moderate yields (62-65%, Scheme 1c). It is noteworthy that the employment of exo-methylene cyclic compounds 9a-9e as dipolarophiles in the cycloaddition reactions resulted in mostly good to high yields of cycloadducts (10a-10e: 61-88%), probably due to their relatively high reactivity as dipolarophiles on the basis of the exo-methylene structure (Scheme 2).

Conversion of cycloadduct 10c to polygalolide intermediate 11 was accomplished according to the modified Snider's method (Scheme 3).¹⁰ Treatment of 10c with Cs_2CO_3 in a 1:1 mixture of THF/H2O solvents at 35 °C for 14 h, followed by acidification with 10% hydrochloric acid to pH 1 furnished 11 in 76% yield over the two steps. The synthetic method of polygalolides A and B from 11 has already been reported by Nakamura and Hashimoto.²⁰ The overall yield from 1 to 11 (54%) was improved by the sequence of Pd-catalyzed [5+2] cycloaddition, hydrolysis, and intramolecular cyclization.

Finally, to gain insight into the mechanism of Pd catalysis for the generation of the oxidopyrylium ylide, control experiments using $Pd_2(dba)_3$ (10 mol%) in the absence and presence of i-Pr₂NEt (1.0 equiv.) were conducted and compared with the conditions of the non-catalytic reaction shown in entry 2 of Table 1 (Scheme 4).²¹



Scheme 2 Pd-Catalyzed [5+2] cycloadditions of exo-methylene cyclic compounds.



Scheme 3 Conversion of cycloadduct 10c to polygalolide intermediate 11.



² Determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard



In the presence of $Pd_2(dba)_3$ and i- Pr_2NEt , cycloadducts 3a (24%) and dimer 4 (29%) were obtained along with 2-pyranone 12 (6%), whereas only 2-pyranone 12 (72%) was afforded with the use of $Pd_2(dba)_3$ in the absence of i-Pr₂NEt, albeit with 100% conversion of 1a in both cases. Based on these results, we propose a plausible mechanism for this [5+2] cycloaddition as follows. (a) The initial reaction of 2H-pyran-3(6H)-one 1 with the Pd(0) species, which could also be generated from $[Pd(\eta^3-C_3H_5)Cl]_2$ and i-Pr₂NEt, produces the π -allyl palladium intermediate.^{15,22} (b) In the presence of i-Pr2NEt, the oxidopyrylium ylide is generated by deprotonation of the carbonyl α -proton of the π -allyl intermediate, wherein the Pd(0) species is regenerated along with formation of i-Pr₂NEt·HOAc. (c) The oxidopyrylium ylide reacts not only with dipolarophiles to afford cycloadducts but also with itself to afford a certain amount of dimer 4 depending on the reaction conditions. Since only β-elimination proceeds in the absence of i-Pr₂NEt and the combined use of a Pd catalyst and base obviously accelerates the cycloaddition, the transient π -allyl species seems to undergo deprotonation by i-Pr₂NEt more effectively than starting material 1.

In conclusion, we have demonstrated the productive generation of an oxidopyrylium ylide from 6-acetoxy-6-acetoxymethyl-2H-pyran-3(6H)-one (1) through Pd catalysis. A variety of dipolarophiles, including styrenes, vinyl ethers, and exo-methylene cyclic compounds, were tolerated to afford the cycloadducts in good to high yields. Conversion of the α -methylene- γ -butyrolactone cycloadduct to the polygalolide intermediate was also accomplished in an acceptable total yield (54%). Further studies for efficient generation methods and synthetic applications of oxidopyrylium ylide cycloadditions are currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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