

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 exomethylene 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 antheclarin,³ polygalolides,⁴ descourainin,⁵ and cartormine,⁶ are biologically and medically important compounds (Figure 1). In addition to being a common structural motif in numerous natural products, the [3.2.1]oxabicyclic ring system has also been shown to be a versatile intermediate for transformation to functionalized seven-membered 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 descourainin,¹¹ and cartormine¹¹ (Figure 1).¹² Typically, oxidopyrylium ylides are generated from 2*H*-pyran-3(6*H*)-one derivatives by thermal, base-promoted, or acid-mediated elimination (Figure 2, classical method).^{8,13,14} However, depending on the substitution pattern of the precursors such as 6-acetoxy-6-acetoxymethyl-2*H*-pyran-3(6*H*)-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 formation of a π -allyl palladium species¹⁵ followed by deprotonation with a base (Figure 2, novel Pd-catalyzed method). Indeed, it has

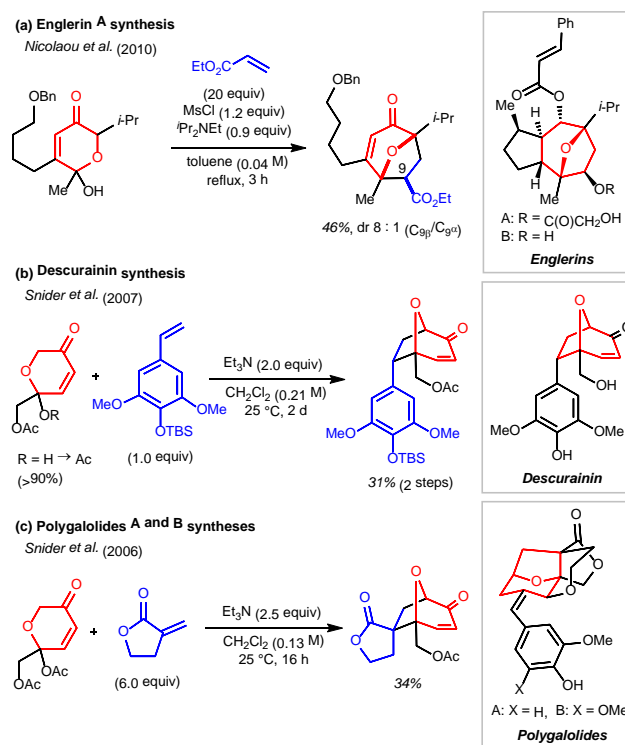


Fig. 1 The oxidopyrylium ylide [5+2] cycloadditions for syntheses of selected natural products containing an 8-oxabicyclo[3.2.1]octane skeleton

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 $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ in the presence of $i\text{-Pr}_2\text{NEt}$

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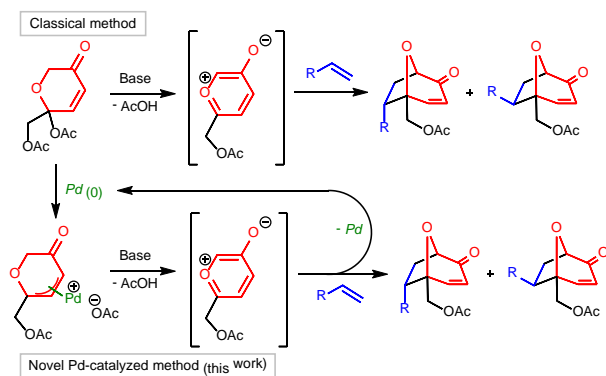


Fig. 2 Our novel Pd-catalyzed method vs. classical method

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

Initially, the reaction of 2H-pyran-3(6H)-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). 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,

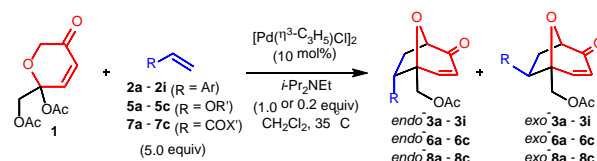
Table 1 Optimization of reactions of 2H-pyran-3(6H)-one **1** with styrene (**2a**)^a

Entry	Pd-catalyst (mol%)	Temp (°C)	Time (h)	Conv (%)	Yield (%) of 3a (<i>endo/exo</i>) ^{b,f}
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)	25	16	100	24 ^e (80 : 20)
5 ^d	PdCl ₂ /PPh ₃ (10)	25	16	100	27 ^c (79 : 21)
6 ^d	Pd(PPh ₃) ₄ (10)	25	16	100	0 ^c
7 ^d	Pd ₂ (dba) ₃ (5)	25	5	100	16 ^c (84 : 16)
8	Pd ₂ (dba) ₃ (5)	25	3	100	26 (81 : 19)
9	[Pd(al)Cl] ₂ ^e (5)	25	72	100	68 (79 : 21)
10	[Pd(al)Cl] ₂ ^e (10)	25	42	100	65 (80 : 20)
11	[Pd(al)Cl] ₂ ^e (5)	35	24	100	60 (82 : 18)
12	[Pd(al)Cl] ₂ ^e (10)	35	20	100	71 (81 : 19)

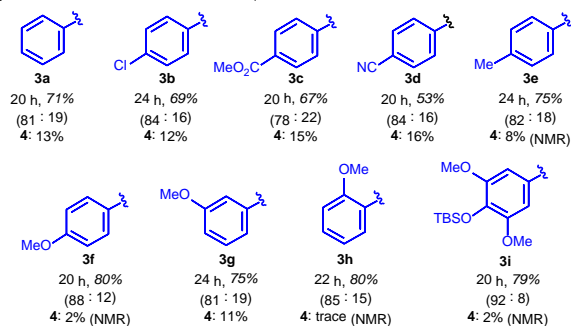
^a The reaction of 2H-pyran-3(6H)-one **1** (0.063 M) with styrene (5.0 equiv) was carried out in the presence of *i*-Pr₂NEt (1.0 equiv) in CH₂Cl₂. ^b Combined yield (isolated). The selectivity (*endo/exo*) was determined by ¹H NMR analysis. ^c Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^d 2.0 equiv of **2a**. ^e [Pd(η³-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%.

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 products (entries 5 and 6). The use of Pd₂(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 Pd₂(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(η³-C₃H₅)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(η³-C₃H₅)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

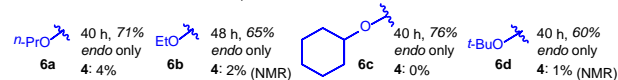
With the optimized conditions in hand, the substrate scope of several electron-deficient and electron-rich styrene derivatives was investigated (Scheme 1a). The reactions with styrenes **2b** – **2d** possessing electron-withdrawing substituents



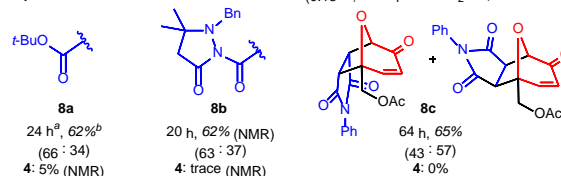
(a) Scope of styrene derivatives: **R = Ar** (0.063 M, 1.0 equiv of *i*-Pr₂NEt)



(b) Scope of vinyl ethers: **R = OR'** (0.13 M, 0.2 equiv of *i*-Pr₂NEt)

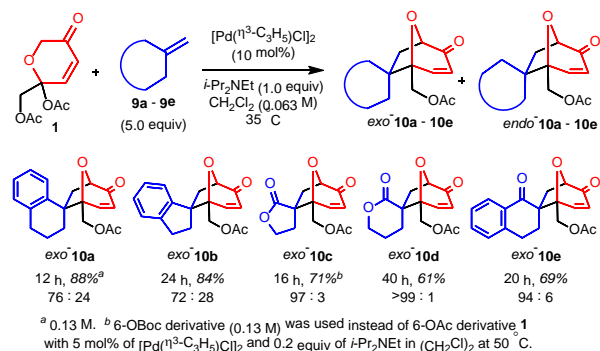


(c) Scope of electron-deficient alkenes: **R = COX'** (0.13 M, 1.0 equiv of *i*-Pr₂NEt)



^a 6-OBoc derivative was used instead of 6-OAc derivative **1** with 5 mol% of [Pd(η³-C₃H₅)Cl]₂ and 0.2 equiv of *i*-Pr₂NEt. ^b Regio selectivity 97%.

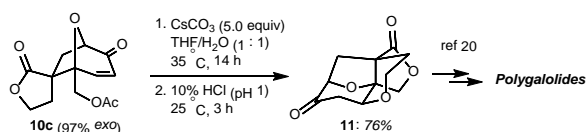
Scheme 1 Pd-catalyzed [5 + 2] cycloadditions of styrenes, vinyl ethers, and electron-deficient alkenes with the oxidopyrylium ylide generated from 2H-pyran-3(6H)-one **1**



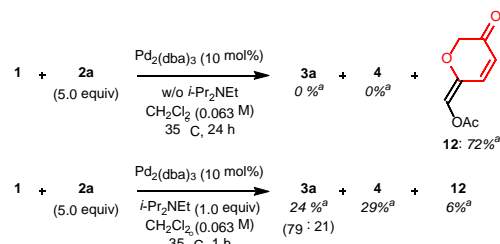
Scheme 2 Pd-catalyzed [5+2] cycloadditions of *exo*-methylene cyclic compounds

at the *para*-position showed lower yields (**3b** – **3d**: 53 – 69%) compared with that of styrene (71%), with 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 minimized as expected (see 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 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 Cs₂CO₃ 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



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



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

Scheme 4 Mechanistic studies: control experiments using Pd₂(dba)₃ in the absence and presence of *i*-Pr₂NEt

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 Pd₂(dba)₃ (10 mol%) in the absence and presence of *i*-Pr₂NEt (1.0 equiv) were conducted and compared with conditions of the non-catalytic reaction shown in entry 2 of Table 1 (Scheme 4).²¹ In the presence of Pd₂(dba)₃ and *i*-Pr₂NEt, 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 Pd₂(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 2*H*-pyran-3(6*H*)-one **1** with the Pd(0) species, which could also be generated from [Pd(η³-C₃H₅)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-acetoxymethyl-2*H*-pyran-3(6*H*)-one (**1**) by 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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- At the outset of our studies, several bases such as tertiary amines, secondary amines, inorganic bases have been tested. However, the reactions using most of them led to β -elimination or decomposition of starting material **1**.
- Dimer **4** was obtained in 73% (NMR yield) in the absence of styrene using 5 mol% of Pd₂(dba)₃ and 1.5 equiv of *i*-Pr₂NEt at 25 °C for 3 h in CH₂Cl₂ (0.063 M).
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- The use of [Pd(η^3 -C₃H₅)Cl]₂ (10 mol%) without *i*-Pr₂NEt under similar conditions (35 °C, 72 h) resulted in 97% recovery of **1** (by ¹H NMR).
- For the reaction of 2H-pyran-3(6H)-one **1** with Pd₂(dba)₃ in methanol-*d*₄, see ESI.