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Synthesis of substituted furans by platinum-catalyzed cyclization of propargylic oxiranes in aqueous media

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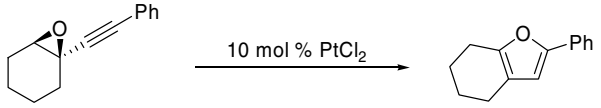
ABSTRACT

The reaction of propargylic oxiranes with platinum catalyst in aqueous media is described. Furans having a variety of substituents were conveniently synthesized with high efficiency.

Substituted furans are an important class of heteroaromatic molecules which are components in a variety of biologically active natural products and industrially useful compounds.[1] They are also extensively utilized as synthetic intermediates for acyclic, carbocyclic, and heterocyclic compounds in organic synthesis.[2] For these reasons, considerable effort has been devoted toward finding an efficient synthesis of substituted furans.[3] Cycloisomerization of propargylic oxiranes, in which a variety of reagents activate the reaction that leads to the corresponding substituted furans, is one of the most useful methodologies.[4] For example, Hashmi reported the gold-catalyzed cycloisomerization of propargylic epoxides to furans.[4h] The reaction allows the synthesis of substituted furans under mild conditions, but the reaction examples were limited to only 2,4-disubstituted furans, and the chemical yields were moderate to low. During the course of our studies on the reaction of propargylic oxiranes with a transition metal catalyst,[5] we focused on the reactivity of the platinum(II) catalyst.[6] We describe herein a platinum-catalyzed reaction of propargylic oxiranes, in which various substituted furans can be conveniently synthesized in aqueous media with high efficiency.

The initial reactions were carried out using the phenyl-substituted propargylic oxirane **1a**.[7] When **1a** was treated with 10 mol % of $PtCl_2$ in dioxane at 100 °C for 180 min, the tetrahydrobenzofuran **2a** was produced in 90% yield (Table 1, entry 1). Further attempts revealed that the presence of water enhanced the reactivity (entries 2 and 3). Thus, the reaction in dioxane/H_2O (2/1) was complete within 10 min to afford the product **2a** in 96% yield (entry 3). The yields of **2a** decreased as the temperature was lowered (entries 4–6). The reaction also proceeded in a mixture of various aqueous solvents to give **2a** in good yields (entries 7–11). The reactivity was maintained even in the presence of 5 mol % of platinum catalyst (entry 12), but with 2 mol % of catalyst

Table 1
Platinum-catalyzed cyclizations of **1a**



1a **2a**

Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	Dioxane	100	180	90
2	Dioxane/H_2O (1/2)	100	10	87
3	Dioxane/H_2O (2/1)	100	10	96
4	Dioxane/H_2O (2/1)	80	15	95
5	Dioxane/H_2O (2/1)	60	45	61
6	Dioxane/H_2O (2/1)	25	600	27
7	MeCN/H_2O (2/1)	100	40	76
8	THF/H_2O (2/1)	100	10	86
9	DMF/H_2O (2/1)	100	10	87
10	Toluene/H_2O (2/1)	100	60	91
11	DMSO/H_2O (2/1)	100	20	83
12[a]	Dioxane/H_2O (2/1)	100	10	94
13[b]	Dioxane/H_2O (2/1)	100	30	34
14[c]	Dioxane/H_2O (2/1)	100	10	10
15[d]	MeCN	25	36 h	21 (29)[e]

[a] 5 mol % of $PtCl_2$ was used.
[b] 2 mol % of $PtCl_2$ was used.
[c] 10 mol % of HCl was used.
[d] 10 mol % of $AuCl_3$ was used.
[e] The yield in parentheses is based on recovered starting material.

the production of **2a** decreased (entry 13). The Brønsted acid-catalyzed reaction in the presence of HCl also proceeded, but the yield was very low (entry 14). When **1a** was treated with 10 mol % of $AuCl_3$ in MeCN at rt in accordance with the Hashmi's procedure,[4h] the product **2a** was obtained in 21% yield (entry 15).

Table 2 shows our attempts using various substituted propargylic oxiranes **1b–i**. The reaction of **1b**, having a butyl group at the alkynyl position, with $PtCl_2$ yielded the tetrahydrobenzofuran

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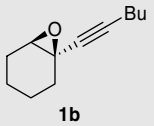
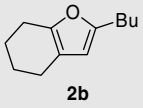
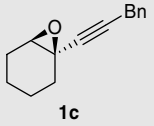
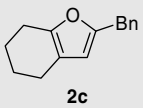
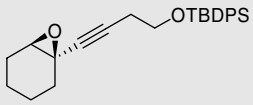
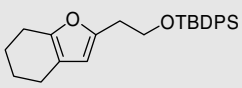
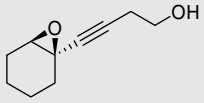
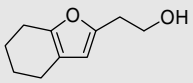
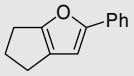
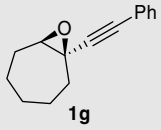
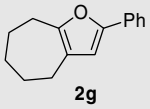
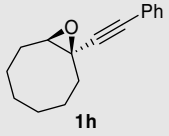
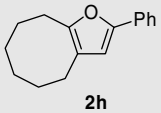
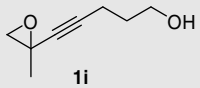
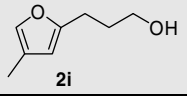
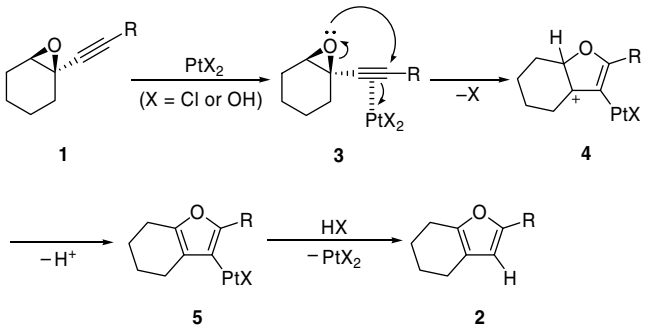
Table 2
Reactions with various propargylic oxiranes **1b–i**[a]

Entry	Substrate	Product	Yield (%)
1	 **1b**	 **2b**	83
2	 **1c**	 **2c**	92
3	 **1d**	 **2d**	92
4	 **1e**	 **2e**	79
5	 **1f**	 **2f**	34
6	 **1g**	 **2g**	92
7	 **1h**	 **2h**	89
8	 **1i**	 **2i**	90

[a] All reactions were carried out in the presence of 10 mol % of $PtCl_2$ in dioxane/H_2O (2/l) at 100 °C for 10 min.

2b in 83% yield (entry 1). The benzyl- and silyloxyethyl-substituted propargylic oxiranes **1c** and **1d** were transformed into the corresponding products **2c** and **2d**, each in 92% yield (entries 2 and 3). Furthermore, the propargylic oxirane with a free hydroxyl group, **1e**, was converted to **2e** in 79% yield (entry 4). When the cyclopentyl-substituted substrate **1f** was subjected to the reaction, 5,6-dihydrocyclopentafuran **2f** was obtained in 34% yield (entry 5). The low yield reflects the difficulties in constructing the strained 5,6-dihydro-4*H*-cyclopenta[*b*]furan ring system. Reactions of the substrates **1g** and **1h**, which contain seven- and eight-membered rings, successfully afforded the corresponding furans **2g** and **2h** in 92% and 89% yields, respectively (entries 6 and 7). When the reaction of the acyclic propargylic oxirane **1i** was carried out, the 2,4-disubstituted furan **2i** was produced in 90% yield (entry 8).[8]

A plausible mechanism for the reaction is shown in Scheme 1. The platinum catalyst activates the carbon–carbon triple bond in the substrate **1** for the addition of the nucleophile by coordination as shown in **3**. The epoxide-oxygen attacks the distal position of the alkyne to form the cyclized intermediate **4**. Aromatization by elimination of the proton followed by proto-demetallation from the resulting furanyl-platinum species **5** produces the furan **2**.

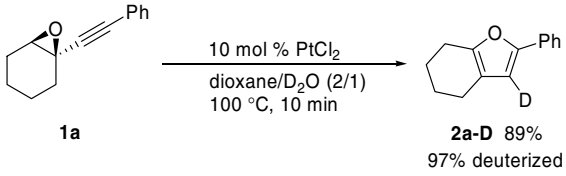


Scheme 1. Proposed reaction mechanism.

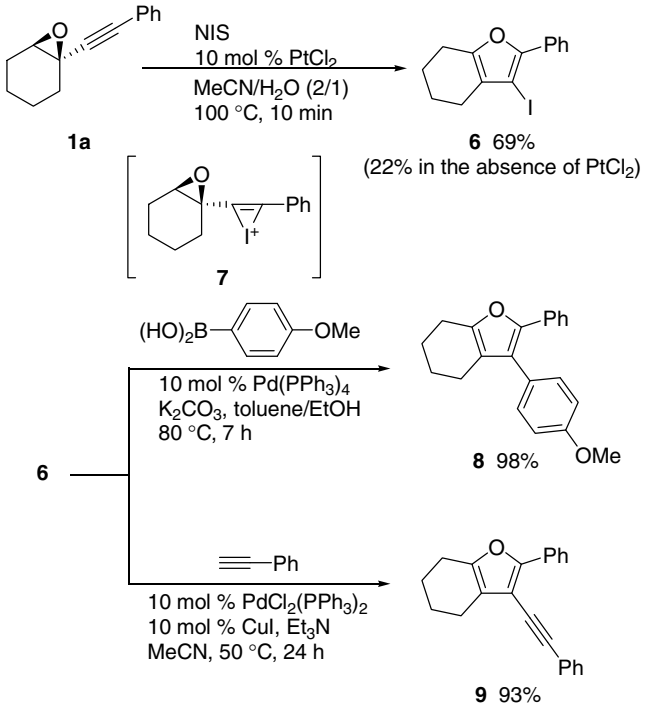
Although the cause of the increased reactivity under aqueous conditions is not clear, it is presumed that the platinum hydroxide complex, which would enhance the reactivity of the proto-demetallation from the intermediate **5**, exists as an active species in the aqueous media.[9]

Information on the reaction mechanism was gained when the reaction of **1a** was conducted in D_2O (Scheme 2). In this case, 97% of deuterium was incorporated at the 3-position on the furan ring to give **2a-D** in 89% yield. The result supports the hypothesis that the reaction proceeds via the formation of the furanyl-platinum intermediate **5**.

To further highlight the potential of this process, we tried to trap the furanyl-platinum species with electrophilic iodine prior



Scheme 2. Reaction in the presence of D_2O.



Scheme 3. Synthesis of tetra-substituted furans.

to protonation.[10] Finally, after several attempts, the 3-iodotetrahydrobenzofuran **6** was produced in 69% yield as the sole product when the substrate **1a** was treated with NIS in MeCN/H_2O (2:1) at 100 °C (Scheme 3). The product **6** was obtained even in the absence of platinum catalyst, but the yield was decreased to 22%. This result indicates that the reaction also proceeds via the iodonium intermediate **7**, but the pathway involving the furanyl-platinum species **5** is preferred. The presence of the iodo functional group on the furan ring provided an opportunity for further functionalization. For example, the 4-methoxyphenyl group was introduced to give **8** in 98% yield using the Miyaura–Suzuki coupling reaction of **6** with 4-methoxyphenylboronic acid. Furthermore, **6** underwent Sonogashira coupling with phenylacetylene to produce the corresponding 3-alkynylfuran **9** in 93% yield.

In conclusion, we have developed a methodology for the synthesis of substituted furans using a platinum catalyst. The reactions afforded a variety of substituted furans under aqueous conditions, and the process provided an efficient and convenient protocol for the preparation of furan derivatives. Efforts to extend the scope of these reactions and their consequent application to the syntheses of natural products are currently in progress.

Acknowledgements

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7. *General procedure for platinum-catalyzed reactions*: To a stirred solution of the propargylic oxirane **1a** (30.0 mg, 0.151 mmol) in 1,4-dioxane/H_2O (2:1) was added $PtCl_2$ (4.0 mg, 0.015 mmol) at rt. After stirring for 10 min at 100 °C, the mixture was cooled to rt and diluted with a minimum amount of Et_2O. The solution was then dried over $MgSO_4$ and filtered through a small amount of silica gel. Concentration at reduced pressure gave the residue, which was chromatographed on silica gel with pentane Et_2O (97:3) as eluent to give the tetrahydrobenzofuran **2a** (28.80 mg, 96%) as a colorless oil. IR (neat) 3079, 3058, 2926, 2849, 1634, 1603, 1549, 1486, 1443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, J = 7.2 Hz), 7.39–7.29 (2H, m), 7.19 (1H, t, J = 7.2 Hz), 6.47 (1H, s), 2.66 (2H, t, J = 6.0 Hz), 2.45 (2H, t, J = 6.0 Hz), 1.89–1.86 (2H, m), 1.85–1.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.53, 150.75, 131.38, 128.51, 126.49, 123.19, 118.94, 105.97, 31.83, 29.69, 23.25, 23.10, 23.04, 22.10. HRMS (ESI) m/z calcd for $C_{14}H_{14}ONa$ 221.0942 (M^++Na), found 221.0936.
8. Hashmi also reported the converion of **1i** using a gold catalyst, in which the reaction was complete in 17 h to afford **2i** in 80% yield; see Ref. 4h.
9. Enhancement of the reactivity for the gold-catalyzed reaction in water has been reported: Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 1953.
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