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Palladium-Catalyzed Intermolecular Heck-Type Reaction of Epoxides

Shenghan Teng, Malcolm E. Tessensohn, Richard D. Webster and Jianrong Steve Zhou*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

Supporting Information Placeholder

ABSTRACT: Palladium-catalyzed intermolecular Heck-type reaction of both cyclic and acyclic epoxides is reported with tolerance of typical polar groups and acidic protons. Suitable alkenes include styrenes, conjugate dienes and some electron-deficient olefins. In reactions of aliphatic terminal epoxides, ring opening occurs selectively at terminal positions and stereocenters of epoxides are fully retained. Mechanistic studies provide evidence for in situ conversion of epoxides to β -halohydrins, generation of alkyl radicals and addition to alkenes as key steps. Cyclic voltammetric determination of reduction potentials suggests that during activation of alkyl iodides by palladium(0) complexes, inner-sphere halogen abstraction is more likely than outer-sphere single electron transfer.

KEYWORDS: Heck reaction, palladium catalysis, alkylation, epoxides, alkyl radicals

Epoxides are versatile in cross-coupling reactions due to ready availability and high tendency towards ring opening with various nucleophiles.¹ In recent years, there has been significant advance in unconventional Heck reaction of unactivated alkyl halides and other alkyl precursors,² but the success of Heck-type alkylation with another common family of alkyl electrophiles, epoxides remains very limited.^{3.4} The products from these reactions, homoallylic alcohols are commonly used in organic synthesis.

(a) Cobalt-catalyzed reaction of epoxides with styrene

$$R \xrightarrow{O} Ph \frac{\text{cat. CoBr_2(dpph)}}{\text{TMSCH_2MgBr 2.5 equiv}} R \xrightarrow{OH} OH OH$$

$$R \xrightarrow{Ph + Ph + Ph} Ph \xrightarrow{Ph + Ph} Ph$$

Strongly basic Grignard reagents are incompatible with polar groups

(b) Palladium-catalyzed Heck-type reaction of epoxides



(c) Attempts at Pd-catalyzed Heck-type reaction using β -iodohydrins



Scheme 1. Examples of Heck-type reaction of epoxides and β -iodohydrins

For example, in 2004, Oshima *et al.* reported Heck-type reaction of epoxides and styrene using a cobalt catalyst ligated with bis(diphenylphosphino)hexane (dpph) as depicted in Scheme 1a.^{3a} Unfortunately, the use of strongly basic Grignard reagents severely limited the compatibility of polar groups in this reaction. In 2016, Morandi *et al.* also reported cobalt-catalyzed intramolecular cyclization between epoxides and alkenes that quickly cyclized to form 5- and 6-

membered rings.^{3b} Unfortunately, strong base NaO*t*-Bu was used in methanolic solvent.

Herein, we report a palladium-catalyzed Heck-type reaction of both cyclic and acyclic epoxides (Scheme 1b). In comparison, direct coupling of a β -iodohydrin and styrene led to low yield of the desired product (30%), under the conditions that we prescribed for Heck-type alkylation with alkyl halides (Scheme 1c).⁵ Other byproducts included cyclohexanone (45%), cyclohexanol (5%) and a small amount of bicyclic ethers (14%). Furthermore, our efforts in trying other Pd catalysts and conditions did not lead to satisfactory results. For example, a catalyst of Pd(PPh₃)₄ and Xantphos together with Et₃N base furnished 55% yield of two isomers in a trans/cis ratio of 3:1.

a)

$$Et_3N+HI \xrightarrow{HO}_{30 \circ C, 2h}^{-1}$$

b) $PhO \xrightarrow{eO}_{13}Et_3N+HI \xrightarrow{HO}_{30 \circ C, 2h}^{-1}$
 $Et_3N+HI \xrightarrow{HO}_{100\%}^{-1}$
c) $Ph \xrightarrow{O}_{100\%}^{-1}$
 $Et_3N+HI \xrightarrow{HO}_{100\%}^{-1}$
 $B0 \circ C, 2h$
 $PhO \xrightarrow{I}_{100\%}^{-1}$
 $Ph \xrightarrow{OH}_{100\%}^{-1}$
 $Ph \xrightarrow{OH}_{17\%}^{-1}$
 $Ph \xrightarrow{OH}_{13\%}^{-1}$
 $(90\% \text{ conversion})$



In our reaction design, a catalytic amount of an alkylamine salt of HI is used to open epoxides in situ under palladium-catalyzed reaction conditions.⁶ The resulting β -iodohydrins then participate in palladium radical catalysis⁷ with alkenes such as styrenes, while the resulting free alkylamine can function as the base in the later partof the Heck-type catalytic cycle. Thus, a mild, nearly neutral condition can be maintained during catalysis and the use of strong bases avoided. After many trials, we identified that 0.2 equiv of Et₃N·HI was sufficient for rapid ring opening of cyclohexene oxide at 80 °C after 2 hours in dioxane or trifluorotoluene, while a terminal aliphatic epoxide underwent exclusive ring opening at the terminal carbon (Scheme 2a-b). In contrast, the reaction of styrene oxide was less regioselective with a ratio of 3.5:1, along with an aldehyde as side product (Scheme 2c).

In a model reaction between cyclopentene oxide 1a and styrene, we established that the use of Pd(PPh₃)₄ (5 mol%) and Xantphos (7 mol%) resulted in 80% yield of 3a with a 10:1 trans/cis ratio (Table 1, entry 3). Other palladium sources $Pd(OAc)_2$ and $Pd(dba)_2$ led to worse results than Pd(PPh₃)₄ (entries 1-2). To our surprise, the performance of the palladium catalysts was highly dependent on natural bite angles of chelating bisphosphines (entries 7-10). For example, the Pd catalysts of dppp or BINAP furnished <10% yield of 3a, while the catalyst of DPEphos or dppf led to only 40% yield. When the solvent was switched to dioxane, toluene and veratrole (1.2dimethoxybenzene), the yield of 3a was 73%, 55% and 70%, respectively. Furthermore, the model reaction did not need additional bases. We found that inorganic bases K₃PO₄ and Cs₂CO₃ inhibited the productive pathway, while addition of 1.5 equiv of Et₃N and *i*-Pr₂NEt led to lower yields of 3a (60% and 57%, respectively). Cy2NMe (1.5 equiv) did not have any deleterious effect (entry 4). Reducing the stoichiometry of 1a to 1.5 equiv resulted in 75% yield of 3a.

Under the optimized conditions with 5 mol% Pd catalyst and Xantphos, many substituted styrenes coupled with satisfactory yields and good *trans* selectivity on the cyclic ring and the products contained exclusively (*E*)-geometry (Scheme 3). We established that both electron-donating and electron-withdrawing groups were tolerated on the styrenes. In particular, alcohols, esters (**3d** and **3h**), a nitrile (**3k**), an acetal (**3g**), a methyl ketone (**3i**) and an indole (**3n**) were compatible with the reaction conditions. Moreover, an *ortho*-methyl group can be present in a styrene derivative (**3f**). In the example of **3g**, addition of Cy₂NMe improved the yield from 42% to 70%. The configuration of the major isomer of **3i** was determined to be *trans* by X-ray diffraction.⁸ Moreover, 1,1-diphenylethylene also coupled with epoxide **1a** to produce **3o** in high yield, while in reaction of *a*-methylstyrene, Pd/dppf was a better catalyst delivering terminal alkene **3p** as major isomer.

 Table 1. Optimization of conditions for Heck-type reaction of a model epoxide

	0 1a (2 equiv)	Ph Photophic (7 in the second	mol%) mol%) ol% C, 48 h 3a	Ph
Entry	Pd source	Phosphine	Conv (%)	Yield (%) $(trans/cis)^b$
1	$Pd(OAc)_2$	Xantphos	50	36 (8:1)
2	Pd(dba)2	Xantphos	48	41 (8:1)
3	Pd(PPh ₃) ₄	Xantphos	87	80 (10:1)
4 ^{<i>a</i>}	Pd(PPh ₃) ₄	Xantphos	87	80 (10:1)
5	Pd(PPh ₃) ₄	none	96	30 (8:1)
6	Pd(PPh ₃) ₄	PCy ₃	57	2
7	Pd(PPh ₃) ₄	dppp	55	0
8	Pd(PPh ₃) ₄	rac-BINAP	70	6
9	Pd(PPh ₃) ₄	DPEphos	90	36 (7:1)
10	Pd(PPh ₃) ₄	dppf	78	42 (8:1)



Scheme 3. Examples of Heck-type reaction of cyclopentene oxide



Scheme 4. Examples of Heck-type reaction of cyclohexene oxide and other cyclic epoxides

We next studied other cyclic epoxides in the Heck-type reaction (Scheme 4). Cyclohexene oxide also reacted with good efficiency with both electron-rich and deficient styrenes, but the trans/cis selectivity was only around 3:1. Notably, very little cyclized byproducts of the

^{*a*} 1.5 equiv of Cy₂NMe was added. ^{*b*} Trans/cis ratio was determined by GC.

fused tetrahydrofurans were detected in the reaction of **1b** and **2a** (2% yield; see Scheme 1c). We also found that cycloheptene oxide was reactive and delivered products **4f** and **4f** in high yields, in a ratio of 4.5:1. Interestingly, other five-membered cyclic epoxides such as 2,5-dihydrofuran oxide and 3,3-disubstituted cyclopentene oxides afforded desired products **4g** and **4h** in a good trans selectivity (>10:1). However, cyclooctene oxide led to low conversion.

We also tested some elaborate cyclic epoxides that have preexisting stereocenters on the ring framework. Remarkably, treatment of (+)*trans*-limonene oxide **1c** with styrene resulted in two diastereomers **4i** and **4i**' with a ratio of 3:1 (Scheme 4b). The configuration of the major isomer **4i** was assigned by a strong NOE signal between hydrogen atoms H² and H⁴. Notably, the new C-C bond in both isomers was formed selectively at the less-substituted carbon of the epoxide. Similarly, β -epoxide **1d** derived from pregnenolone acetate also ringopened at the less-substituted carbon of the strained ring and the new C-C bond in the major product **4j** was formed at the equatorial position, too (Scheme 4c).



Scheme 5. Examples of Heck-type reaction of acyclic epoxides

This Heck-type reaction is not confined to cyclic epoxides. Various terminal epoxides in Scheme 5 delivered the desired products in the presence of a combination of catalytic Pd(PPh₃)₄ and dppf. In comparison, the Pd catalyst of Xantphos gave 5c in only 21% yield. The terminal epoxides opened selectively at the less hindered terminal carbon, with a ratio of >10:1 in most cases. Previously, NH4I was reported to regioselectively open aliphatic epoxides at the less hindered carbon.⁶ The catalytic alkylation was carried out successfully with monoalkyl, 1,1-dialkyl and benzyl substituted epoxides, which resulted in predominant C-C bond formation at the less substituted carbon center of epoxides. Interestingly, nearly enantiopure glycidyl ethers 1f-1h (R = Ph, H and TBS) reacted smoothly under the reaction conditions and delivered the desired products with almost no loss of enantiomeric excess. Unfortunately, we found that enantiopure styrene oxide 1i afforded both products 5n and 5n' in 42% yields, along with a significant amount of byproduct 5n", which was derived from epoxide isomerization to phenylacetaldehyde and subsequent self-aldol condensation.⁹ Notably, **5n** was obtained in only 60% ee. Close examination of the reaction mixture revealed that starting material **1i** underwent partial racemization under the catalytic conditions, for example, its ee value decreased to 88% and 66% after 10 min and 30 min, respectively.



Scheme 6. Examples of Heck-type reaction using 1,3-dienes and electrondeficient alkenes



Scheme 7. Mechanistic studies

Other types of olefins also reacted well (Scheme 6). We found that conjugate dienes such as **2b** and **2c** furnished the corresponding products **6a** and **6b** in good yields. The alkylation proceeded selectively at the terminal position of the dienes. We found that in reactions of electron-deficient *a*-phenylacrylate **2d** and *a*-phenylacrylamides, the alkylation occurred at the terminal carbon of the alkenes to provide (*Z*)-isomers selectively, although the trans/cis ratio on the cyclopentane ring was in the range of 2:1 to 3:1. Moreover, coumarins **2e-f** and *N*-methyl-2-quinolinone also reacted smoothly under the catalytic conditions and notably, the alkylation took place selectively at C3 positions, as confirmed by X-ray crystallography (**6f-h**).⁸ Similar regioselectivity was also reported by Zhang *et al.* in Pd-catalyzed difluoroacetylation of coumarins and quinolinones, which is known to be sensitive to a combination of both electronic and steric effects.^{2f} Unfortunately, methyl

60

1

acrylate and acrylonitrile did not give Heck-type products due to phosphine-promoted polymerization.¹⁰

To understand the reaction mechanism, we initially examined stoichiometric reactions of in situ formed palladium(0) complex of Xantphos with iodohydrin 1j. It formed cyclohexanone and cyclohexanol (83% yield) in a ratio of 11:1 (Scheme 7a). A similar conversion of β -bromohydrins to ketones under photolysis was reported previously.¹¹ Another stoichiometric reaction of the palladium(0) complex with cyclohexene oxide 1b gave similar results in the presence of 1 equiv of Et₃N·HI (77% yield of cyclohexanone and cyclohexanol), while no such a reaction was detected in the absence of Et₃N·HI (Scheme 7b). Additionally, when 1 equiv of TEMPO was added to the model catalytic reaction of cyclopentene oxide 1a and styrene, no desired C-C bond formation was detected. Instead, a TEMPO adduct 7a of β hydroxycyclopentyl radical was isolated in 23% yield; its configuration was determined to be cis (Scheme 7c).¹² The main byproduct in this reaction was found to be cyclopentanone. If the Pd catalyst was omitted in the reaction above, none of the products were detected.

Next, we used a styrene derivative **2f** with *a*-cyclopropyl group in alkylation with epoxide **1a**. It afforded byproduct **7b** in 37% yield, via opening of the cyclopropyl unit (with the ring opening rate of 6×10^4 s⁻¹)¹³ and subsequent radical cyclization on the arene ring (Scheme 7d). Furthermore, we tested an epoxide **1k** carrying a pendant homoallyl group. Only ring-closure isomers **7c** with styrene were isolated (Scheme 7e).

Herein, we propose a catalytic cycle, taking into account of reduction potentials of (Xantphos)PdI (Scheme 8a). The β -iodohydrin, which is in situ produced from the epoxide and Et₃N·HI, reacts with (Xantphos)palladium(0) species to give out β -hydroxyalkyl radical **A** and a (L-L)PdI complex.¹⁴ The latter complex behaves like a persistent radical.¹⁵ In cyclic voltammetry in CH₂Cl₂, the reduction potential of β iodohydrin (-2.2 V vs Fc⁺/Fc) was determined to be much more negative than half-wave reduction potential of (Xantphos)PdI (-1.5 V vs Fc⁺/Fc). Thus, we deduce that an outer-sphere single electron transfer between (phosphine)Pd(0) and alkyl iodides is unfavorable with an endergonics of +16 kcal-mol⁻¹. An alternative mechanism of innersphere halogen abstraction is more likely.

(a) A proposed pathway



Scheme 8. A proposed reaction pathway and discount of involvement of a benzylic cation

Next, radical **A** adds to styrene to produce benzylic radical **B**, which is a fast process.¹⁶ Radical **B** then combines with (L-L)PdI to form alkylpalladium(II) species **C**, followed by β -H elimination¹⁷ to deliver the olefinic product. An alternative pathway involving electron transfer from radical **B** to complexes of Pd(I) (Scheme 8b) or Pd(II) to form benzyl cation **D** is unlikely, owing to high endergonics of the reaction. The half-wave oxidation potential of a secondary benzylic radical is around 0.0 V vs Fc⁺/Fc,¹⁸ while half-wave reduction potentials of (Xantphos)PdI and (Xantphos)PdI₂ were -1.5 V and -1.0 V vs Fc⁺/Fc, respectively. We also discounted a third possibility of a radical chain reaction between benzylic radical **B** and β -iodohydrin, since the resulting radical is much less stable than **B**. Previously, we ruled out a pathway involving based elimination of benzylic halides as key intermediates to produce olefins in Heck-type alkylation.⁵

In summary, we reported Pd-catalyzed intermolecular Heck-type reaction of epoxides and olefins, which was compatible with many sensitive polar groups and acidic hydrogens. In reactions of unsymmetrical epoxides, new C-C bonds were formed regioselectively at the less-substituted positions of epoxides. Moreover, configurations of stereocenters in aliphatic terminal epoxides were well preserved. In comparison, Heck-type alkylations using β -hydroxyalkyl iodides resulted in low yields of alkenes, due to formation of ketones as a major side reaction. There is an advantage of in situ generating β -hydroxyalkyl iodides from epoxides, by maintaining transient alkyl radicals in low concentrations under catalytic conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization of compounds and mechanistic studies.

Supporting information experimental procedures.pdf

Supporting information NMR charts.pdf

AUTHOR INFORMATION

Corresponding Author

E-Mail: jrzhou@ntu.edu.sg

ORCID

Jianrong Steve Zhou: 0000-0002-1806-7436

Notes

The authors declare no competing financial interest.

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