

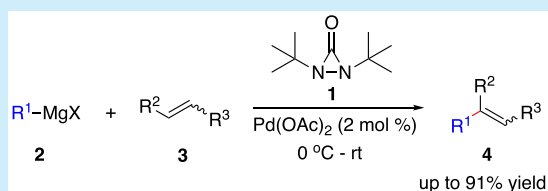
Pd-Catalyzed Oxidative Heck Reaction of Grignard Reagents with Diaziridinone as Oxidant

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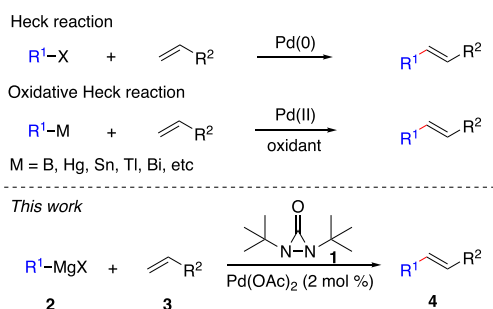
S Supporting Information

ABSTRACT: A novel Pd-catalyzed oxidative Heck reaction with readily available Grignard reagents using di-*t*-butyldiaziridinone as an oxidant has been developed. Various substituted olefins were obtained in 46–91% yields with high regioselectivity under mild reaction conditions.



The Heck reaction is one of the most powerful methods for C–C bond formation and has been widely used in the synthesis of various biologically active and chemically important molecules.¹ Aryl or alkenyl halides and their analogues are traditionally used in this reaction. During the last two decades, the oxidative Heck reaction involving cross coupling of olefins and organometallic compounds in the presence of an oxidant has been developed into a useful complementary process (Scheme 1).² Various organometallic reagents and related

Scheme 1. Pd-Catalyzed Oxidative Heck Reaction of Grignard Reagents



compounds, such as organoborons,³ organomercurials,⁴ organothalliums,⁵ organobismuths,⁶ organotelluriums,⁷ organosilicones,⁸ organotinns,⁹ and others,^{10–12} have been well investigated for such a reaction process. Surprisingly, Grignard reagents, a class of highly accessible and widely used organometallic compounds, have rarely been applied to the oxidative Heck reaction.¹³ Therefore, the development of an oxidative Heck process with Grignard reagents still remains a challenge.

Previously, we have shown that di-*t*-butyldiaziridinone (**1**) is a highly versatile reagent for the diamination of olefins.¹⁴ Our recent studies found that it can also serve as an oxidant for the Cu(I)-catalyzed oxidation of alcohols^{15a} as well as coupling of amines,^{15b} terminal alkynes,^{15c} and Grignard reagents.^{15d} In a further exploration of its reactivity, we have discovered that di-*t*-butyldiaziridinone can effectively promote the oxidative

Heck reaction of Grignard reagents under mild conditions (Scheme 1). Herein we report our preliminary results on this subject.

Grignard reagent **2a** and styrene (**3a**) were used as test substrates for our initial studies for the oxidative coupling (Table 1). To our delight, coupling products **4a** and **5a** were formed in 91% conversion when **2a** and **3a** were treated with di-*t*-butyldiaziridinone (**1**) and 2 mol % Pd(OAc)₂ in ether at room temperature (Table 1, entry 1). No coupling products were formed in the absence of Pd (Table 1, entry 2). High conversion and good regioselectivity were obtained when the reaction was carried out in Et₂O/THF (5:1) at 0 °C to rt (Table 1, entry 4). Higher regioselectivity with lower conversion was obtained with 1,4-dioxane as solvent (Table 1, entry 5). Among the Pd catalysts examined (Table 1, entries 4 and 8–11), Pd(OAc)₂ was the best. Lower conversions were obtained with ligands added (Table 1, entries 12–14). Poor conversions were obtained with other oxidants (Table 1, entries 15–20).

Under the optimized conditions, various aryl Grignard reagents (**2a–f**) reacted effectively with styrene (**3a**) to give the corresponding stilbenes **4a–f** in 46–72% yields with high regioselectivity (Table 2). The Grignard reagents preferentially added at the terminal carbon of styrene (**3a**) in these cases. Sterically hindered Grignard reagents such as (2,6-dimethylphenyl)magnesium bromide (**2e**) and (2,4,6-trimethylphenyl)magnesium bromide (**2f**) were also shown to be effective for the reaction (Table 2, entries 5 and 6). In some cases, the low yields obtained were likely due to the competing homocoupling of the Grignard reagents. Few Heck products were obtained with alkyl Grignard reagents such as benzylmagnesium chloride, isopropyl magnesium bromide, and *tert*-butyl magnesium bromide.

Olefin substrates were subsequently explored with Grignard reagents **2a** and **2e** (Table 3). Both terminal and internal olefins were effective substrates for the reaction. Various

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Table 1. Optimization of Reaction Conditions^a

entry	catalyst	oxidant	conditions	conv. ^b (4a/5a) ^c
1	Pd(OAc) ₂	1	Et ₂ O, rt	91% (3:1)
2		1	Et ₂ O, rt	0%
3	Pd(OAc) ₂	1	Et ₂ O, 0 °C - rt	98% (5:1)
4	Pd(OAc)₂	1	Et₂O/THF (5:1), 0 °C - rt	100% (10:1)
5	Pd(OAc) ₂	1	1,4-dioxane, 0 °C - rt	75% (14:1)
6	Pd(OAc) ₂	1	Et ₂ O/THF (2:1), 0 °C - rt	92% (8:1)
7	Pd(OAc) ₂	1	Et ₂ O/THF (1:2), 0 °C - rt	76% (7:1)
8	Pd ₂ (dba) ₃	1	Et ₂ O/THF (5:1), 0 °C - rt	99% (8:1)
9	Pd ₂ (C ₃ H ₅) ₂ Cl ₂	1	Et ₂ O/THF (5:1), 0 °C - rt	99% (6:1)
10	PdCl ₂	1	Et ₂ O/THF (5:1), 0 °C - rt	65% (8:1)
11	Pd(TFA) ₂	1	Et ₂ O/THF (5:1), 0 °C - rt	100% (6:1)
12 ^d	Pd ₂ (dba) ₃ -PPh ₃	1	Et ₂ O/THF (5:1), 0 °C - rt	0%
13 ^d	Pd ₂ (dba) ₃ -dppf	1	Et ₂ O/THF (5:1), 0 °C - rt	35% (6:1)
14 ^d	Pd ₂ (dba) ₃ -BINAP	1	Et ₂ O/THF (5:1), 0 °C - rt	50% (11:1)
15	Pd(OAc) ₂	Ag ₂ O	Et ₂ O/THF (5:1), 0 °C - rt	0%
16	Pd(OAc) ₂	CuO	Et ₂ O/THF (5:1), 0 °C - rt	22% ^e
17	Pd(OAc) ₂	CuCl ₂	Et ₂ O/THF (5:1), 0 °C - rt	0%
18	Pd(OAc) ₂	CuCl	Et ₂ O/THF (5:1), 0 °C - rt	0%
19	Pd(OAc) ₂	^t BuOOH	Et ₂ O/THF (5:1), 0 °C - rt	0%
20	Pd(OAc) ₂	Br(CH ₂) ₂ Br	Et ₂ O/THF (5:1), 0 °C - rt	10% ^e

^aAll reactions were carried out with styrene (3a) (0.20 mmol), Pd catalyst (0.0040 mmol), Grignard reagent 2a (2.0 M in ether) (0.60 mmol), and oxidant (0.40 mmol) in solvent (0.30 mL) under Ar overnight unless otherwise noted. ^bConversion was determined by ¹H NMR analysis of crude reaction mixtures based on 3a. ^cRatio of 4a to 5a was determined by ¹H NMR analysis of the crude reaction mixture. ^dWith ligand (0.0040 to 0.0080 mmol, Pd/P 1:2). ^eRatio of 4a to 5a was not determined due to the low conversion.

Table 2. Studies of Grignard Reagents 2^a

entry	substrate (2)	product (4)	yield ^b (4/5) ^c
1 ^d	2a	4a	72% (10:1)
2	2b, R = H	4b	72% (9:1) ^e
3	2c, R = Cl	4c	63% (>20:1)
4	2d, R = CH ₃	4d	46% (>20:1)
5	2e	4e	72% (>20:1)
6	2f	4f	56% (>20:1)

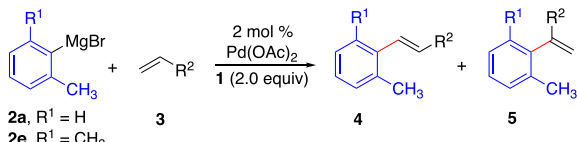
^aAll reactions were carried out with styrene (3a) (0.20 mmol), Pd(OAc)₂ (0.0040 mmol), Grignard reagent 2 (0.60 mmol), and di-*t*-butyldiaziridinone (1) (0.40 mmol) in Et₂O (0.30 mL) under Ar at rt overnight unless otherwise noted. ^bIsolated yield based on 3a. ^cRatio of 4 to 5 was determined by ¹H NMR analysis of crude reaction mixtures. ^dIn Et₂O/THF (0.25 mL/0.05 mL) at 0 °C-rt. ^eLower conversions were obtained with PhMgCl (32%), PhMgI (25%), and Ph₂Mg (18%).

substituted stilbenes (4g–n) were obtained in 63–86% yields from styrenes 3b–h and vinylnaphthalene 3i (Table 3, entries 1–8). The reaction proceeded mainly by the addition of the Grignard reagents 2 at the terminal carbons of the olefins with 9:1 to >20:1 regioselectivities. The substituent on the phenyl group of the olefin appeared to have little effect on the reaction in terms of the yield and regioselectivity. Vinyl silane 3j efficiently reacted with 2e to form *trans*-disubstituted olefin 4o in 91% yield and >20:1 rr (Table 3, entry 9). For aliphatic terminal olefin 3k, product 6p was formed as a major isomer along with small amounts of isomers 4p and 5p with a ratio of 10:1.4:1 (Table 3, entry 10). The reaction can also be extended to internal olefins. (E)-Trisubstituted stilbene 4q and (Z)-trisubstituted stilbene 4r were formed, respectively, from *trans*- β -methylstyrene 3l and *cis*- β -methylstyrene 3m in a stereoselective manner (Table 3, entries 11 and 12). The reaction between aliphatic internal olefin 3n and Grignard reagent 2a proceeded cleanly, giving Heck product 6s in 52% yield (Table 3, entry 13).

Whereas a precise understanding of the reaction mechanism awaits further study, a possible catalytic pathway for the oxidative Heck process is proposed in Scheme 2. The reaction started with the oxidative addition of Pd(0) into the N–N bond of di-*t*-butyldiaziridinone (1) to form the four-membered Pd(II) species 7.¹⁴ Transmetalation of 7 with Grignard reagent 2 led to palladium intermediate 8, which reacted with olefin 3 via migratory insertion to form alkyl palladium complex 9. The β -H elimination of 9 gave olefin product 4 and palladium hydride species 10. The Pd(0) catalyst was regenerated from 10 via reductive elimination to complete a catalytic cycle.

Interestingly, when vinyl ether 3o was used in the reaction, stilbene 4s was obtained rather than the typical arylated Heck product (Scheme 3a). When the reaction was carried out with

Table 3. Studies of Substrate Scope^a

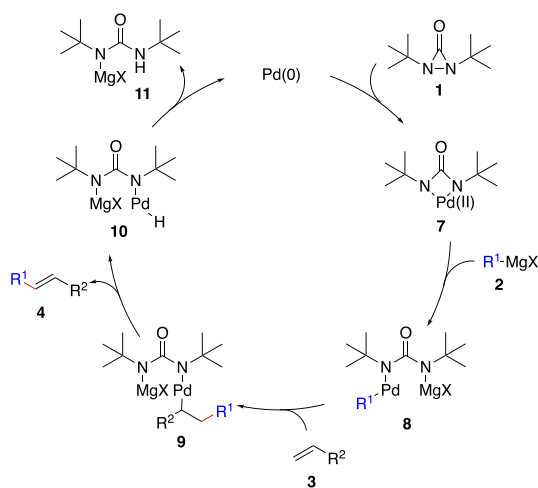
				
entry	2	3	product (4)	yield ^b (4/5) ^c
1	2a	3b, R = 4-F	4g, R ₁ = H	68% (9:1)
2	2a	3c, R = 4-Cl	4h, R ₁ = H	86% (12:1)
3	2a	3d, R = 4-Br	4i, R ₁ = H	70% (9:1)
4	2a	3e, R = 4-CH ₃	4j, R ₁ = H	63% (10:1)
5	2a	3f, R = 4-Ph	4k, R ₁ = H	65% (19:1)
6	2a	3g, R = 3-Me	4l, R ₁ = H	70% (10:1)
7	2e	3h, R = 3-OMe	4m, R ₁ = CH ₃	71% (>20:1)
8	2a	3i	4n	74% (13:1)
9	2e	3j	4o	91% (>20:1)
10	2e	3k	4p	48% (6p:4p:5p = 10:1.4:1)
11	2a	3l	4q	48% (7:1)
12	2a	3m	4r	58% (>20:1)
13	2a	3n	6s	52%

^aAll reactions were carried out with olefin **3** (0.20 mmol), Pd(OAc)₂ (0.0040 mmol), Grignard reagent **2** (0.60 mmol), and di-*t*-butyldiaziridinone (**1**) (0.40 mmol) under Ar overnight unless otherwise noted. For entries 1–6 and 9–10, in Et₂O/THF (0.25 mL/0.05 mL) at 0 °C–rt; for entries 7–8 and 11–13, in Et₂O (0.30 mL) at rt. ^bIsolated yields based on **3**. ^cRatio was determined by ¹H NMR analysis of crude reaction mixtures.

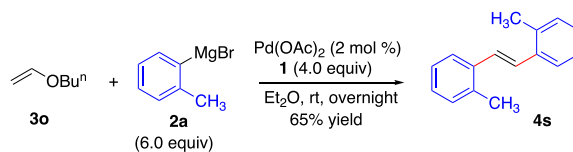
3.0 equiv vinyl ether **3o**, styrene **3p** was formed with 74% conversion (Scheme 3b).¹⁶ Subjecting styrene **3p** and Grignard reagent **2a** to the reaction conditions led to the formation of stilbene **4s** in 72% yield (Scheme 3c).

A possible reaction pathway for the formation of stilbene **4s** from vinyl ether **3o** is outlined in Scheme 4. The palladium complex **12** resulting from the transmetalation between four-membered Pd(II) species **7** and Grignard reagent **2a** reacted

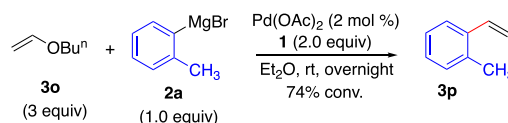
Scheme 2. Proposed Catalytic Pathway for the Oxidative Heck Reaction

Scheme 3. Reaction of Grignard Reagent **2a** with Vinyl Ether **3o**

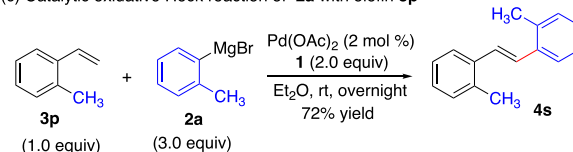
(a) Reaction of Grignard reagent **2a** (6.0 equiv) with vinyl ether **3o** (1.0 equiv)



(b) Reaction of Grignard reagent **2a** (1.0 equiv) with vinyl ether **3o** (3.0 equiv)



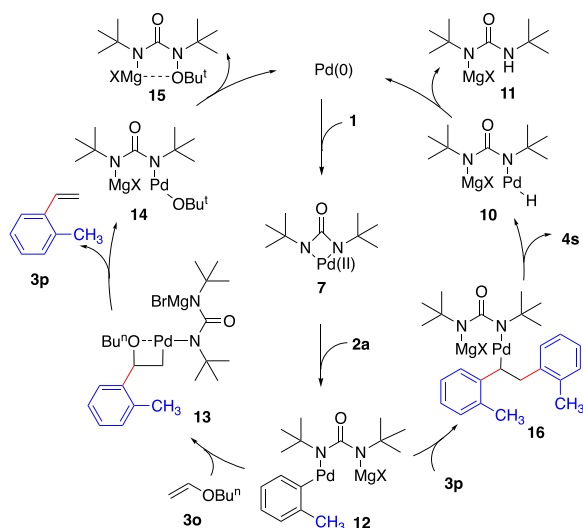
(c) Catalytic oxidative Heck reaction of **2a** with olefin **3p**



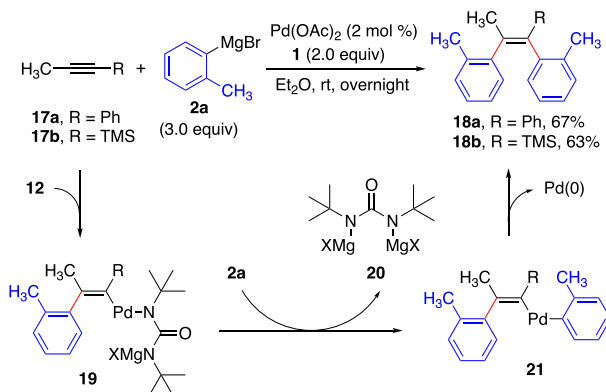
with vinyl ether **3o** via migratory insertion to form palladium complex **13**. Subsequent β-butoxy elimination of **13** led to styrene **3p** and palladium species **14**. The β-H elimination of complex **13** could be suppressed by the coordination of the Pd to the butoxyl group. Compound **14** could undergo reductive elimination to regenerate the Pd(0) catalyst or transmetalation with Grignard reagent **2a** to give palladium complex **12**. The formed styrene **3p** further reacted with palladium complex **12** via the Heck process to give stilbene **4s**.

Tetrasubstituted olefins **18a,b**¹⁷ were obtained in 67 and 63% yield, respectively, when internal alkynes **17a,b** were treated with Grignard reagent **2a**, 2.0 equiv di-*t*-butyldiaziridinone (**1**), and 2 mol % Pd(OAc)₂ at room temperature (Scheme 5). It was likely that palladium complex **12** generated from Pd(OAc)₂, **1**, and **2a**, as described in Scheme 4, reacted with alkyne **17** via migratory insertion to form vinyl palladium intermediate **19**. Transmetalation between **19** and **2a** led to palladium species **21**, which underwent reductive elimination to give tetrasubstituted olefin **18**.

Scheme 4. Possible Reaction Pathways between Grignard Reagent 2a and Vinyl Ether 3o



Scheme 5. Reaction of Grignard Reagent 2a with Alkynes 17



In summary, we have developed a highly effective oxidative Heck reaction of readily available Grignard reagents with $\text{Pd}(\text{OAc})_2$ as the catalyst and di-*t*-butyldiaziridinone (**1**) as the oxidant. Various terminal and internal olefins can react with Grignard reagents under mild conditions to give the corresponding substituted olefins in 46–91% yields with generally high regioselectivity. Sterically congested tetrasubstituted olefins can also be readily formed with internal alkynes. To the best of our knowledge, this work represents the first Pd-catalyzed oxidative Heck reaction with Grignard reagents. The ready availability of Grignard reagents along with the high activity of the reaction system could make the current process synthetically useful. Further development of the reaction process will be pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01762.

Experimental procedures, characterization data for compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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