Dual Rh(II)/Pd(0) Relay Catalysis for One-Pot Synthesis of α-Quaternary Allylated Indolin-2-ones and Benzofuran-2-ones

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Received November 30, 2020, Accepted December 21, 2020, Published online January 4, 2021

Cooperative Rh(II) and Pd(0) dual relay catalysis has been developed, which allowed one-pot synthesis of α-quaternary allylated indolin-2-ones and benzofuran-2-ones. The catalytic reaction proceeded through the sequential Rh(II)-catalyzed intramolecular aromatic C(sp^2)-H bond functionalization of α-diazo carbonyl compounds, followed by Pd(0)-catalyzed allylic alkylation with allylic carbonates to afford the products in high yields (up to 97%).

Keywords: Dual catalysis, Rhodium catalyst, Palladium catalyst, Indolin-2-ones, Benzofuran-2-ones

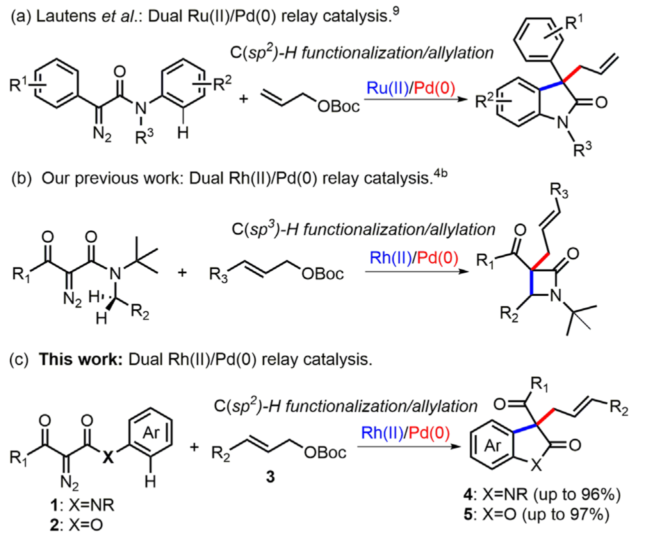
Introduction

Cooperation of two-different catalytic cycles in one-pot is an emerging yet highly attractive synthetic strategy, in which the product(s) of the first catalytic cycle has been used as reactant(s) of the subsequent catalytic cycle.[1] Despite considerable recent advances,[2] the dual catalytic systems composed of two-different transition-metals are still limited, which may attributed in part to the inherent difficulty in insuring of redox compatibility between the catalysts and balanced kinetics, avoiding catalyst deactivation.[3] In this regards, we have previously demonstrated for the first time the redox-compatibility between Rh(II) and Pd(0) catalysts through the synergistic cooperative Rh(II)/Pd(0) dual catalytic reaction between *N*-sulfonyl-1,2,3-triazoles and allylic substrates.[4a] More recently, we have reported a tandem dual Rh(II)/Pd(0) relay catalysis to afford α-quaternary allylated β-lactams through the Rh(II)-catalyzed C(sp^3)-H insertion, followed by Pd(0)-catalyzed allylic alkylation (Scheme 1(b)).[4b] In present work, we extended the tandem dual Rh(II)/Pd(0) relay catalytic reaction for one-pot synthesis of C3-quaternary allylated five-membered heterocyclic compounds through the sequential aromatic C(sp^2)-H functionalization/allylation of α-diazoamides and α-diazoesters (Scheme 1(c)).[5]

The transition metal catalyzed aromatic C(sp^2)-H functionalization has been considered as a powerful method for the formation of C—C or C-X (heteroatoms) bonds.[6] The synthetic utility of aromatic C(sp^2)-H bond functionalization of diazo compounds has also been well developed.[7] On the other hand, the well-known Pd(0)-catalyzed allylic alkylation has frequently been utilized for the construction of quaternary centers.[8] Thus, it can be expected that the tandem combination of these two catalytic reactions would be highly efficient dual catalytic system for the synthesis of quaternary heterocyclic compounds. For example, Lautens *et al.* reported a tandem Ru-catalyzed aromatic C(sp^2)-H functionalization, followed by Pd-catalyzed allylic alkylation of α-diazoamides to afford 3-quaternary allylated oxindoles (Scheme 1(a)).[9] We anticipated that the aromatic C(sp^2)-H functionalization of the Rh(II)-carbenoid, formed from α-diazoamides **1** or α-diazoesters **2**, occurred faster than C (sp^3)-H insertion, the tandem dual Rh(II)/Pd(0) relay catalysis could afford C3-quaternary allylated indolin-2-ones and benzofuran-2-ones. These five-membered heterocyclic moieties are ubiquitous in many bioactive natural products and pharmaceuticals.[10]

Results and Discussion

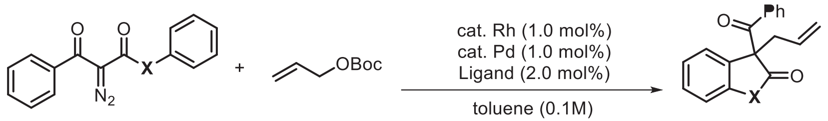
We recently reported the asymmetric dual Rh(II)/Pd(0) relay catalytic reaction of *N*-benzyl-*N*-*tert*-butyl substituted α-diazoamides with allyl *tert*-butyl carbonates, which may proceed through the sequential enantioselective intramolecular benzylic C(sp^3)-H insertion of Rh(II)-carbenoid, followed by Pd(0)-catalyzed diastereoselective allylic alkylation of the resulting chiral β-lactams. During this study, we anticipated that if the *N*-*tert*-butyl substituent of α-diazoamide changed to *N*-phenyl group, the Rh(II)-carbenoid intermediate may selectively react with aromatic C(sp^2)-H bond to result in formation of five-membered indolin-2-one moiety, which may then undergo Pd(0)-catalyzed allylic alkylation to afford C3-quaternary allylated indolin-2-ones. As a proof of concept, the *N*-benzyl-*N*-phenyl substituted α-diazoamide **1a** and allyl *tert*-butyl carbonate **3a** were selected as the model substrates, and subjected under the Rh(II)/Pd(0) dual catalytic conditions used in the formation of β-lactam, *i.e.*, 1.0 mol% of Rh_2[(*S*)-*tert*-PTTL$]_4$, 2.0 mol% of Pd($dba)_2$ and 2.0 mol% of *rac*-BINAP.



Scheme 1. Dual transition metal catalysis using α-diazo carbonyl compounds

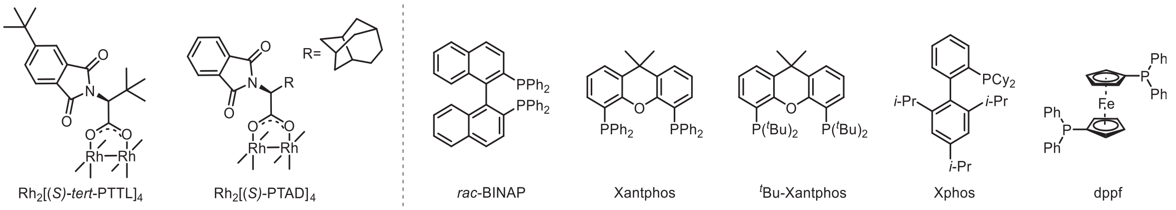
As expected, the reaction favors the Rh(II)-catalyzed aromatic C(sp^2)-H functionalization, then proceeds to Pd(0)-catalyzed allylic alkylation to afford the C3-quaternary allylated indolin-2-ones **4aa** in 84% yield without the formation of β-lactam (entry 1 in Table 1). This result clearly indicated that the Rh(II)-catalyzed intramolecular aromatic C(sp^2)-H functionalization occurs prior to C(sp^3)-H insertion. The reaction condition was also incorporated with α-diazoester **2a** with **3a**, providing C3-quaternary allylated benzofuran-2-one **5aa** in 87% yield (entry 1 in Table 1). To increase the reaction efficiency, the reaction conditions were further optimized as shown in Table 1. It was found that the reaction efficiency of dual Rh(II)/Pd(0) relay catalysis was largely affected by the source of Pd(0) catalysts. When the reaction carried out in the presence of $Pd_2(dba)_3$ or $Pd_2(dba)_3{\cdot}CHCl_3$, the yields of **4aa** and **5aa** were not improved (entries 2 and 3 in Table 1). However, in the presence of $Pd(OAc)_2$, the reaction efficiencies were dramatically decreased to result in **4aa** (70% yield) and **5aa**, which

Table 1. Reaction optimization.[a]



1a, X= NBn
2a, X= O
3a
4aa, X= NBn
5aa, X= O

Entry	cat. Rh	cat. Pd	Ligand	Yield (%)[b]	
				4aa	5aa
1[c]	$Rh_2[(S)$-*tert*-PTTL$]_4$	$Pd(dba)_2$	*rac*-BINAP	84	87
2	$Rh_2[(S)$-*tert*-PTTL$]_4$	$Pd_2(dba)_3$	*rac*-BINAP	55	84
3	$Rh_2[(S)$-*tert*-PTTL$]_4$	$Pd_2(dba)_3{\cdot}CHCl_3$	*rac*-BINAP	78	81
4[c]	$Rh_2[(S)$-*tert*-PTTL$]_4$	$Pd(OAc)_2$	*rac*-BINAP	70	-[d]
5	$Rh_2[(S)$-*tert*-PTTL$]_4$	$[PdCl(allyl)]_2$	*rac*-BINAP	92	70
6	$Rh_2(TMA)_4$	$[PdCl(allyl)]_2$	*rac*-BINAP	90	85
7	$Rh_2(Oct)_4$	$[PdCl(allyl)]_2$	*rac*-BINAP	83	61
8	$Rh_2[(S)$-PTAD$]_4$	$[PdCl(allyl)]_2$	*rac*-BINAP	84	89
9	$Rh_2[(S)$-PTAD$]_4$	$[PdCl(allyl)]_2$	Xantphos	83	92
10	$Rh_2[(S)$-PTAD$]_4$	$[PdCl(allyl)]_2$	^{t}Bu-Xantphos	20	36[d]
11	$Rh_2[(S)$-PTAD$]_4$	$[PdCl(allyl)]_2$	dppf	81	88
12[e]	$Rh_2[(S)$-PTAD$]_4$	$[PdCl(allyl)]_2$	Xphos	57	72



[a] Reaction conditions: **1a** (0.1 mmol), **3a** (0.2 mmol) in the presence of Rh (1.0 mol %), Pd (1.0 mol %), ligand (2.0 mol %) in toluene (1.0 mL) at 25 °C for 24 h for the formation of **4aa**, stirred for 3 h for **5aa**.

[b] Isolated yields.

[c] Pd catalyst was used in 2.0 mol %.

[d] Stirred for 24 h.

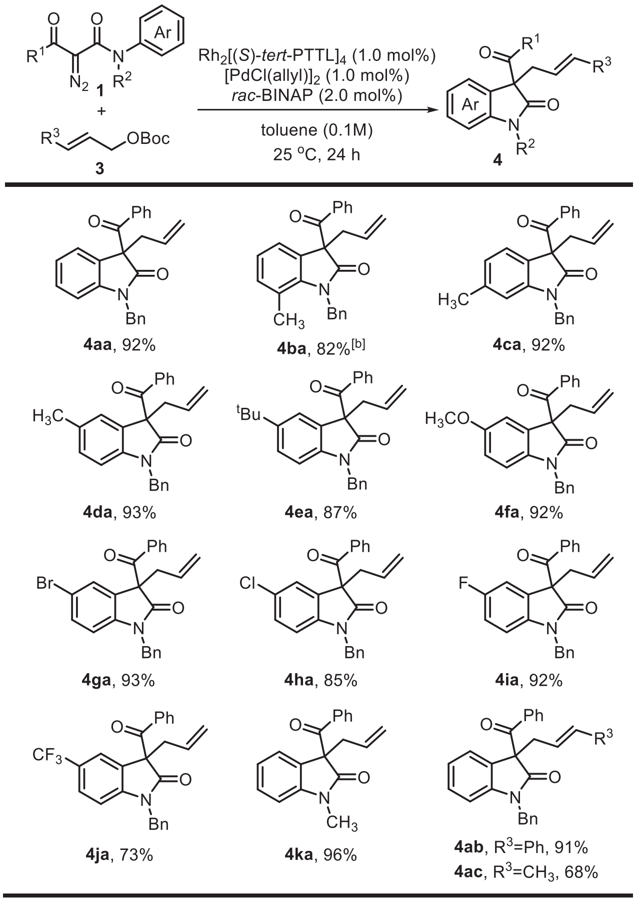
[e] Ligand was used in 4 mol %.

was surprisingly not formed at all (entry 4 in Table 1). In contrast, when [PdCl(allyl)]$_2$ was used as catalyst precursor, the yield for **4aa** was significantly improved to result in 92% yield, whereas the yield of **5aa** was decreased to 70% (entry 5 in Table 1). Among the Rh(II) catalyst screened, the Rh$_2$[(*S*)-PTAD]$_4$ exhibited the best efficiency to afford **5aa** in 89% yield (entry 8 in Table 1). We also screened various phosphine ligands for Pd catalysis (entries 9–12 in Table 1). When the Xantphos was used, the reaction gave the best result to afford **5aa** in 92% yield (entry 9 in Table 1). The electron-rich ^{t}Bu-Xantphos significantly decreased the yields of **4aa** and **5aa**. The ferrocene type ligand dppf or monodentate phosphine ligand Xphos also did not improved the reaction efficiency providing moderate yields of **4aa** and **5aa** (entries 11 and 12 in Table 1).

With the optimal reaction conditions in hand for **4** (entry 5 in Table 1) and **5** (entry 9 in Table 1), we explored the substrate generality of Rh(II)/Pd(0) dual catalytic reaction. For the synthesis of indolin-2-ones **4**, a series of *N*-benzyl-*N*-phenyl substituted α-diazoamides **1** with various substituents on the phenyl ring were examined in the presence of 1.0 mol % of Rh$_2$[(*S*)-*tert*-PTTL]$_4$, 1.0 mol% of [PdCl(allyl)]$_2$, 2.0 mol % of *rac*-BINAP at room temperature for 24 h (Table 2). The electron donating CH$_3$, *tert*-butyl and OCH$_3$ (**1b–1f**) and halogen (Br, Cl, F) (**1g–1i**) substituted α-diazoamides were successfully reacted with allyl *tert*-butyl carbonate **3a** to afford the corresponding quaternary allylated indolin-2-ones **4ba-4ia** with up to 93% yields. The reaction of α-diazoamide **1j** having electron-withdrawing CF$_3$ substituent also afforded **4ja** in 73% yield. The reaction with *N*-methyl-*N*-phenyl substituted α-diazoamide was also tolerated in this dual Rh(II)/Pd(0) relay catalysis to afford the corresponding **4ka** in almost quantitative 96% yield. When allyl carbonate was changed to *tert*-butyl cinnamyl carbonate **3b** and crotyl *tert*-butyl carbonate **3c**, the reaction furnished the corresponding products **4ab** (91% yield) and **4ac** (68% yield).

We next explored the generality for the synthesis of benzofuran-2-ones **5** using various α-diazoeseters **2** and allylic carbonates **3** in the presence of 1.0 mol % of Rh$_2$[(*S*)-PTAD]$_4$, 1.0 mol % of [PdCl(allyl)]$_2$, and 2.0 mol % of Xantphos at room temperature for 3–12 h (Table 3).

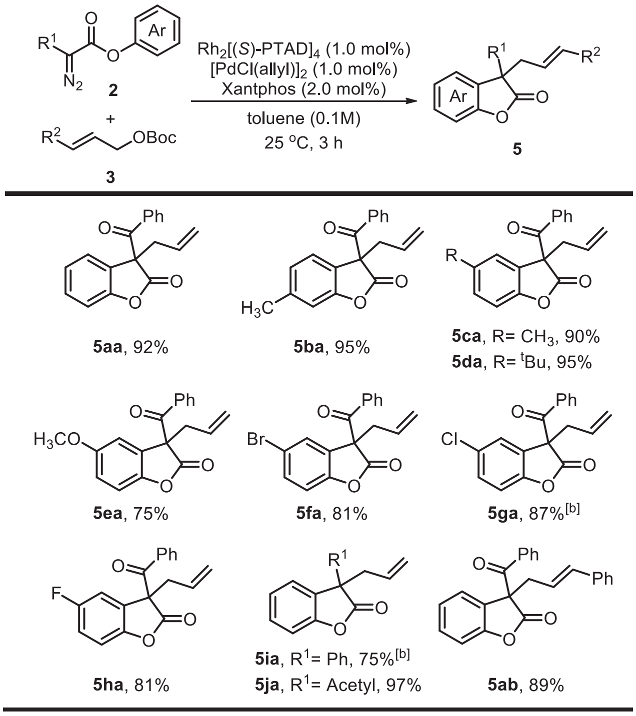
Table 2. One-pot synthesis of α-quaternary allylated indolin-2-ones **4**.[a]



[a] Reaction conditions: **1** (0.1 mmol), **3** (0.2 mmol) in the presence of Rh$_2$[(*S*)-*tert*-PTTL]$_4$ (1.0 mol %), [PdCl(allyl)]$_2$ (1.0 mol %), *rac*-BINAP (2.0 mol %) in toluene (1.0 mL) at 25 °C for 24 h.

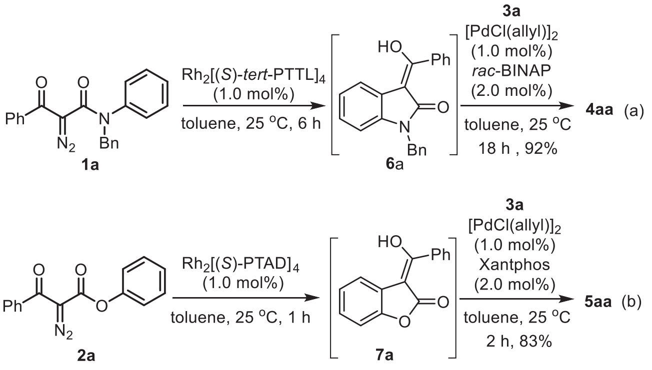
[b] The reaction was stirred at 50 °C. All yields are isolated yields.

Table 3. One-pot synthesis of α-quaternary allylated benzofuran-2-ones[a].



[a] Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol) in the presence of Rh$_2$[(*S*)-PTAD]$_4$ (1.0 mol%), [PdCl(allyl)]$_2$ (1.0 mol %), Xantphos (2.0 mol %) in toluene (1.0 mL) at 25 °C for 3 h.

[b] The reaction was stirred for 12 h. All yields are isolated yields.



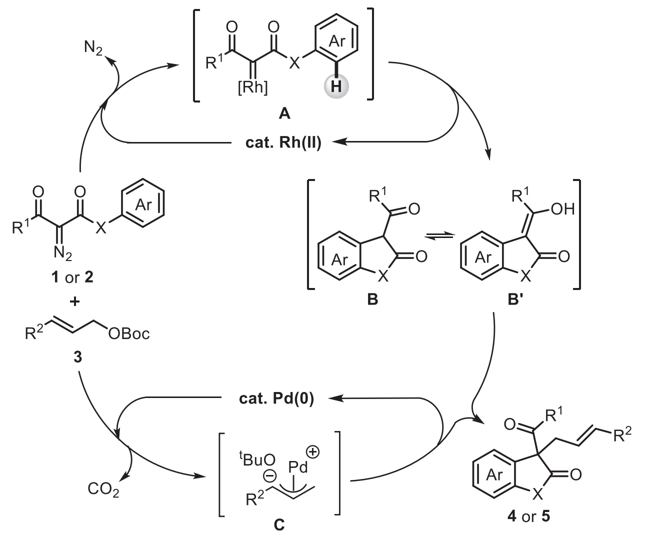
Scheme 2. Stepwise tandem one-pot reactions.

The reactions of α-diazoesters **2b**–**2d** bearing alkyl substituents (CH_3, *tert*-butyl) on the phenyl ring with allyl carbonate **3a** proceeded smoothly to afford C3-quaternary allylated benzofuran-2-ones **5ba**–**5da** in high yields (90%–95%).

In contrast, reaction of the α-diazoester **2e** having *para*-methoxy substituent on the phenyl ring provided the corresponding **5ea** in moderate yield of 75%. It was observed that the reaction efficiency of electron withdrawing halogen (Br, Cl, F) substituent on phenyl ring of α-diazoesters **2f**–**2h** was slightly diminished to afford the corresponding **5fa**–**5ha** in 81%–87% yields. The α-diazoesters **2i** (R^1 = Ph) and **2j** (R^1 = Acetyl) were also well tolerated in this dual Rh(II)/Pd(0) relay catalysis and afforded the corresponding **5ia** in 75% yield and **5ja** in excellent 97% yield. The reaction of α-diazoester **2a** with *tert*-butyl cinnamyl carbonate **3b** was also performed to result in **5ab** in 89% yield.

In order to confirm the relay catalysis, the diazo compounds **1a** or **2a** were treated with Rh(II) catalyst alone resulting in the corresponding cyclic adducts **6a** and **7a**. When the reactions were conducted in a tandem one-pot manner, the corresponding α-quaternary allylated indolin-2-one **4aa** in 92% yield (Scheme 2(a)) and benzofuran-2-one **5aa** in 83% yield (Scheme 2(b)) were obtained. These results clearly supported that the two-catalytic reactions, *i. e.*, Rh(II)-catalyzed $C(sp^2)$-H bond functionalization and Pd (0)-catalyzed allylic alkylation, are integrated in a relay manner.

The plausible reaction mechanism is shown in Scheme 3. The reaction of α-diazo carbonyl compounds with Rh(II) catalyst generated the electrophilic Rh(II)-carbenoid **A**. Then, it would undergo intramolecular aromatic $C(sp^2)$-H bond functionalization through electrophilic aromatic substitution to afford the 1,3-dicarbonyl compound **B** and/or its tautomer **B'**. In the presence of Pd catalyst, the allyl *tert*-butyl carbonates **3** undergo decarboxylation to generate the electrophilic π-allyl palladium complex **C**. Subsequently, allylic alkylation of **B**/**B′** with **C** could provide the α-quaternary allylated indolin-2-ones **4** and benzofuran-2-ones **5** with regeneration of Rh(II) and Pd(0) catalysts.



Scheme 3. Plausible reaction pathway

Conclusion

A straightforward dual Rh(II)/Pd(0) relay catalytic reaction of α-diazo carbonyl compounds with allyl carbonates **3** has been developed for one-pot synthesis of α-quaternary allylated indolin-2-ones and benzofuran-2-ones. The catalytic reactions were proceeded through the sequential Rh (II)-catalyzed intramolecular aromatic $C(sp^2)$-H functionalization of α-diazo carbonyl compounds, followed by Pd(0)-catalyzed intermolecular allylic alkylation of π-allyl palladium complex, which was generated from allyl carbonates. Under mild reaction conditions, a series of α-quaternary allylated indolin-2-ones and benzofuran-2-ones were synthesized in good to excellent yields, ensuring the good functional groups tolerance. Further development on dual catalysis for the synthesis of heterocyclic compounds is undergoing in our laboratory.

Acknowledgments. This work was made possible by the support of the National Research Foundation (NRF-2019R1A2B5B02069449).

Conflict of interest

The authors declare no conflict of interest.

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