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Combining Ru-Catalyzed C−H Functionalization with Pd-Catalyzed Asymmetric Allylic Alkylation: Synthesis of 3-Allyl-3-aryl Oxindole Derivatives from Aryl α-Diazoamides

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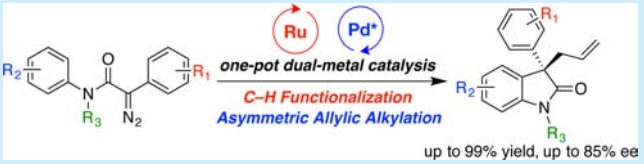
Supporting Information

ABSTRACT: Ruthenium-catalyzed C−H functionalization was successfully combined with palladium-catalyzed asymmetric allylic alkylation in one pot. The novel dual-metal-catalyzed reaction provides a variety of 3-allyl-3-aryl oxindoles from the corresponding α-diazoamides in up to 99% yield with up to 85% ee. The appropriate ligand choice is important to promote the sequential reaction, avoiding undesired metal interaction or ligand exchange.

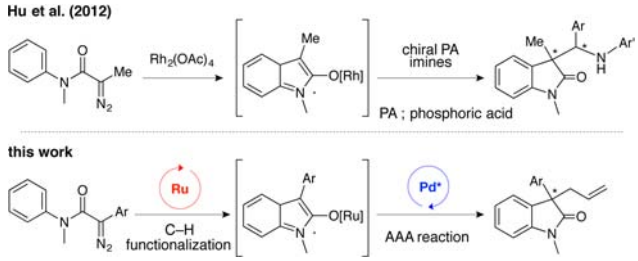


The development of synthetic methods to construct enantioenriched molecules in an efficient manner continues to be a goal for synthetic chemists.[1] More recently, significant effort has been made to develop novel one-pot asymmetric multicatalyst reactions.[2−5] The exploitation of combinations of multimetal catalysts to achieve C−C and C−X bond formation in a single operation can afford more efficient processes by reducing the number of isolation and purification steps and can also offer valuable reactivity and selectivity. In this context, our group has demonstrated a number of multimetal-catalyzed tandem reactions, including asymmetric and racemic reactions.[2h−k,6]

Chiral oxindole derivatives are important skeletons found in a wide variety of biologically active molecules and natural products.[7] To date, considerable effort has been devoted to the catalytic construction of oxindoles bearing a chiral quaternary carbon center using both transition metal catalysts[8a−g] and organocatalysts.[8h−k] We envisioned that these targets could be readily accessed in a novel enantioselective dual-metal-catalyzed process by trapping the oxindole enolate intermediate from a metal-catalyzed C−H functionalization with a chiral electrophilic allylpalladium complex (Scheme 1). In 2012, Hu and co-workers reported a related process whereby an enantioselective synthesis of oxindoles and indoles was designed using a synergistic dual-catalytic system consisting of Rh-catalyzed C−H functionalization followed by 1,2-addition to a chiral phosphoric acid-activated imine.[9]

Herein we report a dual-metal-catalyzed enantioselective one-pot synthesis that combines ruthenium-catalyzed C−H functionalization and palladium-catalyzed asymmetric allylic alkylation (AAA) to afford chiral 3-allyl-3-aryl oxindoles. We found that the appropriate palladium source and ligand were crucial for both promoting the tandem reactions and providing the products with high enantiopurity. To the best of our knowledge, this is the first example of an enantioselective tandem reaction involving a ruthenium carbenoid and an allylpalladium complex to form two new C−C bonds with a chiral quaternary carbon center.[10,11]

Scheme 1. Synthetic Approaches for the Synthesis of Chiral Oxindoles: (A) Rh-Catalyzed C−H Insertion Followed by Addition to Activated Imines; (B) Ru-Catalyzed C−H Functionalization Followed by Pd-Catalyzed Asymmetric Allylic Alkylation



We began this study with an optimization of a transition-metal-catalyzed C−H functionalization of 4-(trifluoromethyl)-phenyl-substituted α-diazoamide **1a** (Table 1). In 2012, Yu and co-workers had demonstrated the use of $[Ru(p\text{-cymene})Cl_2]_2$ in the synthesis of 3-alkylideneoxindoles from acyl α-diazoamides.[12] We found that $[Ru(p\text{-cymene})Cl_2]_2$ could also be employed in constructing 3-aryl oxindoles. With 2 mol % ruthenium catalyst in toluene at −25 °C, **2a** was isolated in 90% yield (entry 1).[6f] Dirhodium(II) catalysts are among the most powerful reagents for generating metal carbenoid species from diazo compounds.[13] Under the same conditions, Rh(II) catalysts gave a complex product mixture and provided **2a** in poor yields (entries 2−4). When a solution of **1a** was stirred at

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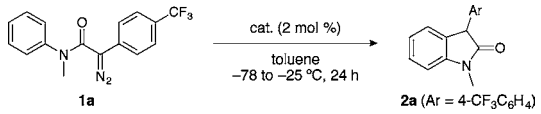
Table 1. Catalyst Optimization of C−H Functionalization of Aryl α-Diazoamide 1a[a]



1a 2a (Ar = 4-$CF_3C_6H_4$)

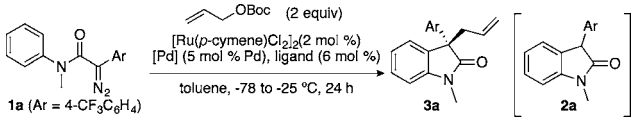
entry	cat.	yield (%)[b] 2a	1a
1	$[Ru(p\text{-cymene})Cl_2]_2$	91 (90)	0
2	$Rh_2(OAc)_4$	8	26
3	$Rh_2(TFA)_4$	32	0
4	$Rh_2((S)\text{-PTV})_4$	50	0
5	–	1	96

[a]Representative procedure: in a 2 dram vial, **1a** (0.1 mmol) and catalyst (2 mol %) were dissolved in toluene (1 mL) at −78 °C, and the mixture was stirred at −25 °C for 24 h. [b]Yields were determined by ^{1}H NMR spectroscopy. The yield in parentheses is an isolated yield.

−25 °C in the absence of catalyst, we observed unreacted **1a** and a negligible amount of **2a** by ^{1}H NMR analysis (entry 5).

Next, we investigated the combination of the Ru(II)-catalyzed C−H functionalization and a Pd(0)-catalyzed AAA reaction (Table 2). Initial reactions were performed with $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol %), $Pd(PPh_3)_4$ (5 mol %), or a Pd catalyst/ligand (5 mol % [Pd], [Pd]/L = 1:1.2) and allyl *tert*-butyl carbonate (2 equiv) as an allyl source. Using $Pd(PPh_3)_4$ as the Pd catalyst led to unreacted **1a** in 93% yield (entry 1). The result indicated that the ruthenium catalyst might be deactivated in the presence of free phosphine ligands (PPh_3 dissociates in solution from $Pd(PPh_3)_4$). To minimize the detrimental Ru−phosphine interaction, we premixed the Pd phosphine prior to starting the reaction.

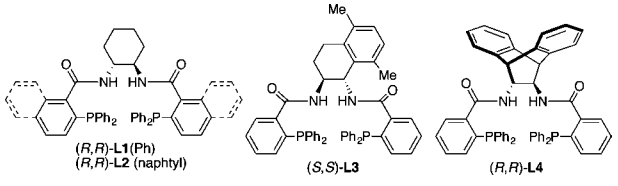
Table 2. Optimization of Pd Catalyst and Ligand in the One-Pot Dual-Metal Reaction[a]



1a (Ar = 4-$CF_3C_6H_4$) 3a 2a

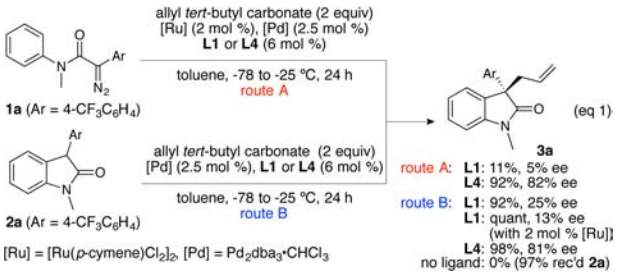
entry	[Pd]	ligand	yields of 1a/2a/3a (%)[b]	ee of 3a (%)[c]
1	$Pd(PPh_3)_4$	–	93/0/0	n.d.
2	$Pd(OAc)_2$	**L1**	66/22/2	n.d.
3	$Pd(allyl)Cl_2$	**L1**	2/92/3	n.d.
4	$Pd_2dba_3{\cdot}CHCl_3$	**L1**	1/80/11	5 (*S*)
5	$Pd_2dba_3{\cdot}CHCl_3$	**L2**	0/82/2	n.d.
6	$Pd_2dba_3{\cdot}CHCl_3$	**L3**	0/68/20	30 (*S*)
7	$Pd_2dba_3{\cdot}CHCl_3$	**L4**	0/0/**89** (**92**)	**82** (*S*)
8	–	–	0/92/0	n.d.
9	–	**L4**	92/0/0	n.d.
10[d]	$Pd_2dba_3{\cdot}CHCl_3$	**L4**	92/0/0	n.d.

[a]Representative procedure: $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol %) and **1** (0.1 mmol) were dissolved in the premixed (20 min at rt) solution of $Pd_2dba_3{\cdot}CHCl_3$/**L** in toluene (1.5 mL); allyl *tert*-butyl carbonate (2 equiv) was added at −78 °C, and the mixture was stirred at −25 °C for 24 h. [b]Yields were determined by ^{1}H NMR spectroscopy. The yield in parentheses is an isolated yield. [c]Determined by chiral HPLC analysis. The absolute configuration was determined by comparison of the optical rotation with that from the literature (ref 8b). n.d. = not determined. [d]The reaction was performed without $[Ru(p\text{-cymene})Cl_2]_2$ at −25 °C.



(*R*,*R*)-**L1**(Ph) (*R*,*R*)-**L2** (naphtyl) (*S*,*S*)-**L3** (*R*,*R*)-**L4**

It is noteworthy that when isolated intermediate **2a** was subjected to the AAA reaction using **L4** without the ruthenium catalyst (eq 1, route B), we obtained **3a** in 98% NMR yield with 81% ee, indicating that the inherent enantioselectivity of **L4** in the AAA reaction was maintained regardless of the presence of the ruthenium catalyst (route A vs route B). However, in the case of **L1**, the yield and also the ee value decreased in the dual-metal-catalyzed reaction (92% yield, 25% ee in route B vs 11% yield, 5% ee in route A). Although neither $[Ru(p\text{-cymene})Cl_2]_2$ nor $[Ru(p\text{-cymene})Cl_2]_2$/**L1** catalyzed the allylic alkylation reaction under our conditions,[18] we also observed a decrease in ee when the AAA of **2a** was conducted using Pd/**L1** in the presence of 2 mol % $[Ru(p\text{-cymene})Cl_2]_2$. From the results obtained with **L4**, we proposed that each catalyst participates in one of two independent reactions via sequential catalysis.



With a successful Ru/Pd-catalyzed sequence toward chiral oxindoles in hand, we examined the effect of the catalyst loading and the amount of allyl *tert*-butyl carbonate (Table 3). When the reaction was performed at −25 °C from the outset, we obtained **3a** without any loss of the yield and enantioselectivity (entry 1). Halving the Ru or Pd catalyst loading resulted in incomplete conversion after 24 h (entries 2 and 3). Decreasing the ratio of the ligand to palladium from 1.2 to 1.0 and halving the amount of the carbonate also resulted in a decrease in yield (entries 4 and 5). Importantly, the catalyst/ligand/allyl carbonate loadings did not affect the ee, and thus, we chose the conditions in entry 1 for our studies.

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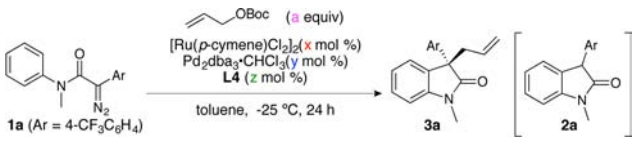
Table 3. Effect of the Catalyst and the Carbonate Loading on the Dual-Metal-Catalyzed Reaction[a]

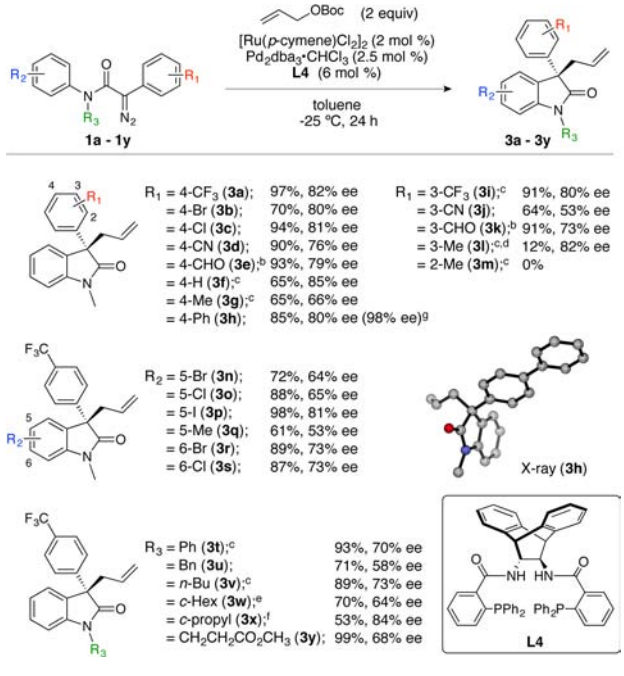


					yields (%)[b]		
entry	*a*	*x*	*y*	*z*	**3a**	**2a**	ee of **3a** (%)[c]
1	2	2	2.5	6	(97)	0	82
2	2	1	2.5	6	54	28	82
3	2	2	1.25	3	32	54	82
4	2	2	2.5	5	88	7	82
5	1	2	2.5	6	67	22	82

[a]See Table 2 for the representative procedure. The reaction was performed at −25 °C from the outset. [b]Yields were determined by ^{1}H NMR spectroscopy. The yield in parentheses is an isolated yield. [c]Determined by chiral HPLC analysis.

We next synthesized and applied a variety of electronically disparate diazo compounds **1** in the Ru/Pd-catalyzed reaction (Scheme 2). The starting α-diazoamides **1** were synthesized by either the palladium-catalyzed arylation of the corresponding acyl α-diazoamides[19] or a condensation reaction of aniline derivatives with carboxylic acid counterparts. An electron-withdrawing group (R_1) at the 4- or 3-position of the aryl ring attached to the diazo-bearing carbon was tolerated, affording the desired oxindoles **3** in good to excellent yields with high enantioselectivity (**3a**−**d**, **3i**). A 3-cyano group afforded **3j** with lower ee, probably as a result of coordination to the Pd or Ru metal center. Although the substrates bearing a 3- or 4-formyl group did not participate in the AAA reaction under the standard protocol, a one-pot telescoping protocol, namely, the Ru-catalyzed C−H functionalization reaction at room temperature followed by the Pd-catalyzed AAA reaction at −25 °C, afforded the desired products in excellent yield with high enantioselectivity (**3e**, **3k**). Electron-neutral or electron-donating groups led to incomplete reaction even with prolonged reaction time (**3f**, **3g**, **3l**). The results indicate that the acidity of the intermediate oxindole is crucial for the AAA reaction. Substrates with lower pK_a values facilitate enolization, resulting in faster allylation. A substrate with an *o*-tolyl group (R_1 = 2-Me) was incompatible in this protocol, affording a 7% yield of intermediate **2m** and an 85% yield of **1m** as measured by ^{1}H NMR spectroscopy. The steric hindrance obstructs the ruthenium step, and unreacted starting material was recovered. In terms of R_2, halogen atoms (**3n**−**p**, **3r**, **3s**) at the 5- or 6-position were tolerated, which could be utilized for further functionalization of the oxindole scaffold. The substituents on the nitrogen atom were also examined (**3t**−**y**). A linear alkyl group afforded **3x** in 89% yield with 73% ee. More sterically demanding substituents such as cyclohexyl (**3w**) or cyclopropyl groups (**3x**) diminished the reactivity, affording the products in moderate yields. An ester group was also tolerated, affording **3y** in excellent yield with moderate enantioselectivity. The absolute configuration of **3h** was unambiguously determined to be *S* by single-crystal X-ray diffraction.[20]

Scheme 2. Substrate Scope of the C−H Functionalization/Asymmetric Allylic Alkylation of Aryl α-Diazoamides[a]



[a]See Table 2 for the representative procedure. The reaction was performed at −25 °C from the outset. Isolated yields after column chromatography are reported. The ee values were determined by chiral HPLC analysis. [b]The reaction was performed using a telescoping protocol. See the Supporting Information for details. [c]The reaction was performed for 48 h. [d]4 equiv of allyl *tert*-butyl carbonate was used. [e]The reaction was performed for 72 h. [f]The reaction was performed for 96 h. [g]After a single recrystallization.

In summary, we have developed a Ru/Pd-catalyzed enantioselective dual-catalyst reaction that provides a series of chiral 3-allyl-3-aryl oxindoles in good to excellent yields with moderate to high enantioselectivity. The combination of the appropriate palladium source and ligand enables the Ru(II)/Pd(0)-catalyzed sequential reaction in a one-pot manner without any loss of catalytic activity and enantioselectivity. Further investigation of Ru(II)/Pd(0)-catalyzed reactions is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02423.

Detailed experimental procedures and full compound characterization data (PDF)

Crystallographic data for **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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(20) CCDC 1495287 (**3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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