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Rhodium-Catalyzed Oxidative Annulation of Sulfonylhydrazones with Alkenes

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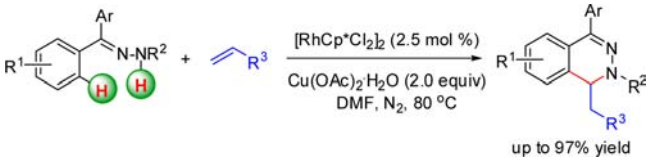
ABSTRACT



An efficient rhodium-catalyzed tandem C−H bond olefination and annulation approach was developed to afford 1,2-dihydrophthalazines in good to excellent yields from easily accessible sulfonylhydrazones and alkenes.

Dihydrophthalazine derivatives represent a major class of nitrogen-containing heterocycles with a wide range of biological and pharmacological activities and play an increasingly important role in drug discovery.[1] 1,2-Dihydrophthalazine antifolates are a novel family of antibacterial drugs; for example, BAL30544 and BAL30545 are new dihydrophthalazine inhibitors of dihydrofolate reductase (DHFR) with activity against a broad range of Gram-positive bacteria,[2] and the 1,2-dihydrophthalazine based trimethoprim derivative RAB1 is an effective inhibitor for *Bacillus anthracis* and *Staphylococcus aureus*.[3] On the other hand, the use of 1,2-dihydrophthalazines as synthetic intermediates has also added to their importance.[3a,4] Despite this promising precedence, synthetic methods for the construction of dihydrophthalazine scaffolds have only scarcely been studied. The early synthetic efforts for 1,2-dihydrophthalazines dated back to the 1890s when Gabriel and Muller reported that a mixture of 2-methyl-l,2-dihydrophthalazine and 2-methyl-l(2*H*)-phthalazinone could be converted from 2-methylphthalazinium iodide.[5] Other improved synthetic methods to build this useful scaffold include the addition reaction of phthalazine and Grignard reagent,[3a] reduction reaction of phthalazines[3a,6] or phthalazinones,[4] and microwave irradiated cyclocondensation of hydrazines with dihalides.[7] However, most of the existing methods suffer from a limited scope of starting materials, use a stoichiometric catalyst, or require multistep procedures. In this context, the development of efficient syntheses of dihydrophthalazines from

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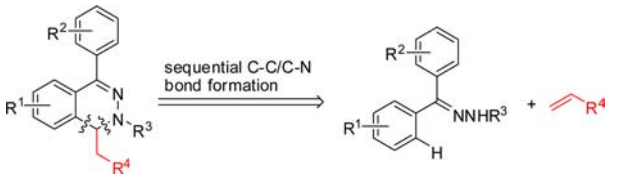
readily available starting materials continues to be an active and rewarding research area.

Owing to the prevalence of heterocycles in medicinal chemistry, many methods have been developed recently through a metal-catalyzed C−H bond functionalization strategy,[8] which provides an efficient and environmentally benign process compared to traditional procedures. Among all these methods, a vast majority of tandem C−H olefination and annulation reactions are devoted to the synthesis of nitrogen-containing heterocycles via metal-catalyzed reactions.[9] Recently, *N*-tosylhydrazones, which are readily prepared from carbonyl compounds with tunable reactivity and potential usage in various transformations, have rapidly become versatile cross-coupling partners in transition-metal-catalyzed reactions.[10] However, *N*-substituted hydrazones are rarely utilized in the C−H bond activation reactions to construct nitrogen-containing heterocycles.[11] As a part of our continuing efforts to assemble heterocycles through a tandem reaction strategy,[12] we herein report a rhodium-catalyzed tandem process consisting of a sequential C−C/C−N bond formation to give 1,2-dihydrophthalazines as a privileged structural motif for many pharmaceuticals from readily available sulfonylhydrazones and alkenes (Scheme 1).

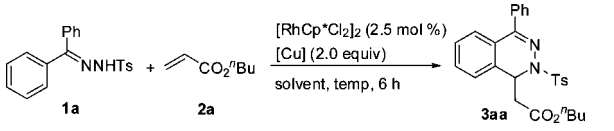
At the outset of this investigation, we started our study by exploring the reaction of *N*′-(diphenylmethylene)-4-methylbenzenesulfonohydrazide (**1a**) with *n*-butyl acrylate

Scheme 1. Tandem C−H Olefination/Annulation Strategy to 1,2-Dihydrophthalazines from Hydrazones and Alkenes



(**2a**) in the presence of $[RhCp^*Cl_2]_2$ (2 mol %) in DMF using $Cu(OAc)_2 \cdot H_2O$ as an oxidant. Intriguingly, the dihydrophthalazine product **3aa** was produced in 75% yield after reacting for 6 h at 120 °C under nitrogen (Table 1, entry 1). A diminished yield was afforded when the reaction was conducted under air or atmospheric oxygen (entries 2−3). By lowering the reaction temperature, a clean reaction was achieved at 80 °C in DMF, and the yield of **3aa** was increased to 86% (entries 4−6). When the solvent was switched from DMF to DMA or NMP, the yield was slightly decreased (entries 7−8); other solvents provided limited reaction and gave trace amounts of product (entries 9−14). The copper acetate monohydrate is essential to the success of

Table 1. Condition Optimizations of 1,2-Dihydrophthalazines[a]



1a 2a 3aa

entry	Cu source	solvent	temp (°C)	atmos	yield (%)[b]
1	$Cu(OAc)_2 \cdot H_2O$	DMF	120	N_2	75
2	$Cu(OAc)_2 \cdot H_2O$	DMF	120	air	69
3	$Cu(OAc)_2 \cdot H_2O$	DMF	120	O_2	45
4	$Cu(OAc)_2 \cdot H_2O$	DMF	90	N_2	83
5	$Cu(OAc)_2 \cdot H_2O$	DMF	80	N_2	86
6	$Cu(OAc)_2 \cdot H_2O$	DMF	75	N_2	80
7	$Cu(OAc)_2 \cdot H_2O$	DMA	80	N_2	79
8	$Cu(OAc)_2 \cdot H_2O$	NMP	80	N_2	84
9	$Cu(OAc)_2 \cdot H_2O$	DMSO	80	N_2	0
10	$Cu(OAc)_2 \cdot H_2O$	*t*-AmylOH	80	N_2	0
11	$Cu(OAc)_2 \cdot H_2O$	Toluene	80	N_2	0
12	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	80	N_2	0
13	$Cu(OAc)_2 \cdot H_2O$	THF	80	N_2	0
14	$Cu(OAc)_2 \cdot H_2O$	PhCN	80	N_2	0
15	$Cu(TFA)_2$	DMF	80	N_2	0
16	$Cu(acac)_2$	DMF	80	N_2	0
17	$CuCl_2$	DMF	80	N_2	0
18	$Cu(OAc)_2$	DMF	80	N_2	85
19	$Cu(OAc)_2.H_2O$	DMF	80	N_2	87[c]
20	$\mathbf{Cu(OAc)_2 \cdot H_2O}$	**DMF**	**80**	$\mathbf{N_2}$	**92**[c,d]

[a] Reaction conditions: **1a** (0.30 mmol), *n*-butyl acrylate **2a** (3.0 equiv), [Cu] (2.0 equiv), $[RhCp^*Cl_2]_2$ (2.0 mol %), and solvent (1.5 mL) were allowed to react in a tube. $Cu(acac)_2$ = Cupric acetylacetonate, $Cu(TFA)_2$ = Cupric trifluoroacetate, NMP = *N*-Methyl pyrrolidone. $[RhCp^*Cl_2]_2$ = Pentamethylcyclopentadienylrhodium(III) chloride dimer. [b] Isolated yield. [c] $[RhCp^*Cl_2]_2$ (2.5 mol %). [d] In DMF (1.0 mL).

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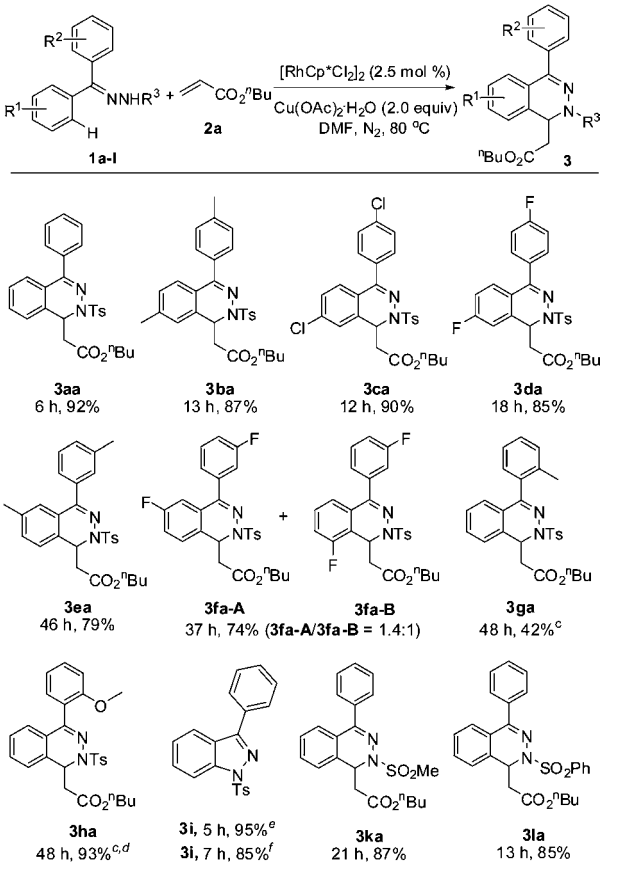
this transformation, while other copper sources such as $Cu(TFA)_2$, $Cu(acac)_2$, and $CuCl_2$ gave only a trace amount of product (entries 15–17) or led to a similar result when using $Cu(OAc)_2$ (entry 18). An improved yield could be achieved using 2.5 mol % of rhodium catalyst with an elevated concentration (entry 20, Condition A).

With the optimized reaction conditions in hand, we then extended the reaction with a range of substrates. As illustrated in Scheme 2, hydrazones containing both electron-donating (**3ba**, **3ea**) and electron-withdrawing groups (**3ca**, **3da**, and **3fa**) or bearing *para*- (**3ba**–**3da**) and *meta*-groups (**3ea**, **3fa**) proceeded efficiently with good to excellent yields. The regioselectivity of this reaction mainly depends on the steric hindrance of substrates. For example, moderate regioselectivity of **3fa-A**/**3fa-B** (1.4:1) was observed for a *meta*-fluoro containing substrate (**1f**), and the major product (**3fa-A**) corresponds to the C–C coupling at a less hindered position. Notably, the methyl and methoxyl substituent at the *ortho* position retarded the reaction, and the products were obtained in moderate yields with high regioselectivity (**3ga**, **3ha**).

Scheme 2. Reaction of Hydrazones with *n*-Butyl Acrylate[a,b]

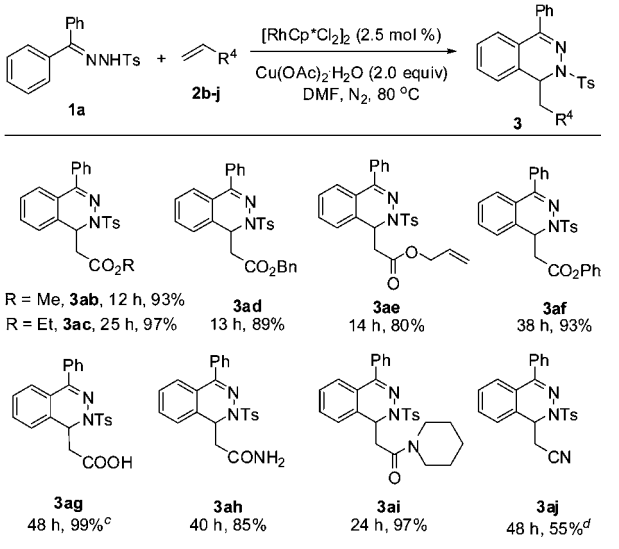


[a] Reaction conditions: **1** (0.3 mmol), **2a** (3.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) in DMF (1.0 mL), 80 °C, under nitrogen. [b] Isolated yield. [c] At 120 °C. [d] The yield based on 39% conversion of **1h**. [e] *N*′-((2-Bromophenyl)(phenyl)methylene)-4-methylbenzenesulfonohydrazide (**1i**) was used. [f] *N*′-((2-Chlorophenyl)(phenyl)methylene)-4-methylbenzenesulfonohydrazide (**1j**) was used.

The identity of **3ga** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis.[13] When *ortho*-brominated (**1i**) or *ortho*-chlorinated (**1j**) substrates were used, no corresponding dihydrophthalazine product could be isolated, and an intramolecular annulation reaction was accomplished to give 3-phenyl-1-tosyl-1*H*-indazole (**3i**) in high yields. It is worth mentioning that *N*-methyl or *N*-phenyl sulfonylhydrazones could also produce the corresponding products (**3ka**, **3la**) in good yields. However, attempts to replace the tosyl group with amide or aryl groups failed under the same conditions, which suggested that the acidity of the N–H is critical to the reaction.[9d]

To define the scope of this reaction better, we further applied other alkenes as the coupling partners for this oxidative olefination/annulation process (Scheme 3). Reactions involving alkenes conjugated with an alkyl or aryl acrylate led to good to excellent product yields (**3ab**–**3af**). For acrylate esters bearing an allyl group (**2e**), the electron-rich C=C double bond remained intact under optimized conditions and resulted in the formation of **3ae** in high yield. It should be noted that substrates bearing an acrylic acid or an unsubstituted amide group could be tolerated in this reaction and afforded products in good yields (**3ag**, **3ah**); the free –COOH or $-CONH_2$ group remained untouched in the reaction. *N,N*-Disubstituted amide and acrylonitrile could also be employed in this transformation and afforded the desired products in good yields (**3ai**, **3aj**).

Scheme 3. Reaction of *N*-Tosylhydrazone with Alkenes[a,b]

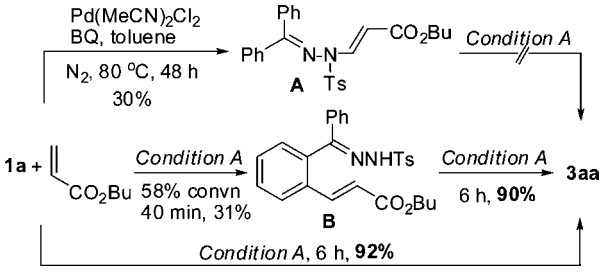


[a] Reaction conditions: **1a** (0.3 mmol), **2** (3.0 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol %), and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) in DMF (1.0 mL), 80 °C, under nitrogen. [b] Isolated yield. [c] The yield based on 69% conversion of **1a**. [d] $Cu(OAc)_2 \cdot H_2O$ (4.0 equiv) was used. The yield based on 84% conversion of **1a**.

(13) Crystal data for **3ga**: $C_{28}H_{30}N_2O_4S$, MW = 490.60, Monoclinic, $P21/n$, final R indices [$I > 2\sigma(I)$], $R1 = 0.0812$, $wR2 = 0.2240$, $a = 11.5309(16)$ Å, $b = 8.3030(12)$ Å, $c = 27.839(4)$ Å, $\alpha = 90°$, $\beta = 98.030(2)°$, $\gamma = 90°$, $V = 2639.2(7)$ Å^3, Crystal size = 0.40 × 0.20 × 0.20 mm, $T = 293(2)$ K, $Z = 4$, reflections collected/unique = 15995/5991 [R(int) = 0.0387]; Data, 5991; restraints, 0; parameters, 317.

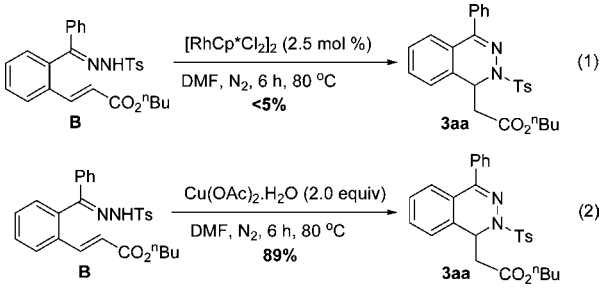
Two key compounds are proposed as possible intermediates for this reaction (Scheme 4), intermediate **A** generated through a Wacker-type mechanism[9k] or intermediate **B** via a Heck-type mechanism.[8d] To define the possible intermediate and pathway, several control experiments were performed. From intermediate **A**, which could be synthesized by palladium-catalyzed oxidative coupling of **1a** with *n*-butyl acrylate,[14] no annulation product **3aa** was obtained under Condition A (Scheme 4). This result implied that the reaction did not mainly proceed via intermediate **A**. When the reaction time was shortened to 40 min under Condition A, with 58% conversion of **1a**, intermediate **B** was isolated in 31% yield together with 25% yield of **3aa**, and **3aa** was further produced in 90% yield from synthesized **B** after reacting for 6 h under condition A (Scheme 4).

Scheme 4. Formation of **B** and **3aa** under Condition A[a]



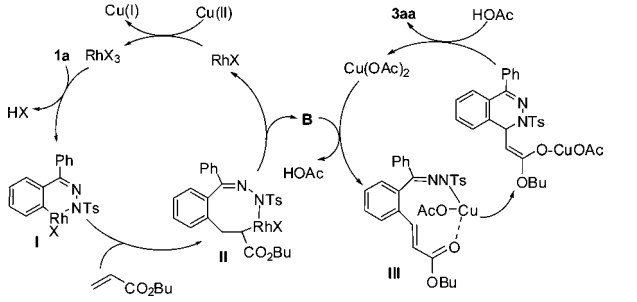
[a] Condition A: $[RhCp^*Cl_2]_2$ (2.5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) in DMF (1.0 mL), 80 °C, 6 h, under nitrogen.

To probe the role of rhodium and copper catalysts in this tandem process, several experiments were performed under the optimized reaction conditions. A trace amount of dihydrophthalazine **3aa** was produced without using copper acetate (eq 1), while an 89% yield of **3aa** was isolated in the absence of a rhodium catalyst (eq 2), which indicated that the $Cu(OAc)_2$ was crucial to facilitate this reaction.[15]



On the basis of these investigations, we proposed a plausible mechanism for this tandem reaction as depicted in Scheme 5. Coordination of hydrazone **1a** to a Rh(III) species facilitates the formation of the N−Rh bond, which in turn promotes the generation of a rhodacycle (**I**). This rhodacycle can coordinate 1 equiv of alkene and then undergo alkene insertion to give intermediate **II**. Subsequently, reductive elimination of **II** yields the intermediate **B** and a Rh(I) species, which is then re-oxidized by Cu(II) to regenerate Rh(III). The formed intermediate **B** presumably reacts with copper acetate to afford intermediate **III** with concomitant elimination of HOAc. Intermediate **III** likely undergoes a Michael addition followed by subsequent enolate protonation to give dihydrophthalazine **3aa**.

Scheme 5. Plausible Mechanism for Synthesis of **3aa** from **1a**



In summary, we have developed an efficient rhodium-catalyzed tandem C−H olefination and copper acetate promoted intramolecular C−N bond-forming protocol for the straightforward synthesis of 1,2-dihydrophthalazines. This approach provides one of the easiest pathways for accessing this class of valuable compounds from easily accessible sulfonylhydrazones and alkenes. The characteristics of excellent functional group tolerance and synthesis modularity will provide the described reaction with broad utility in organic synthesis. Further applications are under investigation in our group.

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Supporting Information Available. Experimental procedures and characterization data for all compounds, and X-ray structure of compound **3ga** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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