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Rhodium-Catalyzed Regio- and Stereoselective [2 + 2] Cycloaddition of Allenamides

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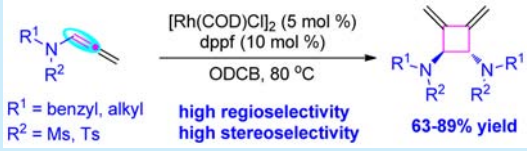
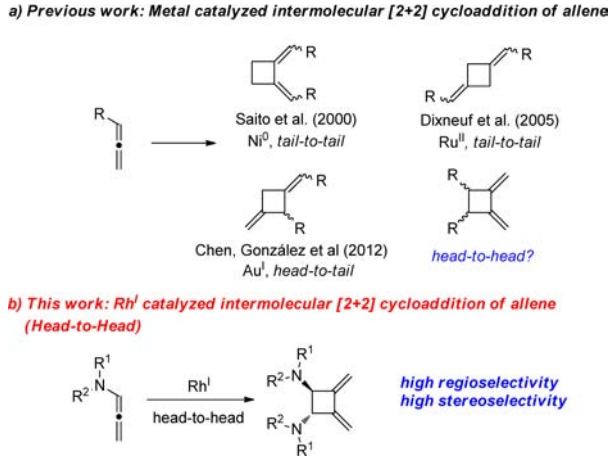
Supporting Information

ABSTRACT: A highly regio- and stereoselective Rh-catalyzed intermolecular head-to-head [2 + 2] cycloaddition of allenamides was developed. The intermolecular cycloadducts, *trans*-dimethylenecyclobutane-1,2-diamine derivatives, were achieved in good yields with high regioselectivity and stereoselectivity.



The [2 + 2] cycloaddition of allenes is a highly atom-economic and straightforward approach for the synthesis of cyclobutane derivatives.[1] Cyclobutanes are privileged structural motifs which constitute the core structure of many biologically active molecules including natural products[2] and are also expedient intermediates for various chemical transformations.[3] They can be achieved by either thermal or catalyzed [2 + 2] cycloaddition of allenes. Although the thermal [2 + 2] cycloaddition of allenes has been investigated extensively,[4] the control of regioselectivity (head-to-tail, tail-to-tail, head-to-head)[5] remains a formidable challenge. On the other hand, transition-metal-catalyzed [2 + 2] cycloaddition of allenes has been less explored, and highly regioselective intermolecular methods are scarce.[6−11] In 2000, Saito and co-workers reported nickel-catalyzed [2 + 2] cycloaddition of electron-deficient allenes in a tail-to-tail fashion to give 1,2-dimethylenecyclobutanes (Scheme 1a).[8f] Later, the Dixneuf group realized ruthenium catalyzed tail-to-tail cycloaddition of allenyl boronate to generate 1,3-dimethylenecyclobutanes (Scheme 1a).[9] In 2012, the Chen[7b] and González[7c] groups independently reported gold-catalyzed dimerization of allenamides to afford head-to-tail cyclobutane derivatives (Scheme 1a).

Scheme 1. Metal-Catalyzed Approaches toward Intermolecular [2 + 2] Cycloaddition of Allenes



Due to their unique reactivity, selectivity, and ease of accessibility, *N*-allenamides[12] have been widely employed as useful partners for [2 + 2],[13] [2 + 3],[14] [2 + 4],[15] and cascade cycloaddition[16] to construct four- to seven-membered carbocyclic or heterocyclic skeletons. Considering the fact that highly regio-, stereo-, and enantioselective head-to-head [2 + 2] cycloaddition[17] of allenes has not yet been explored, herein we report our recent findings on a rhodium-catalyzed head-to-head [2 + 2] cycloaddition of allenamides toward the synthesis of *trans*-dimethylenecyclobutane−diamine derivatives in a highly regio- and stereoselective manner (Scheme 1b).

We initiated our studies by investigating the cycloaddition of allenamide **1a** in the presence of commonly used Pd^0, Ir^I, and Ru^{II} complexes (Table 1, entries 1−3). Unfortunately, none of them worked for the designed cycloaddition. Pleasingly, we found that $[\{Cp^*RhCl_2\}_2]$ exhibited catalytic activity for this transformation. In the presence of 5 mol % of $[\{Cp^*RhCl_2\}_2]$ and 10 mol % of dppf (**L1**) in DCE at 80 °C, the head-to-head cycloaddition of **1a** took place to furnish the desired 3,4-dimethylenecyclobutane-1,2-diamine derivative **2a** in 17% yield (Table 1, entry 4). The structure of **2a** was unambiguously confirmed as *trans*-3,4-dimethylenecyclobutane-1,2-diamide by single-crystal X-ray diffraction analysis (Figure 1).[18]

Encouraged by this result, we tested other Rh^I precursors such as $[\{Rh(COD)OH\}_2]$ and $[\{Rh(COD)Cl\}_2]$ together with dppf and found that the catalyst derived from $[\{Rh(COD)Cl\}_2]$ is the most efficient one, affording **2a** in 64% yield (Table 1, entry 6). Further screening of solvents and ligands (see the Supporting Information and Table 1, entries 7−13) revealed that allenamide **1a** in 1,2-dichlorobenzene (0.1 M) in the presence of 5 mol % $[\{Rh(COD)Cl\}_2]$ and 10 mol % dppf at 80 °C leads to the

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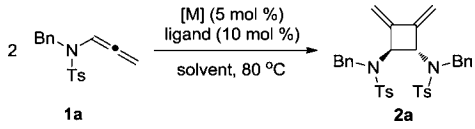
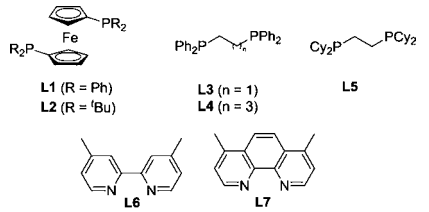
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	[M]	ligand	solvent	yield[b] (%)
1	$Pd(PPh_3)_4$		DCE	0
2	$[Ru(p\text{-cymene})Cl_2]_2$	L1	DCE	0
3	$[Ir(COD)Cl]_2$	L1	DCE	0
4	$(Cp^*RhCl_2)_2$	L1	DCE	17
5	$[Rh(COD)OH]_2$	L1	DCE	33
6	$[Rh(COD)Cl]_2$	L1	DCE	64
7	$[Rh(COD)Cl]_2$	L1	ODCB	83
8	$[Rh(COD)Cl]_2$	L2	ODCB	0
9	$[Rh(COD)Cl]_2$	L3	ODCB	59
10	$[Rh(COD)Cl]_2$	L4	ODCB	73
11	$[Rh(COD)Cl]_2$	L5	ODCB	41
12	$[Rh(COD)Cl]_2$	L6	ODCB	27
13	$[Rh(COD)Cl]_2$	L7	ODCB	<5

[a]Reaction conditions: 0.30 mmol of **1a**, 5 mol % of metal catalyst, and 10 mol % of ligand in solvent (0.1 M) at 80 °C. [b]Yield of isolated product **2a**. ODCB: 1,2-dichlorobenzene.



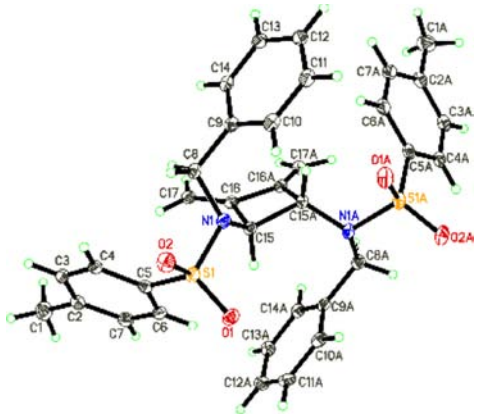
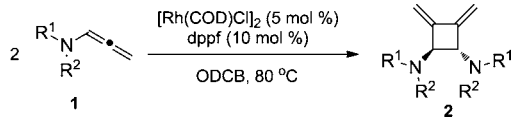


Figure 1. X-ray derived ORTEP of **2a** with thermal ellipsoids shown at the 35% probability level (symmetry transformations used to generate equivalent atoms: no. 1, $-x + 1, -y + 1, z$).

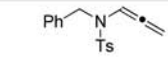
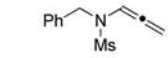
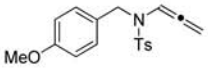
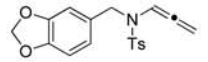
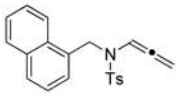
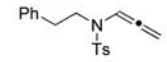
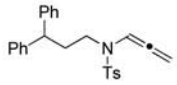
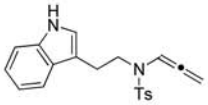
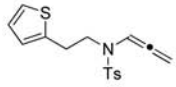
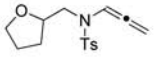
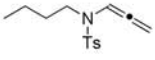
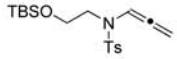
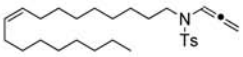
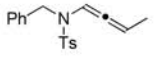
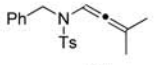
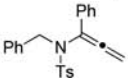
formation of dimethylenecyclobutane-1,2-diamine **2a** in 83% yield.[19]

With the optimized reaction conditions in hand (entry 7, Table 1), the generality of the intermolecular [2 + 2] cycloaddition of allenamides was explored (Table 2). The cycloaddition of mesyl-derived *N*-benzylallenamide **1b** resulted in the corresponding cyclobutane **2b** in 70% yield (Table 2, entry 2). Various *N*-benzyl allenamides **1c**−**e** with different substituents on the phenyl rings also worked well to furnish their corresponding products in good yields (Table 2, entries 3−5). Intriguingly, *N*-phenylethyl allenamide **1f** exhibited slightly improved reactivity to give the cyclobutane derivative **2f** in 89% yield (Table 2, entry 6). However, 3,3- diphenylpropyl

Table 2. Substrate Scope of [2 + 2] Cycloaddition of Allenamides[a]



1 2

entry	1		2, yield (%)[b]
1		1a	2a, 83
2		1b	2b, 70
3		1c	2c, 76
4		1d	2d, 86
5		1e	2e, 71
6		1f	2f, 89
7		1g	2g, 63
8		1h	2h, 88
9		1i	2i, 65
10		1j	2j, 71 (4:3 dr)
11		1k	2k, 66
12		1l	2l, 84
13		1m	2m, 76
14		1n	2n, 0
15		1o	2o, 0
16		1p	2p, 0

[a]Reaction conditions: 0.30 mmol of **1a**, 5 mol % of $[Rh(COD)Cl]_2$, and 10 mol % of dppf in 1,2-dichlorobenzene (0.1 M) at 80 °C. [b]Yield of isolated product **2**.

allenamide **1g** showed slightly low reactivity to furnish **2g** in moderate yield (63%, Table 2, entry 7). Allene amides comprising heterocyclic moiety were also well tolerated under the optimized reaction conditions (Table 2, entries 8−10). The reaction of the tryptamine-derived allenamide **1h** gave the

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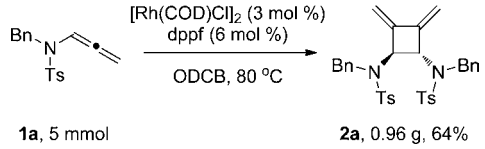
desired cyclobutane **2h** in 88% yield (Table 2, entry 8). Likewise, thiophene- or tetrahydrofuran-containing allenamides **1i** and **1j** also gave the corresponding cyclobutanes **2i** and **2j** in good yields (Table 2, entries 9 and 10). Silyl ether functionality such as OTBS was also found to be compatible under the optimized reaction conditions as the efficient cycloaddition of allenamide **1l** afforded corresponding cycloadduct **2l** in 84% yield (Table 2, entry12). Notably, allenamide **1m** with a long alkyl chain comprising an internal alkene motif also performed well, resulting in head-to-head product **2m** in 76% yield (Table 2, entry 13). However, allenamides with substituents on the allene motif (**1n–p**, Table 2, entries 14–16) exhibited no reactivity, probably due to steric hindrance.

To illustrate the practical utility of this methodology, a gram-scale experiment was performed. Accordingly, 1.50 g of **1a** was subjected to the optimized reaction conditions to give **2a** in 64% yield (Scheme 2).

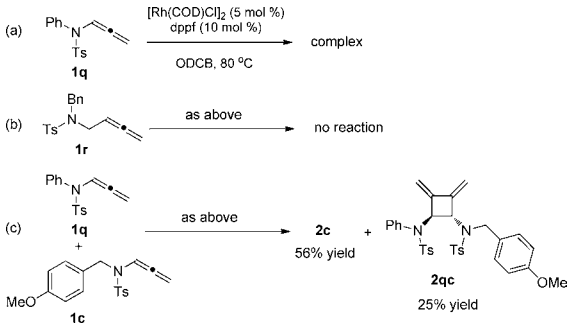
Scheme 2. Scale up Reaction



1a, 5 mmol **2a**, 0.96 g, 64%

In order to shed light on the reaction mechanism, the following control experiments were performed (Scheme 3). The

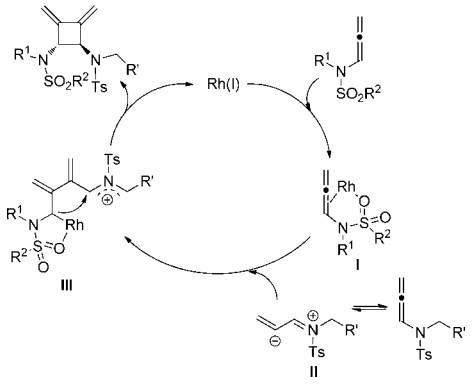
Scheme 3. Control Experiments



reaction of *N*-phenyl-substituted allenamide **1q** under the optimized conditions led to the formation of a complex mixture of several unidentified products. However, allene **1r** with a CH_2 group between the amide and allene motifs exhibited no reactivity. Interestingly, when the allenamides **1q** and **1c** were subjected to the optimized reaction conditions, 25% yield of the heterodimerization product **2qc** was achieved along with 56% yield of the dimer **2c**.

A proposed mechanism for the [2 + 2] cycloaddition of allenamides based on the control experiments is depicted in Scheme 4. The sulfonyl group assisted activation of the allenamide by the Rh catalyst affords intermediate **I**.[20] The intermolecular nucleophilic capture of **I** by zwitterion **II** generated from allenamide provides intermediate **III**. Finally, a ring-closing process through the attack of C–Rh to iminium and elimination of the Rh complex generates the [2 + 2] cycloaddition product. In consonance with this mechanism, the Rh-catalyzed reaction of **1q** showed low selectivity, possibly due to the lack of formation of stabilized iminium. However, when allenamides **1c** and **1q** were introduced to the reaction, the stable

Scheme 4. Proposed Mechanism for the [2 + 2] Cycloaddition of Allenamides



iminium intermediate **III** could be formed and afforded the heterodimerization product.

In conclusion, we have developed an efficient rhodium-catalyzed intermolecular head-to-head [2 + 2] cycloaddition of allenamides. The *trans*-dimethylenecyclobutane-1,2-diamine derivatives were obtained in moderate to good yields with high regioselectivity and stereoselectivity. Further investigations on the enantioselective variant of this protocol and deep study of reaction mechanism are currently underway in the laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01731.

X-ray data for compound **2a**, full screening of the reaction conditions, experimental procedures, characterization, and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Only one example of transition-metal-catalyzed head-to-head dimerization of allenes is available in the literature without identified stereoselectvity; see ref 9.

(18) CCDC-1447827 contains the supplementary crystallographic data for compound **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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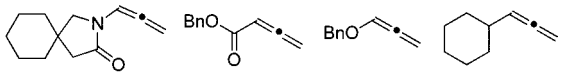
(20) Several allenes (**1r**−**u**) were investigated in our catalytic system. Compounds **1r** and **1u** exhibited no reactivity under optimal reaction conditions. Substrates **1s** and **1t** gave unidentified mixtures.



1r no reaction | **1s** complex | **1t** complex | **1u** no reaction

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