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Synthesis of Cyclopropanes via 1,3-Migration of Acyloxy Groups Triggered by Formation of α-Imino Rhodium Carbenes

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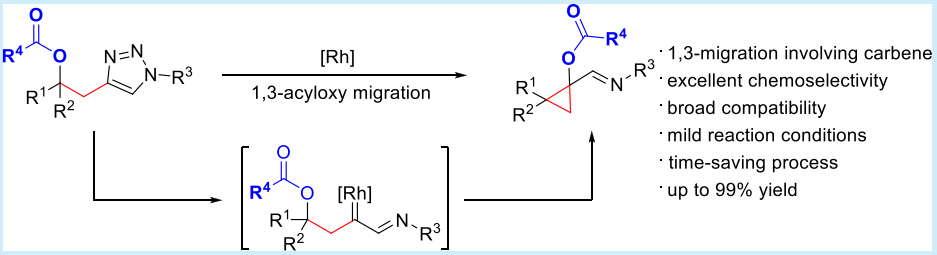

ABSTRACT: A novel and highly efficient synthetic approach to cyclopropanes was realized via 1,3-migration of acyloxy groups triggered by α-imino rhodium carbenes. Excellent chemoselectivity ensured broad compatibility of common functional groups. Merits such as readily available substrates, mild reaction conditions, and time-saving processes qualified this transformation as an attractive alternative strategy to synthesize multifunctionalized cyclopropanes. Primary investigations and discussion on the mechanism are presented.

Metallocarbene is one of the most important intermediates in modern organic chemistry, which shows versatile reactivity in the synthesis of complex chemicals.[1] In 2008, Gevorgyan, Fokin, and co-workers revealed that rhodium(II) salt could efficiently catalyze the transformation of 1-sulfonyl-1,2,3-triazole to α-imino rhodium carbene,[2] which enriches carbene chemistry remarkably.[3,4]

It is well-known that intramolecular 1,*n*-migration (or named as 1,*n*-insertion) is a common reaction mode in carbene chemistry.[5] The popular 1,2-migration of hydride, alkyl, as well as a heteroatom could deliver various substituted alkenes;[6] 1,4- and 1,5-H migration are convenient ways to prepare four- and five-membered cycles, respectively.[7,8] Specifically, we reported a 1,4-halo migration of α-imino rhodium carbene producing a dihydroquinoline skeleton.[9] The 1,6-, 1,7-, and even 1,14-migration involving carbene were reported, as well.[10,11]

Cyclopropane is unique not only due to its special structure but also due to its widespread presence in diverse bioactive molecules. The synthesis of cyclopropane is a well-investigated topic, in which Simmons−Smith−Furukawa cyclopropanation, Corey−Chaykovsky cyclopropanation, and transformations derived from them are the most popular classical methods.[12] However, the chemoselectivity of the reaction may be an issue when substrates bear carbene-sensitive or base-sensitive groups.

It is well-known that 1,3-migration triggered by carbene, predictably affording cyclopropane, is difficult to occur because a high barrier was required for the four-membered ring transition state. To the best of our knowledge, only two cases were reported before.[13] In 1962, Yates and Danishefsky reported that bicyclic diazoisofenchone could be converted to cyclopropane-fused tricyclic ketone in 53% yield via a 1,3-methyl migration mediated by a large excess of copper bronze in refluxing benzene under a nitrogen atmosphere (Scheme 1A). Due to the rigid conformation of the bicyclic skeleton, only 1,3-migration was achievable in the reaction.[13a] In 2005, Wang and co-workers reported the second 1,3-migration, in which the β-tosyl-α-diazo ester was converted to cyclopropane via rhodium-catalyzed 1,3-H migration (Scheme 1B). The presence of the β-tosyl group induced a predominant rigid conformation in which the migrating C−H bond paralleled the Rh=C bond, and the conformation favored the 1,3-migration over 1,2- or 1,5-migration.[13b] Accordingly, a conformational requirement was essential in both cases, whereas such a particular conformational requirement, on the other hand, limited the application of 1,3-migration in organic synthesis.

Transformation of carbene is a long-term topic in our group.[14] Except for the above-mentioned 1,4-halo migration,[9] formal 1,2-migration of acyloxy in a special α-imino rhodium carbene **2** was realized recently in our lab (Scheme 1C), and the in situ generated azadiene **4** was utilized as an effective 1-aza-[4C] synthon in the synthesis of piperidine derivatives.[15] Benefiting from the stability of the five-membered 1,3-dioxolane

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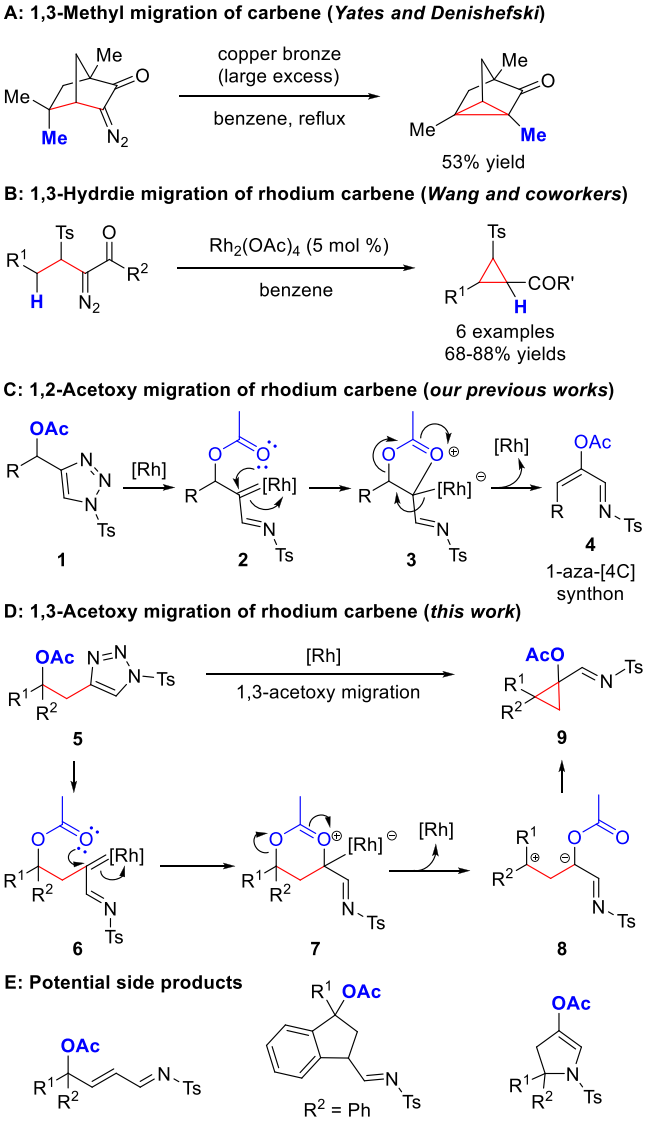
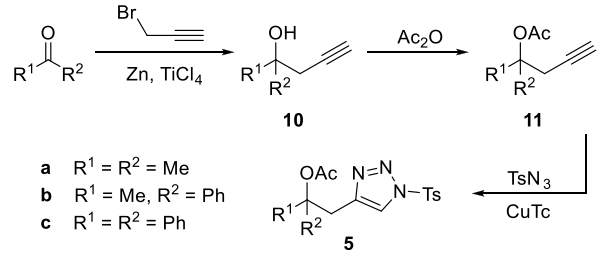
Scheme 1. Background and Reaction Design



intermediate **3**, the 1,2-acyloxy migration had excellent chemoselectivity. It is well-known that the six-membered ring was also stable enough and easily accessible. Accordingly, we envisioned whether, if a two-carbon linker was introduced between triazole and acyloxy, a similar six-membered 1,3-dioxane intermediate **7** would be generated, which may overcome the unachievable barrier in forming a four-membered transition state in the direct 1,3-migration reaction. The following ring opening by C−O bond cleavage along with the departure of rhodium catalyst produces 1,3-dipole **8**, which undergoes convenient ring closure to give cyclopropane **9** as the formal 1,3-acyloxy migration product (Scheme 1D). Based on the above proposal, we report herein the successful 1,3-migration of the acyloxy group induced by α-imino rhodium carbene and the application of such a method in cyclopropane synthesis.

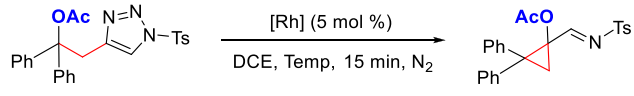
Initially, as depicted in Scheme 2, 1-sulfonyl-4-(2-acetoxylethyl)-1,2,3-triazole **5a−c** were prepared conveniently within three simple steps starting from commercially available materials (see Supporting Information for details).[16,17] *gem*-Dimethyl-substituted triazole **5a** was first submitted to $Rh_2(OAc)_4$ (5 mol %) in refluxing 1,2-dichloroethane (DCE) under a nitrogen atmosphere. Unfortunately, along with gradual decomposition of

Scheme 2. Synthesis of Triazole 5



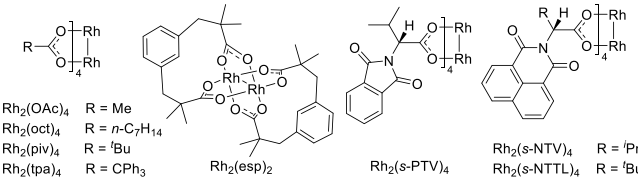
the substrate, nothing recognizable was obtained (entry 1, Table 1). In order to improve the stability of the carbocation in

Table 1. Optimization of Reaction Conditions[a]



entry	[Rh]	solvent	temp (°C)	yield (%)[b]
1[c]	$Rh_2(OAc)_4$	DCE	reflux	0
2[d]	$Rh_2(OAc)_4$	DCE	reflux	0
3	$Rh_2(OAc)_4$	DCE	reflux	90
4	$Rh_2(esp)_2$	DCE	reflux	74
5	$Rh_2(oct)_4$	DCE	reflux	92
6	$Rh_2(piv)_4$	DCE	reflux	86
7	$Rh_2(tpa)_4$	DCE	reflux	14
8	$Rh_2(s\text{-}ntv)_4$	DCE	reflux	87
9	$Rh_2(s\text{-}ptv)_4$	DCE	reflux	75
10	$Rh_2(s\text{-}nttl)_4$	DCE	reflux	16
11	$Rh_2(piv)_4$	DCE	60	91
12	$Rh_2(piv)_4$	DCM	reflux	0
13	$Rh_2(piv)_4$	chloroform	60	85
14	$Rh_2(piv)_4$	toluene	60	83
15	$Rh_2(piv)_4$	ethyl acetate	60	73
16	$Rh_2(piv)_4$	DMF	60	80
17	$Rh_2(piv)_4$	DMSO	60	0
18[e]	$Rh_2(piv)_4$	DCE	60	98
19[f]	$Rh_2(piv)_4$	DCE	60	89
20		DCE	60	0

[a]Reagents and conditions: **5c** (0.2 mmol, 1.0 equiv), [Rh] (5 mol %), solvent (1 mL), N_2 atmosphere. [b]Isolated yield. [c]**5a** was used, and the reaction time was 40 min. [d]**5b** was used, and the reaction time was 40 min. [e]3 mol % of $Rh_2(piv)_4$ was used. [f]2 mol % of $Rh_2(piv)_4$ was used. Ts = tosyl, DCE = 1,2-dichloroethane, DCM = dichloromethane, DMF = dimethylformamide, DMSO = dimethyl sulfoxide.



intermediate **8**, **5b** was employed but produced no desired product either (entry 2). Gratifyingly, when *gem*-diphenyl-substituted triazole **5c** was exposed to the same conditions, the desired 1,3-acyloxy migration product **9c** was obtained in 90% yield (entry 3). No predicted side products, as shown in Scheme 1E, were detected, illustrating excellent chemoselectivity of the 1,3-migration.

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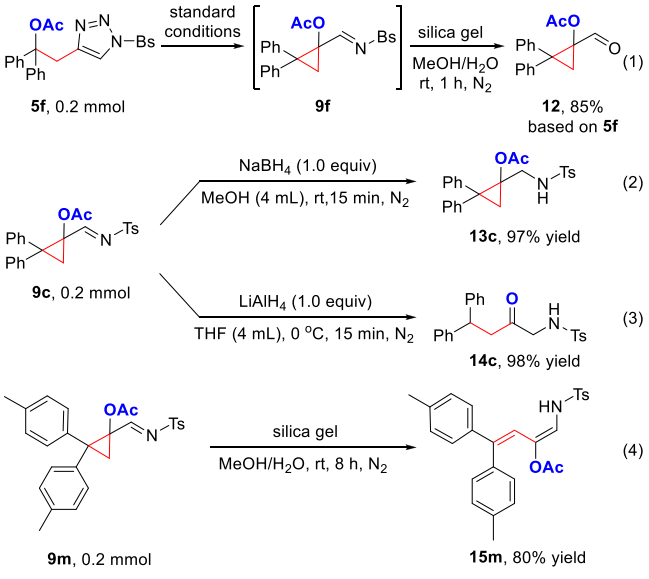
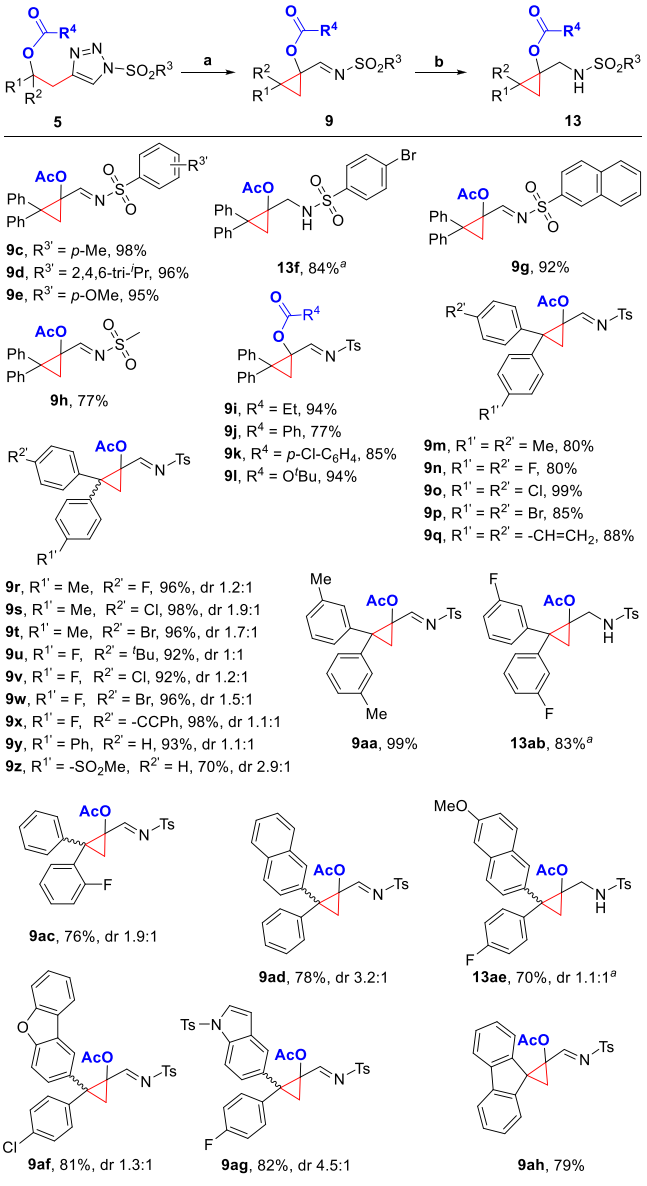
Consequently, **5c** was selected as the model substrate to establish the optimal reaction conditions. Various rhodium(II) salts were evaluated (entries 4−10). Generally, most of the tested rhodium salts exhibited high efficiency in this transformation. When 5 mol % of $Rh_2(esp)_2$ was used, the desired **9c** was generated in 74% yield (entry 4); $Rh_2(oct)_4$ performed well, and **9c** was isolated in 92% yield (entry 5); bulky catalyst $Rh_2(piv)_4$ worked well, too, giving **9c** in 84% yield (entry 6), whereas bulkier $Rh_2(tpa)_4$ was slower in the reaction, and **9c** was isolated in only 14% yield (entry 7); bowl-shaped catalysts exhibited diverse activities in the reaction; for instance, $Rh_2(s\text{-}NTV)_4$ and $Rh_2(s\text{-}PTV)_4$ were suitable catalysts for the transformation and produced **9c** in 87 and 75% yields, respectively (entries 8 and 9); however, when $Rh_2(s\text{-}NTTL)_4$ was employed, only 16% yield was achieved (entry 10). $Rh_2(piv)_4$ was proven to be more suitable for further screening because, at a lower temperature (60 °C), 91% yield of **9c** was obtained (entry 11). Further survey of solvents was conducted. Reaction in refluxing DCM could not provide any product, which attributed to the low boiling point (entry 12); chloroform and toluene were also suitable for the reaction (85 and 83% yield, respectively, entries 13 and 14). Remarkably, polar solvents such as ethyl acetate and DMF could also be employed (73 and 80% yields, respectively, entries 15 and 16), and no side reaction between triazole and DMF[18a] occurred, indicating high chemoselectivity of this reaction. DMSO could coordinate to the vacant site of the rhodium catalyst,[18b] thus giving no product (entry 17). The dosage of $Rh_2(piv)_4$ could be reduced to 3 mol %, producing **9c** in nearly quantitative yield (98%, entry 18). No **9c** was generated without rhodium catalyst (entry 20).

As depicted in Scheme 3, the scope of the 1,3-migration was evaluated starting with various sulfonyl groups in 1,2,3-triazole **5**. Electron-donating-group-substituted aryl sulfonyls were perfectly compatible, and the corresponding cyclopropanes **9c−e** were obtained in excellent yields (95−98%); however, pure *p*-bromophenyl-sulfonyl-substituted product **9f** was not obtained directly because of partial hydrolysis (aldehyde **12** was generated; see eq 1); it could be reduced in situ to **13f**, which



was isolated in 84% yield in two steps. The steric effect of sulfonyl influenced the reaction marginally as 2,4,6-tri-isopropylphenyl- and 2-naphthyl-substituted **9d** and **9g** were produced in excellent yield, as well (96 and 92%). Alkyl sulfonyl performed less

Scheme 3. Reaction Scope



Condition **a**: **5** (0.2 mmol), $Rh_2(piv)_4$ (3 mol %), DCE (2.0 mL), 60 °C, 15 min, N_2. Condition **b**: crude **9** from 0.2 mmol **5**, $NaBH_4$ (1.0 equiv), MeOH (4.0 mL), rt, 15 min, N_2. [a]**13** was obtained from a one-pot reaction from triazole **5**, and the yield was calculated based on the corresponding triazole.

effectively, and **9h** was generated in 77% yield. Different kinds of migrating acyloxy groups were examined next. Propionyloxy migrated favorably, delivering **9i** in 94% yield, whereas benzoxy groups slightly retarded the reaction, and **9j** and **9k** were generated in 77−85% yields. Gratifyingly, the Boc group survived during the reaction, affording **9l** in excellent yield (94%). Various R^1 and R^2 groups were compatible, as well. When R^1 and R^2 were the same group, **9m-q**, **9aa**, and **13ab** could be isolated in 80−99% yields. If R^1 was different than R^2, **9r-z** and **9ac-ag** were obtained in 70−98% yields, yet the diastereoselectivity was low for most examples except for **9ag** (dr 4.5:1). Common functionalities, including strong electron-withdrawing and electron-donating groups (such as sulfonyls and −OMe), were compatible (**9z**, **13ae**, and **9ag**), and the position of the functionalities was not limited (**9aa**, **13ab**, **9ac**, **13ae**, and **9ag**).

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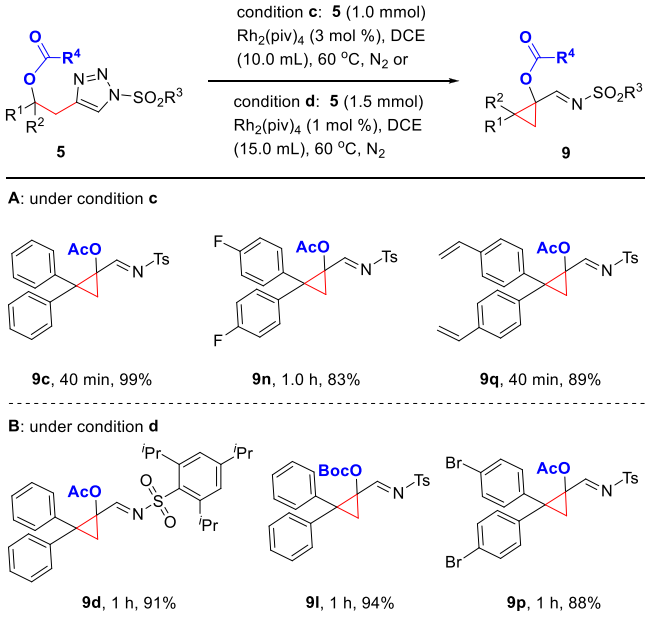
Heteroaromatics were also tolerated (**9af** and **9ag**). Remarkably, carbene-sensitive groups, such as a carbon−carbon double bond and triple bond, survived in **9q** and **9x**. Gratifyingly, spiro[2.4]-heptane **9ah** could be generated in satisfactory yield, elucidating the power of this protocol in organic synthesis.

The reaction could be enlarged to a preparative scale with the yields maintained (Scheme 4). For instance, **9c**, **9n**, and **9q** could

Scheme 4. Reactions in Preparative Scale



be obtained in even higher yields via 1.0 mmol scale reactions under standard conditions (Scheme 4A). Gratifyingly, the dosage of the catalyst could be reduced to 1 mol % when the reactions were conducted in 1.5 mmol scale, and the yields of **9d**, **9l**, and **9p** were almost the same as that obtained under standard conditions (Scheme 4B).

The potential of the protocol in organic synthesis was further illustrated by derivatization of the target cyclopropanes. As revealed, the imino group of **9f** could be hydrolyzed easily. Accordingly, a one-pot synthesis of aldehyde **12** from triazole **5f** was conducted, and **12** was obtained in 85% yield (eq 1). As performed for **9f**, the imine group in **9c** could also be reduced with 1.0 equiv of $NaBH_4$, giving sulfamide **13c** in 97% yield (eq 2). Interestingly, when 1.0 equiv of $LiAlH_4$ was used as the reductant, α-amino ketone **14c** was produced in 98% yield (eq 3). The cyclopropane ring in **9m** could be opened easily under acidic conditions, as well, and diene **15m** could be afforded in 80% yield after treatming **9m** with wet silica gel in methanol at rt (eq 4).

To confirm whether the migration is intramolecular or not, a mixture of **5e** and **5j** was submitted to the standard conditions. Only intramolecular migrating products **9e** and **9j** were isolated in 84 and 75% yields, respectively, and no cross-migrating products were detected (eq 5). The acyl group was essential for the 1,3-migration reaction because when hydroxyl-substituted triazole **5ai** was submitted to the standard conditions, no 1,3-migration product **9ai** was detected, whereas cyclobutanone **16** was generated in 65% yield via O−H insertion and rearrangement (eq 6). Subsequently, competitive reaction between same amount of *gem*-di-*p*-tolyl triazole **5m** and *gem*-di-*p*-Cl-phenyl triazole **5o** was conducted under the standard conditions, and the reaction progress was monitored by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard (Figure 1). Obviously, the initial reaction rate of electron-rich triazole **5m**

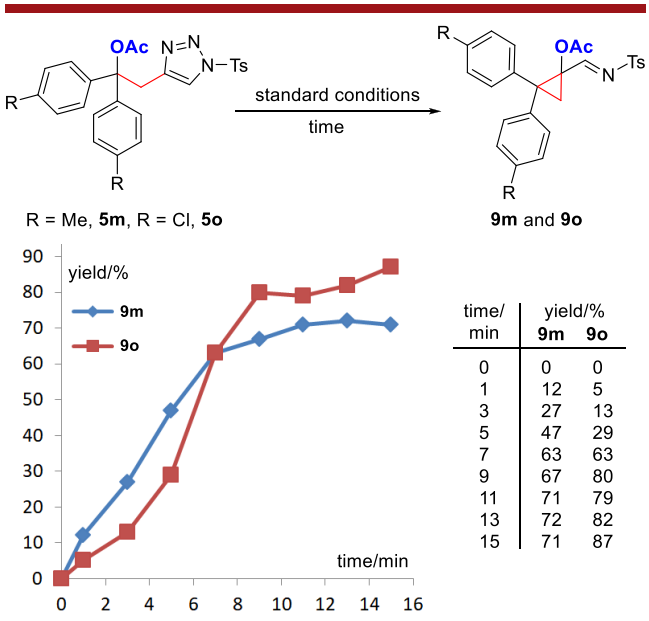
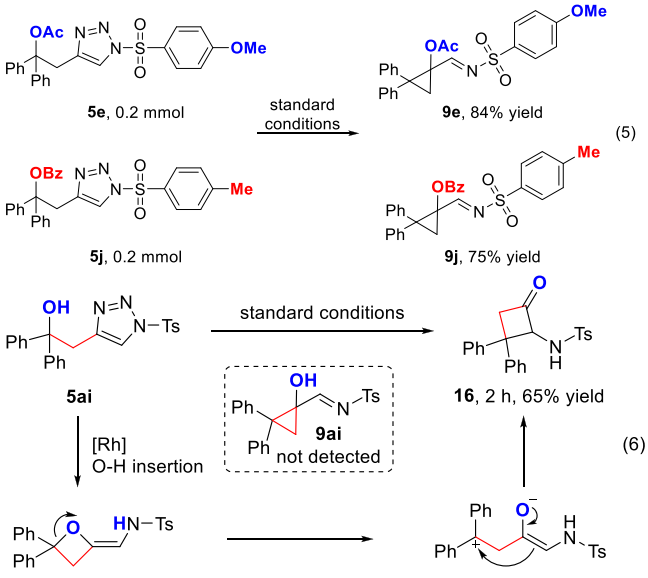


Figure 1. Competitive reaction of **5m** and **5o**. Conditions: **5m** (0.2 mmol), **5o** (0.2 mmol), $Rh_2(piv)_4$ (6 mol %), DCE (4.0 mL), 60 °C, time, N_2. The yields were obtained by ^{1}H NMR with 1,3,5-trimethoxybenzene (0.4 mmol) as the internal standard.

was faster than that of electron-poor triazole **5o**, illustrating that the electron-donating group accelerated the reaction, whereas the electron-withdrawing group decelerated the reaction. This result is consistent with the fact that the electron-donating group increases the stability of intermediate **8**. After 7 min, the yield of **9o** was higher than the yield of **9m**, and we believe this fact is attributed to the relative stability of **9o** and **9m**. **9m**, which bears an electron-rich aromatic ring, is easier to participate in a ring-opening reaction possibly because of the Lewis acidity of the rhodium catalyst (see eq 4). Accordingly, based on the experimental facts reported herein as well as in the literature, the mechanism proposed in Scheme 1D was reasonable.



In conclusion, a novel and practical synthetic method of functionalized cyclopropane was achieved via 1,3-migration of an

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acyloxy group triggered by α-imino rhodium carbene. Acyloxy reacted with rhodium carbene chemospecifically, and the excellent chemoselectivity ensured compatibility of common functional groups, especially carbene-sensitive groups. Readily available substrates, mild reaction conditions, and time-saving processes enhanced the synthetic potential of this protocol. The reaction could be scaled up without decreasing the yields with only 1 mol % of Rh catalyst. A three-membered ring, ester, and imine could act as powerful functional groups for further transformation, and several useful derivatizations have been realized, illustrating the power of this protocol. Investigations of the 1,3-migration of other groups induced by diverse types of carbenes, as well as the detailed mechanism, are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01764.

Details of experimental procedures (PDF)

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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