Rhodium Catalysis

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Synthesis of Highly Functionalized Cyclohexenone Rings: Rhodium-Catalyzed 1,3-Acyloxy Migration and Subsequent [5+1] Cycloaddition**

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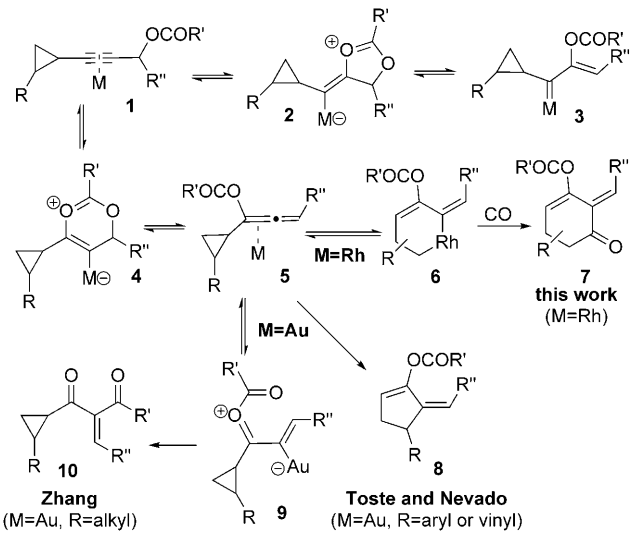
The Diels–Alder cycloaddition represents the most powerful technology for the preparation of substituted cyclohexenes and has proven to be extremely valuable in organic synthesis.[1] However, efficient syntheses of cyclohexenes having diverse substitutions, stereochemistry, and functionalities are still challenging and continue to stimulate the development of novel cycloaddition reactions.[2] We report herein a stereoselective synthesis of highly functionalized cyclohexenones from substituted cyclopropanes through a rhodium-catalyzed 1,3-acyloxy migration and subsequent [5+1] cycloaddition. Given the well-documented strategies for the preparation of optically pure cyclopropanes,[3] this promises to be a versatile method for the synthesis of complex cyclohexenones from cyclopropanes.[4]

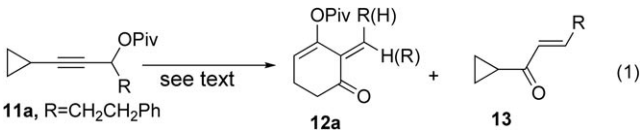
We previously reported a synthesis of highly substituted cyclobutenes from cyclopropyl metal carbenes derived from transition metal catalyzed decomposition of diazo compounds.[5,6] A more convenient and atom-economical[7] alternative for generating metal carbene intermediates would be the 1,2-acyloxy migration of propargyl esters, which has been realized using Au^{I},[8] Pt^{II},[9] Ru^{II},[10] Pd^{II},[11] and more recently Rh^{I},[12] the reports of which appeared while we were conducting our investigation.[13] When we searched for reaction conditions to form the cyclopropyl metal carbene **3** through 1,2-acyloxy migration, we isolated the highly functionalized cyclohexenone **7** when $[\{Rh(CO)_2Cl\}_2]$ was employed as the catalyst (Scheme 1).

Cyclohexenone **7** was presumably generated by insertion of CO into the metallocyclohexene **6** (M = Rh),[14] which was derived from the 1,3-acyloxy migration[15] of propargyl ester **1** and subsequent ring expansion of the allenyl ester **5**.[16] Gold catalysts could promote the formation of cyclopentene **8**, enone **10**, and some other isomerization or hydrolysis products from cyclopropane **1**.[17,18] Cyclopentene **8** was derived from direct ring expansion of allene **5** when R was either an aryl or vinyl group.[17] The cyclopropane ring was not required for the transformation of allene **5** into the intermediate **9**.[18] Clearly, allenyl ester **5** may undergo a variety of different reactions including isomerization (e.g., formation of **8** and **9**) and hydrolysis when it was generated by π-acidic metals. We found for the first time that allenyl ester **5** could be trapped by the $[\{Rh(CO)_2Cl\}_2]$ catalyst for a [5+1] cycloaddition. The ability of this rhodium catalyst to promote both the acyloxy migration and the subsequent cycloaddition not only increases the synthetic efficiency but also allows the development of new cycloaddition reactions.



Scheme 1. Diverse products from the metal-catalyzed acyloxy migration.

The cyclohexenone **12a** was obtained as an mixture of isomers (*E*/*Z* = ca. 1:1) in about 30% yield from **11a** in the presence of 20 mol% of the $[\{Rh(CO)_2Cl\}_2]$ catalyst in toluene at room temperature [Eq. (1); Piv = pivaloate]. The



(1)

product **12a** was isolated in 93% yield by running the reaction with an attached CO balloon for 5 hours at 60°C. The temperature can be reduced to room temperature without

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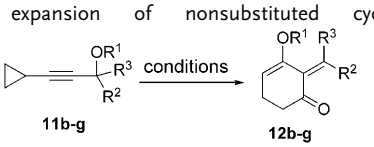
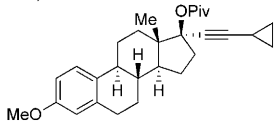
decreasing the yield of **12a** by lowering the CO pressure to between 0.1 and 0.2 atm through diluting the CO in the balloon with nitrogen.[19] Separation of the two geometric isomers of **12a** and resubmitting each of them to the reaction conditions did not change the configuration, suggesting that the *E*/*Z* isomers did not equilibrate under the reaction conditions. A significant amount of the enone **13** was isolated when a cationic rhodium catalyst (e.g., $[\{Rh(CO)_2Cl\}_2]$/AgOTf or $[Rh(cod)_2]BF_4$) (cod = 1,5-cyclooctadiene) was employed. The addition of ligands (e.g., phosphine, phosphite, and pyridine) either decreased the conversion or completely shut down the reaction.

We then examined the tandem 1,3-acyloxy migration/[5+1] cycloaddition for substrates **11b–g**, which were prepared from commercially available cyclopropyl acetylene and either an aldehyde or ketone (Table 1). The reaction was still conducted under 1 atm of CO at 60 °C for convenient operation and consistent results. High yields of products were isolated for substrates derived from various aldehydes and ketones. High *E*/*Z* selectivity could be obtained for propargyl esters having bulky substituents (Table 1, entries 3 and 6), and a single product was obtained for substrate **11e** (Table 1, entry 4). The cycloaddition worked well when the ester was changed from pivaloate to acetate (Table 1, entry 5). A highly functionalized product can also be prepared from **11g**, which is derived from steroids (Table 1, entry 6).

Table 1: Ring expansion of nonsubstituted cyclopropanes.[a]



11b-g **12b-g**

Entry	Substrate	*E*/*Z*	Yield [%]
1	**11b**, R^1 = Piv, R^2 = H, R^3 = Ph	2:1	95[b]
2	**11c**, R^1 = Piv, R^2 = H, R^3 = *i*Pr	1:1	87[b]
3	**11d**, R^1 = Piv, R^2 = H, R^3 = *t*Bu	10:1	92[b]
4[c]	**11e** R^1 = Piv, R^2 = R^3 = Me	–	88
5	**11f**, R^1 = Ac, R^2 = R^3 = Me	–	85
6	**11g** 	13:1	91[b]

[a] Reaction conditions: $[\{Rh(CO)_2Cl\}_2]$ (5 mol%), CO (1 atm), toluene, 60 °C, 5 h. [b] Yield of product including both isomers. [c] 2.5 mol% catalyst, 60 °C, 1 h.

For unsymmetrically substituted cyclopropanes, the cleavage of different cyclopropane C–C σ bonds may lead to different isomers. Our research group[5] and that of others[20,21] have found that the regioselectivity for the cleavage of C–C σ bonds in cyclopropanes depends on the stereochemistry of the cyclopropane ring, the electronic properties of the substituents, and the nature of the metal catalysts. Indeed, the opposite regioselectivity was observed for *trans*- and *cis*-phenyl-substituted cyclopropanes **14** and **17**, respectively (Table 2). In the case of alkyl substituents, both *trans*-**18** and *cis*-**21** gave product **19** as the major isomer and much higher

Table 2: Ring expansion of substituted cyclopropanes.[a]

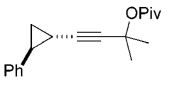
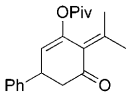
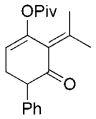
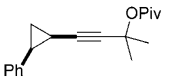
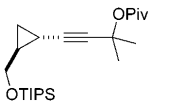
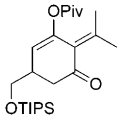
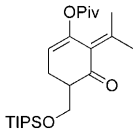
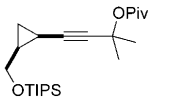
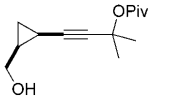
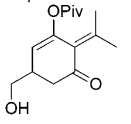
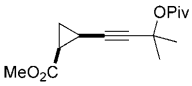
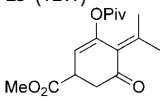
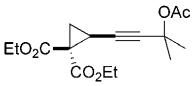
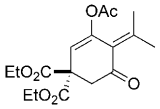
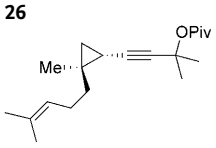
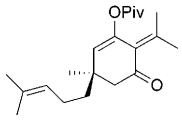
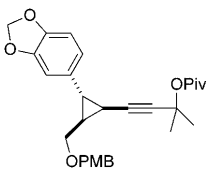
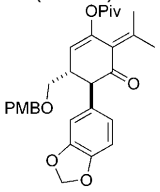
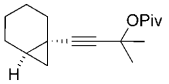
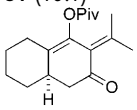
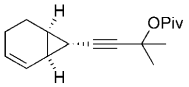
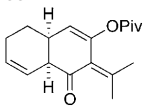
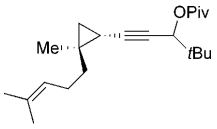
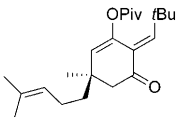
Cyclopropane	Cyclohexenones[b]		Yield [%][c]
			
14	**15**	**16**	
	15/16 = 1:2.5[b]		90[d]
			
17	**15/16** = 3.5:1[b]		95[d]
			
18	**19**	**20**	
	19/20 = 10:1[b]		91
			
21	**19/20** > 20:1[b,e]		93
			
22	**23** (12:1)[b]		79
			
24	**25**		76[f]
			
26	**27**		74
			
28 (87% *ee*)	**29** (87% *ee*)		86
			
30	**31** (16:1)[b]		80
			
32	**33**		80[g]
			
34	**35**		82[g]

Table 2: (Continued)

Cyclopropane	Cyclohexenones[b]	Yield [%][c]
		
36 (d.r. = 1:1)	**37** (*E*/*Z* = 10:1)	74[h]

[a] Reaction conditions: see footnote [a] of Table 1, unless noted otherwise. [b] Regioisomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yields are of the major isomer (isolated) unless noted otherwise. [d] Yield is for **15** and **16** combined. [e] The reaction was run at RT. A 16:1 ratio was observed at 60 °C. [f] Other unidentified by-products were observed. [g] Products without CO insertion were also isolated. See text for details. [h] 80 °C, 24 h. TIPS = triisopropylsilyl.

selectivity was observed for the *cis*-isomer **21**. The tandem reaction worked at room temperature for the *cis*-isomer **21** even with 1 atm of CO and a slightly higher regioselectivity was obtained at room temperature. The same trend of regioselectivity was observed for the cyclopropanes **22** and **24**. Substrates having quaternary carbon atoms, such as cyclopropanes **26** and **28** yielded only one isomer. High regioselectivity was also observed for the 1,2,3-trisubstituted cyclopropane **30**. The aryl and $PMBOCH_2$ groups in cyclopropane **30** should direct the cleavage of the same C–C σ bond on the basis of regioselectivity observed for the substrates **14** and **21**.

The chirality of cyclopropane **28** was completely transferred to cyclohexenone **29**,[22] thus confirming that cyclohexenones can be enantioselectively synthesized from optically pure cyclopropanes. The highly functionalized decalin rings **33** and **35** were also prepared in high yields from bicyclic substrates with high regioselectivity. Five-membered ring isomerization products were isolated in 19% and 11% yields from substrates **32** and **34**, respectively under the standard reaction conditions.[20] Interestingly, no five-membered ring isomerization product was observed in the monocyclic system even in the absence of a CO atmosphere.

Cleavage of the less hindered C–C σ bonds occurred selectively for most cyclopropanes in Table 2. The substituent that is *cis* to the propargyl ester generally has a more significant steric effect than the corresponding *trans* substituent. For cyclopropanes **14** and **34**, the C–C σ bonds that are adjacent to aryl or vinyl groups were selectively cleaved presumably because of the electronic effect of the adjacent π system.[5,20,21] Relatively low regioselectivities observed for the phenyl-substituted cyclopropanes **14** and **17** may be the result of competing steric and electronic effects.

The *E*/*Z* ratio is 10:1 for the product **37** when a mixture of cyclopropane **36** (d.r. = 1:1) is employed as the starting material. We demonstrated that the two *Z*/*E* isomers of cyclohexenone **12a** did not equilibrate under the reaction conditions. If the Rh^I-catalyzed 1,3-acyloxy migration of the propargyl ester is stereospecific and the configuration of the resulting allene is stable under the reaction conditions, one would expect a 1:1 *E*/*Z* ratio for **37**. Our result suggests that either the 1,3-acyloxy migration is not stereospecific or the two diastereomeric allenes can interconvert, which is similar to what was observed for gold catalysts.[17]

In summary, we have developed an efficient and highly selective method for the synthesis of polysubstituted cyclohexenones. Regioselective cleavage of C–C σ bonds can be achieved for various substituted cyclopropanes. The π-acid property of the $[\{Rh(CO)_2Cl\}_2]$ catalyst and its ability to readily undergo oxidative addition/reductive elimination will lead to a number of opportunities for mechanistic investigations, the design of new reactions, and target-oriented synthesis of natural products and pharmaceutical agents, such as cyclohexenone-containing compounds.[23]

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Keywords: carbocycle · cycloaddition · rhodium · ring expansion · synthetic methods

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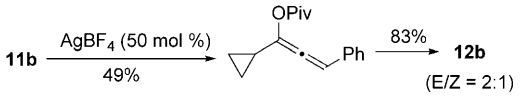

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