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Rh-catalysed [5 + 1] cycloaddition of allenylcyclopropanes and CO: reaction development and application to the formal synthesis of (–)-galanthamine†

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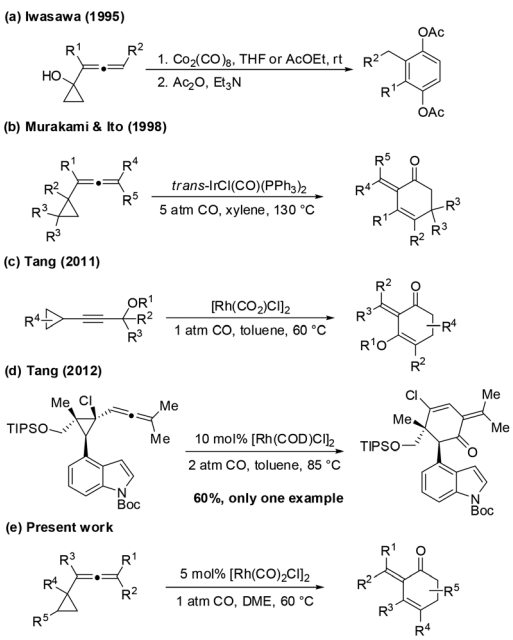
A Rh-catalysed [5 + 1] cycloaddition of allenylcyclopropanes and CO has been developed to synthesize functionalized 2-methylidene-3,4-cyclohexenones. The scope of this methodology has been investigated, showing that various functional groups can be tolerated. Both di- and tri-substituted allenylcyclopropanes can be applied to this cycloaddition and the [5 + 1] cycloadducts with the *E* configuration were obtained as the major products. In addition, the present [5 + 1] cycloaddition reaction has been utilized as a key step in the formal synthesis of the natural product (–)-galanthamine.

During the past few decades, transition-metal-catalysed cycloadditions, which provide powerful approaches to synthesize various sized ring compounds ranging from three- to nine-membered rings, have attracted many researchers' attention. These reactions usually take place under mild reaction conditions and give high yields of cycloadducts of various scaffolds. Among them, developing new metal-catalysed cycloadditions to synthesize six-membered non-benzenoid carbocycles is one of the most actively pursued research fields, considering that six-membered non-benzenoid carbocycles are the most ubiquitous ring skeletons in organic molecules.

Until now, many elegant transition-metal-catalysed cycloadditions,[1] for example, the metal-catalysed [3 + 3], [4 + 2], [5 + 1], [2 + 2 + 2], [3 + 2 + 1], and [4 + 1 + 1] reactions, have been developed for the synthesis of six-membered carbocycles. Among them, the [5 + 1] reactions of vinylcyclopropanes (VCPs) and CO to various functionalized cyclohexanones have been under intensive investigations. As early as 1969, Sarel reported the [5 + 1] reaction of 1,1-dicyclopropylethylene with CO to generate a cyclohexanone product.[2] They also discovered that this reaction could be induced by photoirradiation for VCPs with various functional groups.[3,4] Soon after that, Taber's group deeply investigated such a reaction[5] and applied the methodology to the synthesis of several natural products.[6] Recently we reported that $Fe_2(CO)_9$ could also mediate the [5 + 1] reaction of VCPs and CO without photoirradiation.[7] Apart from iron, other metal catalysts could also be used to catalyse or promote these transformations. In 2005, de Meijere reported the [5 + 1] reaction catalysed by $Co_2(CO)_8$ and $[Rh(CO)_2Cl]_2$,[8] yet only limited substrates can be applied to this methodology. In 2012, our group reported the cationic Rh-catalysed [5 + 1] cycloaddition of VCPs and CO, which can use a broad range of VCP substrates and gave good yields of [5 + 1] cycloadducts.[9] Despite the [5 + 1] cycloadditions involving VCPs having been deeply investigated, there are few examples involving the cycloadditions of allenylcyclopropanes (ACPs)[10] and CO where ACPs act as the five-carbon unit (Scheme 1).



Scheme 1 Selected [5 + 1] reactions and the present investigated one.

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In 1995, Iwasawa's group reported the synthesis of substituted hydroquinone using the Co-catalysed [5 + 1] strategy of 1-allenylcyclopropanols with CO (Scheme 1a).[11] Several years later, Murakami and Ito found that, Vaska's complex IrCl(CO)$(PPh_3)_2$ can catalyse the [5 + 1] reaction of ACPs and CO to generate the functionalized 2-methylidene-3,4-cyclohexenones (Scheme 1b).[12] However, harsh reaction conditions were needed (temperature was higher than 130 °C and 5 atm CO was used), and the separation of the [5 + 1] cycloadducts was resorted to using preparative thin layer chromatography, which seriously restricted the application of this methodology in large scale synthesis. Tang and co-workers elegantly developed a Rh-catalysed tandem 1,3-acyloxy migration/[5 + 1] cycloaddition reaction to produce highly functionalized cyclohexanones with alkoxy groups attaching the six-membered rings (Scheme 1c).[13] Tang and co-workers also showed in their synthesis of the core of welwitindolinones C that Rh-catalyzed [5 + 1] cycloaddition directly using the trisubstituted ACP substrate and CO (only one example) can give the [5 + 1] cycloadduct (Scheme 1d).[14]

Considering the existence of the 3,4-cyclohexenone skeleton in many natural products and pharmaceuticals (Fig. 1)[15] and the importance of developing six-membered ring formation reactions, together with inspiration from the seminal discoveries of the Ir-catalysed [5 + 1] cycloaddition and Tang's synthesis of the core of welwitindolinones C, we were challenged to test whether a Rh complex catalysed [5 + 1] reaction of ACPs and CO, which may have a broad substrate scope, reasonable reaction yields, and easy separation of the [5 + 1] cycloadducts, could be developed (Scheme 1e). Herein we report our success in developing this general [5 + 1] reaction of ACPs and CO and the application of this reaction to the asymmetric formal synthesis of (−)-galanthamine.

We first synthesized compound **1a** and commenced our investigation. Treating substrate **1a** with 5 mol% $[Rh(CO)_2Cl]_2$ in toluene at 60 °C, the 2-alkylidene-3,4-cyclohexenone product **2a** was isolated in 72% yield (Table 1, entry 1). This transformation showed good stereoselectivity, and only the [5 + 1] product with the *E* configuration was observed. This was similar to Murakami and Ito's Ir-catalysed cycloaddition, where product **2a** was obtained in 28% yield (they did not observe other geometric isomers in their reaction system by ^{1}H NMR either). Adding 4 Å molecular sieves to the present reaction system did not improve the yield of the Rh-catalysed [5 + 1] reaction, implying that water did not have a deleterious

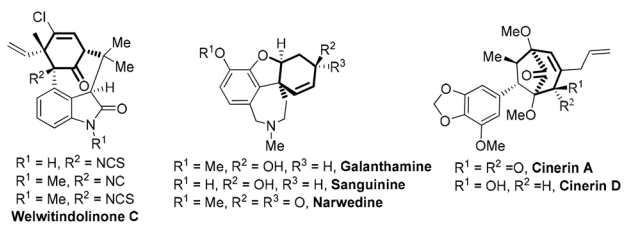
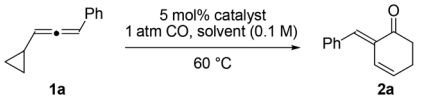


Fig. 1 Natural products containing the 3,4-cyclohexenone skeleton.

Table 1 Optimization of reaction conditions



Entry	Catalyst	Solvent	Time [h]	Yield[a]
1	$[Rh(CO)_2Cl]_2$	Toluene	2	72%
2	$[Rh(CO)_2Cl]_2$ [b]	Toluene	2	69%
3	$[Rh(COD)_2]BF_4$	Toluene	3	No reaction
4	$Rh(CO)(PPh_3)_2Cl$	Toluene	3	No reaction
5	$[Rh(COE)_2Cl]_2$	Toluene	2	68%
6	$[Rh(COD)Cl]_2$	Toluene	2	65%
7	$[Rh(CO)_2Cl]_2$	DCE	2	60%
8	$[Rh(CO)_2Cl]_2$	Dioxane	9	58%
9	$[Rh(CO)_2Cl]_2$	THF	10	66%
10	$[Rh(CO)_2Cl]_2$	DME	3	77%
11	$[Rh(CO)_2Cl]_2$	MeCN	8	Low conversion
12	$[Rh(CO)_2Cl]_2$ [c]	DME	7	34%
13	$[Rh(CO)_2Cl]_2$ [d]	DME	3	68%
14	$[Rh(CO)_2Cl]_2$ [e]	DME	3	66%
15	$[Rh(CO)2Cl]_2$ [f]	DME	6	64%
16	**$[Rh(CO)_2Cl]_2$** [g]	**DME**	**2**	**81%**
17	$[Rh(CO)_2Cl]_2$ [g,h]	DME	2	71%
18	$[Rh(CO)_2Cl]_2$ + dppp[g,i]	DME	2	Trace
19	$[Rh(CO)_2Cl]_2$ + dppm[g,i]	DME	2	No reaction

The reaction was performed in a 0.3 mmol scale and 3 mL solvent was used. [a] Isolated yields. [b] 4 Å molecular sieves were added. [c] 80 °C. [d] 0.5 atm CO. [e] 0.2 M. [f] 2 mol% catalyst was used. [g] The substrate was dissolved in solution and added slowly (*ca.* 1 h). [h] 0.05 M. [i] 5 mol% ligand was used.

effect on the reaction outcome (in contrast, our previous Rh-catalysed [5 + 1] reaction of VCPs and CO was sensitive to the moisture in the reaction system)[9] (Table 1, entry 2). We also tested other rhodium catalysts, finding that no desired [5 + 1] product was obtained using either $[Rh(COD)_2]BF_4$ or $Rh(CO)(PPh_3)_2Cl$ as the catalyst (Table 1, entries 3 and 4).[16] Other dimeric Rh catalysts such as $[Rh(COE)_2Cl]_2$ and $[Rh(COD)Cl]_2$ did not improve the reaction yields compared to $[Rh(CO)_2Cl]_2$ (Table 1, entries 5 and 6).

We then investigated how solvents affect the reaction results, finding that the [5 + 1] cycloaddition can take place in most commonly used solvents with the exception of MeCN, in moderate reaction yields (Table 1, entries 7–10). Among these tested solvents, 1,2-dimethoxyethane (DME) turned out to be the best one. In this case the [5 + 1] product **2a** was obtained in 77% yield (Table 1, entry 10). Increasing either the reaction temperature (Table 1, entry 12) or concentration of the allenylcyclopropane substrate (Table 1, entry 14) did not significantly improve the reaction yield. Decreasing the CO pressure from 1 atm to 0.5 atm (Table 1, entry 13) did not affect the reaction yield either. When we reduced the loading of the catalyst from 5 mol% to 2 mol%, only 64% product **2a** could be isolated in the [5 + 1] reaction.

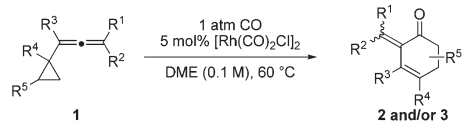
We were still not satisfied with the [5 + 1] reaction's yield mentioned above and wanted to search for another approach to get a higher yield of the desired [5 + 1] product. We hypothesized that the yield of the [5 + 1] cycloadduct was due to the competing side reactions of the ACP substrate, which is

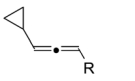
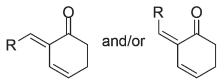
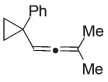
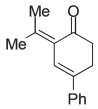
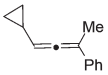
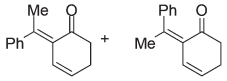
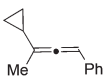
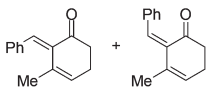
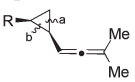
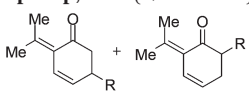
usually regarded as a very reactive species, in the reaction system. Experimentally, several products with polarities between the substrate **1a** and the cyclohexanone product **2a** were observed by analytical TLC. We reasoned that some of these unknown byproducts in the [5 + 1] reaction system may come from the dimerization of ACP in the presence of the Rh catalyst.[17,18] Therefore, we tried to add a solution of substrate **1a** in DME slowly (about 1 hour), with the help of a syringe pump, to another solvent containing the catalyst at 60 °C under 1 atm CO, with the hope that the Rh-catalysed or mediated dimerization of **1a** can be suppressed significantly by this operation. A similar strategy has been used by Alexanian in the nickel-catalysed [2 + 2] cycloaddition of ene–allenes.[19] To our delight, the yield of product **2a** can be increased to 81% and formation of the side products can be significantly suppressed, as judged by analytical TLC (Table 1, entry 16).[20] We also tried to decrease the concentration of the substrate to further minimize the dimerization of ACP, but no better result was obtained (Table 1, entry 17). Finally, we investigated whether adding a phosphine ligand to the [5 + 1] reaction could further increase the reaction yield. Unfortunately, adding either dppp or dppm to the reaction system gave much lower yields.

Based on the results in Table 1, we chose the reaction conditions of entry 16 in Table 1 as the optimal reaction conditions and the scope of the target [5 + 1] cycloaddition was presented in Table 2. We firstly investigated the influence of the substitution patterns in the allene moiety of ACPs. Apart from the phenyl used in the standard substrate, other aryl groups such as 4-bromophenyl and 4-methoxyphenyl could also be used and the corresponding [5 + 1] reaction yields were high (Table 2, entries 2 and 3). Interestingly, in these [5 + 1] reactions, only the products with the *E* configuration were observed. Changing the phenyl group to the 2-thienyl group, the corresponding [5 + 1] reaction gave a decreased reaction yield, 56% (Table 2, entry 4). Furthermore, we found that replacing the aryl groups by an alkyl group such as the 2-phenylethyl group in ACPs, the [5 + 1] reaction of the resulting substrate could also occur (Table 2, entry 5). It was found that two geometric isomers of the [5 + 1] reaction of **1e**, which can be separated by flash column chromatography in 70% and 21% yields separately, were obtained. The ACP substrate **1f** with a free hydroxyl group was not a good substrate for the [5 + 1] reaction and a complex mixture was obtained under the optimized conditions (Table 2, entry 6). Protecting the hydroxyl group in **1f** by a Ts group, the resulting substrate **1g** was still not suitable for the [5 + 1] reaction (Table 2, entry 7) and decomposition of substrate **1g** under the [5 + 1] reaction conditions was observed. We reasoned that the OTs group in **1g** was a good leaving group and this caused the decomposition of the substrate during the [5 + 1] reaction. Fortunately, the hydroxyl group in **1f** can be protected by the TBS or TBDPS group, and the resulting substrates **1h** and **1i** can undergo the [5 + 1] reactions to give both *E* and *Z*-cycloadducts (Table 2, entries 8 and 9). Substrate **1j** with an amine substituent was also a good substrate for the [5 + 1] reaction, giving both *E* and *Z*-cycloadducts (Table 2, entry 10). We also tried substrate **1k** with an ester group in the terminal position of the allene moiety, but only a complex mixture could be afforded, indicating that substrates with electron withdrawing groups attaching the allene moieties were not good substrates (Table 2, entry 11).

ACPs with terminal allenes, for example, **1l** and **1m**, were synthesized and subjected to the optimal [5 + 1] reaction conditions (Table 2, entries 12 and 13). We found that both **1l** and **1m** failed to produce the desired [5 + 1] products, similar to the Ir-catalysed [5 + 1] reaction of terminal ACPs.[12] We

Table 2 Scope of this Rh-catalysed [5 + 1] cycloaddition reaction



Entry[a]	Substrates	Time	Products and yields[b]
			
1	**1a**, R = Ph	2 h	**2a**, 80%
2	**1b**, R = 4-BrPh	3 h	**2b**, 86%
3	**1c**, R = 4-MeOPh	2 h	**2c**, 78%
4	**1d**, R = 2-thienyl	1.5 h	**2d**, 56%
5	**1e**, R = CH_2CH_2Ph	2 h	**2e**, 70%, **3e**, 21%
6	**1f**, R = CH_2OH	—	Decomposed
7	**1g**, R = CH_2OTs	—	Decomposed
8	**1h**, R = CH_2OTBS	2 h	**2h** + **3h**, 66% (*E*/*Z* = 5.1 : 1)
9	**1i**, R = $CH_2OTBDPS$	2 h	**2i**, 64%, **3i**, 12%
10	**1j**, R = CH_2NMeTs	2 h	**2j**, 60%, **3j**, 15%
11	**1k**, R = CO_2Et	2 h	Decomposed
			
12	**1l**, R_1 = Ph, R_2 = H	—	Decomposed
13	**1m**, R_1 = H, R_2 = Ph	—	Decomposed
			
14	**1n**	2 h	**2n**, 90%
			
15	**1o**	2 h	**2o**, 74%, **3o**, 9%
			
16	**1p**	2 h	**2p** + **3p**, 94% (*E*/*Z* = 1.7 : 1)
			
17	**1q**, R = CH_2OBn	2 h	**2q** + **4q**, 80% (**2q** : **4q** = 4.3 : 1)

[a] The reaction was performed in a 0.3 mmol scale and 2 mL solution of substrate was added slowly to another 1 mL solution of catalyst using a syringe pump. [b] Average yields of two runs.

reasoned that, in this case, the rhodium catalyst preferred to coordinate at the allenic π-bond that is distal to the cyclopropyl group.[21] Consequently, cleavage of the cyclopropane ring in ACPs becomes more difficult and many competing side reactions[18c] could override the desired [5 + 1] reaction, leading to the generation of complex mixtures for these terminal ACPs.

Under the standard [5 + 1] reaction conditions, trisubstituted ACPs were good substrates and the desired products were obtained in high yields (Table 2, entries 14–16). For substrate **1o** with methyl and phenyl groups at the end of the allenyl moiety of ACPs, a mixture of **2o** and **3o** was obtained. This was different from Murakami and Ito's report, where only product **2o** was isolated using Vaska's complex. For substrate **1p**, which had a methyl group at the internal allenyl position, the [5 + 1] reaction could also occur, even though the *E*/*Z* ratio of the desired products was relatively low (Table 2, entry 15).

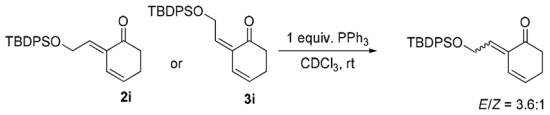
We also investigated the selectivity of the cyclopropane ring cleavage for substrate **1q** with a substituent in the cyclopropyl ring (Scheme 2), finding that the cyclopropane preferred to be cleaved at the position opposite to the substitution at the cyclopropane ring (bond "a" cleavage). As a result, product **2q** was the major product of the [5 + 1] reaction, which was similar to Taber's report using a Fe mediator.[5a]

To identify whether the ratio of the two isomers was determined by thermodynamics or kinetics, we resubjected **3i** and **2i** to the reaction separately. No change of the configuration could be observed from the ^{1}H NMR spectra. This suggested that the *E*/*Z* isomers did not equilibrate under the reaction conditions and the ratio was controlled by kinetics (see the ESI† for details).

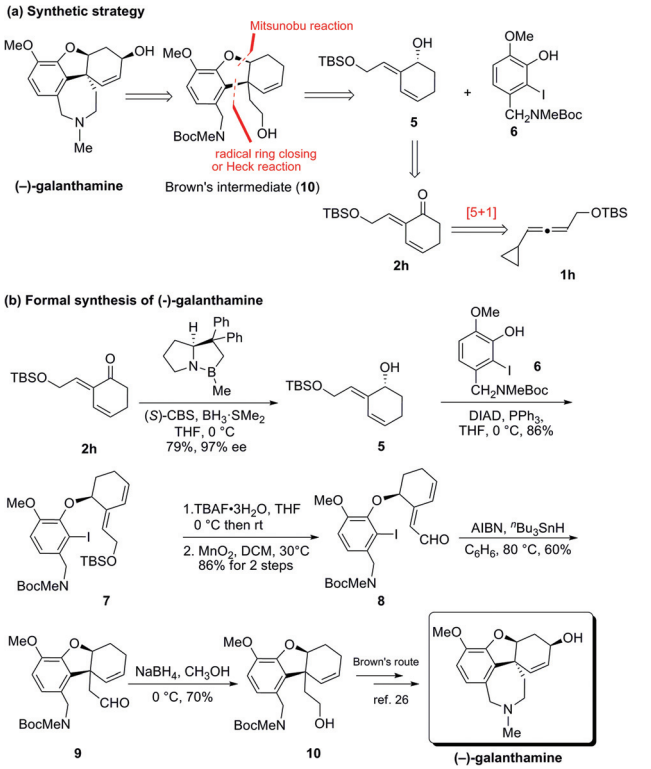
We also added PPh_3 to the two isomers separately and observed the transformations between **3i** and **2i** (Scheme 2). The *Z* and *E* isomers could reach a thermodynamic equilibrium and a ratio of 3.6 : 1 could be achieved after 36 h at room temperature, both for **2i** and **3i**.

Finally, we want to apply this methodology to the synthesis of natural products. (−)-Galanthamine (**11**)[22,23] is an alkaloid isolated from the bulb of the Amaryllidaceae family containing the 3,4-cyclohexenol skeleton (Scheme 2).[24] It is a reversible and competitive acetylcholine esterase inhibitor and has been used in the early treatment of Alzheimer's disease.[25] The unique 3,4-cyclohexenol skeleton in (−)-galanthamine, which is similar to our [5 + 1] adducts, and the pharmacodynamic effects of galanthamine, promoted us to synthesize this drug using our [5 + 1] cycloaddition of allenylcyclopropanes and CO as the key step.

Our strategy toward (−)-galanthamine is presented in Scheme 3a. (−)-Galanthamine can be synthesized by the known procedures, from Brown's intermediate **10** *via* Riley oxidation and ring closing reaction.[26] Intermediate **10** can be afforded by the Mitsunobu reaction of alcohol **5** and phenol **6**,



Scheme 2 Transformations between **3i** and **2i**.



Scheme 3 Synthetic strategy and formal synthesis of (−)-galanthamine.

followed by a radical ring closing reaction or Heck reaction to form the central five-membered ring in (−)-galanthamine. The alcohol **5** could be achieved easily from the reduction of the [5 + 1] cycloadduct **2h**.

Presented in Scheme 3b is the formal synthesis of (−)-galanthamine. The alcohol product **5** could be obtained in 79% yield with an ee value of 97% using the CBS reduction.[27] Then alcohol **5** and phenol **6** underwent the Mitsunobu reaction to form ether **7** in 86% yield. The TBS group was deprotected using TBAF and then the alcohol intermediate was oxidized to aldehyde **8** by activated MnO_2 in 86% yield over two steps. The five-membered ring in the natural product (−)-galanthamine was then formed using the radical ring closing strategy in 60% yield.[28] Finally, $NaBH_4$ was applied to reduce the aldehyde **9** to Brown's intermediate **10** and therefore a formal asymmetric synthesis of (−)-galanthamine from the [5 + 1] cycloadduct was realized.

In summary, we have developed a general Rh-catalysed [5 + 1] cycloaddition of ACPs and CO to synthesize functionalized 2-methylidene-3,4-cyclohexenones, which are difficult to obtain by using traditional methods. The scope of this methodology has been investigated. When substrates with aromatic groups attached to the allenyl moiety of ACPs were applied to this method, only the [5 + 1] cycloadducts with the *E* configuration were generated. In addition, various functional groups could be tolerated in the ACP substrates. Importantly, both di- and trisubstituted ACPs could be applied as the substrates for the present [5 + 1] cycloaddition reaction. In

addition, the cycloadduct **2h** has been applied in the formal synthesis of the natural product (−)-galanthamine. Further applications of this methodology and the study of the reaction mechanism are underway in our laboratory.

Acknowledgements

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