Heterocycles

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Progress in Carbonylative [2+2+1] Cycloaddition: Utilization of a Nitrile Group as the π Component**

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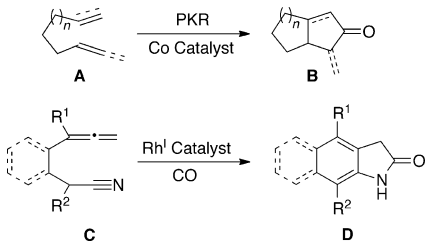
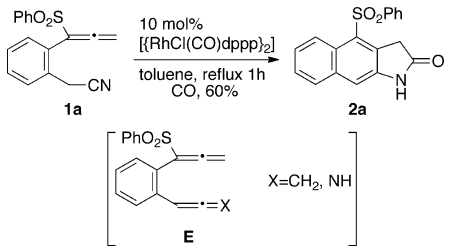
The Pauson–Khand reaction (PKR)[1] of the enynes **A** provides the most straightforward as well as powerful methodology for the construction of the cyclopentenone-fused cyclic frameworks **B** (Scheme 1). Several so-called Pauson–Khand-type [2+2+1] reactions (PKTR) using an alternative π component[2] instead of the alkyne or alkene π bond of **A** have also been developed. In contrast, these reactions would generally be referred to as the hetero-Pauson–Khand-type reaction (HPKTR) if more than one carbon atom of the newly generated cyclopentenone framework of **B** was replaced by an oxygen atom or nitrogen functionalities. Both ketone[3] and aldehyde[3f,4] groups (oxa-alkene π bond) have been employed in this context, and the imine functionalities[3f,4e,5] were shown to serve as the aza-alkene π bond. Furthermore, the carbodiimide groups (diaza-allene)[6] provided an alternative aza-alkene π bond. The nitrile group can be used as an aza-alkyne π bond in the transition-metal-catalyzed [2+2+2] cyclcoaddition,[7] but this has not been the case in which the nitrile group served as a π component in the carbonylative [2+2+1] cycloaddition. This study describes the unprecedented intramolecular rhodium(I)-catalyzed carbonylative [2+2+1] cycloaddition of the nitrile-allene substrates **C** and CO leading to the construction of the azabicyclo[m.3.0] frameworks **D**.



Scheme 1. [2+2+1] Cycloaddition of two π components and carbon monoxide.

During our continuous investigations of the carbonylative [2+2+1] cycloaddition,[6b,d,8] we noticed that the two allenyl functionalities [e.g., **E** (X = CH_2) in Scheme 2] served as the proper combination of two π components ending up with the efficient construction of the carbonylative [2+2+1] products.[8] We envisaged that if the phenylketenimine species such as **E** (X = NH; isoelectronic structure of allene) could be generated in situ from the phenylacetonitrile group, the resulting phenylketenimine intermediate might subsequently react with the allene counterpart under a CO atmosphere as in the case of bis(allene)s. In contrast, the phenylsulfonyl-substituted allenes have been utilized as substrates for most of our allenyne, allenene, and bis(allene) cyclometallation reactions[8,9] because of their ready availability as well as their ability to selectively react at the terminal double bond. Thus, our initial evaluation for the rhodium(I)-catalyzed carbonylative [2+2+1] cycloaddition of nitrile-allene substrates was performed using the *o*-allenylphenylacetonitrile **1a** having a phenylsulfonyl group on the allenyl moiety (Scheme 2). A solution of **1a** with 10 mol% [{RhCl(CO)$_2$}$_2$] in toluene was refluxed under a CO atmosphere, but produced an intractable mixture. Changing the rhodium(I) catalyst to [{RhCl(CO)dppp}$_2$] (1 h reflux in toluene) gratifyingly produced the desired benzo[*f*]oxyindole derivative **2a** in 60% yield,[10] which should have been derived by the formal [2+2+1] cycloaddition of the distal double bond of the allene, ketenimine (or nitrile intact), and CO.[11] Increasing the loading amounts of the rhodium(I) catalyst (20 mol% [{RhCl(CO)dppp}$_2$]) produced a better yield (74%) of **2a**.[12]



Scheme 2. Rhodium(I)-catalyzed HPKTR of **1a**. dppp = 1,3-bis(diphenylphosphanyl)propane.

Our endeavor then focused on the application of suitable reaction conditions (10 mol% [{RhCl(CO)dppp}$_2$] in refluxing toluene under an atmosphere of CO)[13] to other nitrile-allene substrates. The results are summarized in Table 1, including our initial result with **1a** (entry 1). The nitrile-phenylsulfonylallene substrate **1b** having a methoxy group at the *p*-position of the cyanomethyl group afforded the

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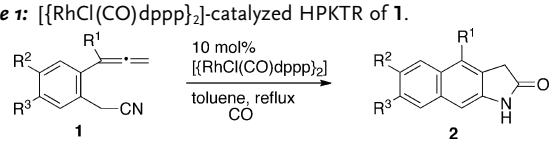
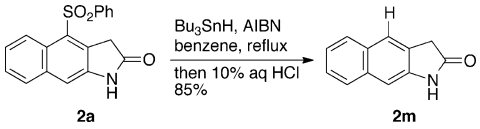
Table 1: [{RhCl(CO)dppp}$_2$]-catalyzed HPKTR of **1**.



1 **2**

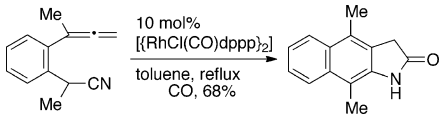
Entry	Substrate	R^1	R^2	R^3	*t* [h]	Yield [%]
1	**1a**	SO_2Ph	H	H	1	**2a:** 60
2	**1b**	SO_2Ph	OMe	H	4	**2b:** 79
3	**1c**	SO_2Ph	Cl	H	3	**2c:** 54
4	**1d**	SO_2Ph	H	OMe	5	**2d:** 26
5	**1e**	SO_2Ph	OCH_2O		3	**2e:** 37
6	**1f**	Me	H	H	1.5	**2f:** 88
7	**1g**	Me	OMe	H	5	**2g:** 65
8	**1h**	Me	Cl	H	31	**2h:** 62
9	**1i**	Me	NO_2	H	0.5	**2i:** 72
10	**1j**	Me	H	OMe	2	**2j:** 66
11	**1k**	Me	OCH_2O		4	**2k:** 79
12	**1l**	Me	H	NO_2	0.5	**2l:** 80
13	**1m**	H	H	H	0.5	**2m:** 15

corresponding [2+2+1] cycloadduct **2b** in a higher yield (entry 2). Similarly, the chloro derivative **1c** furnished **2c** in 54% yield (entry 3). Upon exposure of compound **1d**, having a methoxy group at the *p*-position of the allene functionality, to the standard reaction conditions for 5 hours, however, the yield of the product **1d** drastically decreased to 26% (entry 4). A similar low yield (37%) was observed when the methylenedioxy derivative **1e** was treated with the rhodium(I) catalyst (entry 5). It was found that the introduction of a methyl group instead of a phenylsulfonyl group to the allenyl moiety consistently produced the benzo[*f*]oxyindole framework in good yields. Indeed, the exposure of **1f** to the rhodium(I) catalyst produced the benzo[*f*]oxyindole derivative **2f** in 88% yield (entry 6). Similar treatment of both the methoxy (**1g**) and chloro (**1h**) derivatives afforded the corresponding ring-closed products **2g** and **2h** in the respective yields of 65 and 62% (entries 7 and 8). Introduction of a nitro group at the *p*-position of the cyanomethyl group did not affect the reaction and **1i** smoothly provided the desired product **2i** (0.5 h) in 72% yield (entry 9). The compound **1j** with a methoxy group at the *p*-position of the allene functionality afforded the desired product **2j** in 66% yield (entry 10), and a satisfactory yield of **2k** was also achieved when the methylenedioxy derivative **1k** was used (entry 11). These two experimental results are obviously different from those obtained by the reactions of **1d** and **1e** in which the ring-closed products were obtained in rather low yields (entries 4 and 5). The nitro derivative **1l** efficiently (0.5 h) provided the corresponding ring-closed product **2l** in 80% yield (entry 12). The unsubstituted allene **1m** afforded the benzo[*f*]oxyindole **2m**, but the yield was fairly low (entry 13). However, it is not a serious drawback to this newly developed HPKTR. A phenylsulfonyl group can be regarded as a surrogate of hydrogen and be easily converted into a hydrogen atom by conventional means.[14] In fact, the phenylsulfonyl group attached to the aromatic ring of **2a** was easily removed by the reaction with tributyltin hydride in the presence of AIBN and the subsequent acidic workup to furnish **2m** in 85% yield (Scheme 3). In addition, it became apparent that



2a **2m**

Scheme 3. Dephenylsulfonylation of **2a**. AIBN = 2′,2′-azobis(2-methylpropionitrile).

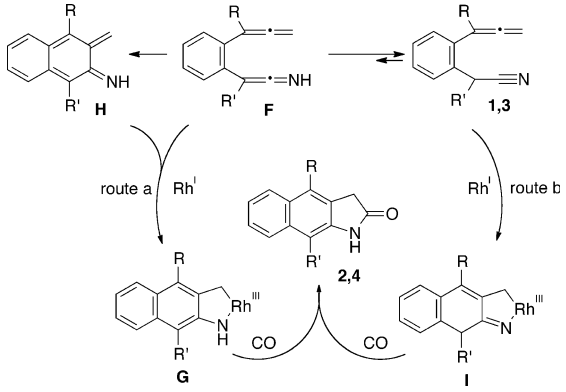


3 **4**

Scheme 4. Rhodium(I)-catalyzed HPKTR of methylallenes **3**.

the substituent at the α position to the nitrile group was tolerated in this ring-closing reaction (Scheme 4). In fact, the methylallene-nitrile derivative **3** produced the dimethyl compound **4** in 68% yield. Thus, it is concluded that nitrile-methylallene derivatives consistently produced the benzo-[*f*]oxyindole derivatives in good yields irrespective of the electronic property of the substituent on the benzene ring.

The two plausible mechanisms for the production of the benzo[*f*]oxyindole skeletons **2** and **4** could be tentatively interpreted by either of the following two routes (Scheme 5).

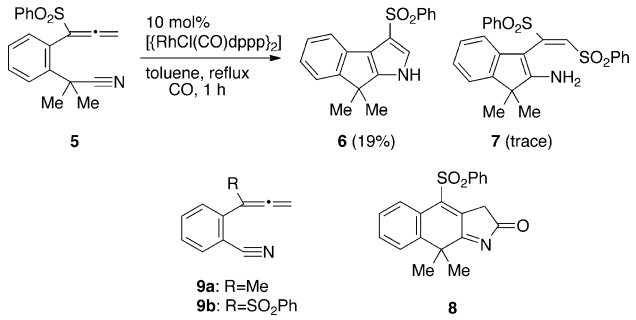


Scheme 5. Plausible mechanism for construction of **2** or **4** from **1** or **3**, respectively.

Route a, which is our working hypothesis, might be initiated by isomerization of the nitrile group into the phenylketenimine **F**. The subsequent oxidative addition of the imine part and the distal double bond of the allene functionality to Rh^I would afford the rhodacycle intermediate **G**. The resulting intermediate **G** would end up with the production of **2** or **4** by successive insertion of CO and reductive elimination. The phenylketenimine **F** may alternatively undergo the 6π-electrocyclic reaction to furnish the naphthoazaquinodimethane **H**,[15] which might immediately be captured by Rh^I to furnish **G**. Another possible route b involves the direct oxidative addition of both the nitrile group and the distal double bond of the allene functionality into Rh^I leading to the formation of the rhodacycle intermediate **I**, which would

collapse to the final products **2** or **4** by the insertion of CO, reductive elimination, and aromatization.

To confirm whether the reaction proceeded by the proton tautomerization of the nitrile functionality, the dimethyl derivative **5** was exposed to the standard reaction conditions to furnish the indenopyrrole derivative **6**[16,17] in 19% along with a trace amount of the indene derivative **7**, both of which are obviously different from the expected [2+2+1] cycloaddition product **8** (Scheme 6). In addition, neither the

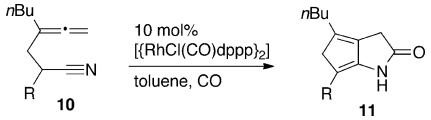


Scheme 6. Rhodium(I)-catalyzed ring-closing reaction of **5** and **9**.

benzonitrile **9a** nor **9b** afforded the desired carbonylative products at all. Based on these three experiments, it might be tentatively concluded that the transformation of **1** or **3** into **2** or **4**, respectively, must occur through the initial isomerization of the nitrile group into the intermediates **F** and/or **H** (route a in Scheme 5).

We next examined the rhodium(I)-catalyzed carbonylative [2+2+1] cycloaddition of the aliphatic nitrile derivatives. The hexa-4,5-dienenitrile **10a** (R = H) was treated with 10 mol% [{RhCl(CO)dppp}$_2$] for a prolonged time, but no reaction occurred (Table 2, entry 1). We anticipated that introduction of a suitable electron-withdrawing substituent at the α position to the nitrile group of **10a** would accelerate the isomerization into the ketenimine form (e.g. intermediate **F** in Scheme 5). Thus, the malononitrile derivative **10b** was refluxed in toluene to gratifyingly furnish the desired product

Table 2: [{RhCl(CO)dppp}$_2$]-catalyzed HPKTR of hexa-4,5-dienenitriles (**10**).



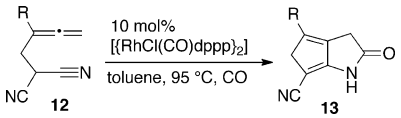
Entry	Substrate	R	*T* [°C]	*t* [h]	Yield [%]
1	**10a**	H	reflux	20	–[a]
2	**10b**	CN	80	4	**11b:** 69
3	**10c**	CO_2Et	reflux	4.5	**11c:** 43
4	**10d**	SO_2Ph	95	8	**11d:** 48
5	**10e**	Piv	95	5	**11e:** 83
6	**10f**	*o*-$NO_2C_6H_4$	95	32	**11f:** 16[b]
7	**10g**	*p*-$NO_2C_6H_4$	95	29	**11g:** 37[c]

[a] No reaction took place. [b] The compound **10f** was recovered in 49% yield. [c] The compound **10g** was recovered in 23% yield.

11b in 32% yield. Lowering the reaction temperature to 80°C effected improvement of the yield (69%)[18] in this case (Table 2, entry 2). The structure of **11b** was unambiguously confirmed by its X-ray crystallographic analysis.[19] The effect of other electron-withdrawing groups was also investigated. The ethoxycarbonyl derivative **10c** was treated with the rhodium(I) catalyst to produce **11c** in 43% yield (entry 3), and the phenylsulfonyl-substituted substrate **10d** furnished the cycloadduct **11d** in similar yield (entry 4). The highest yield (83%) was attained when the pivaloyl derivative **10e** was used (entry 5). The *o*- and *p*-nitrophenyl groups could serve as weak electron-withdrawing functionalities in this reaction, thus resulting in the formation of the azabicyclo-[3.3.0] derivatives **11f** (16% yield) and **11g** (37%), respectively, with the recovery of the starting materials **10f** and **10g** (entries 6 and 7).

Since the nitrile group was found to be one of the two suitable electron-withdrawing groups, several malononitrile derivatives (**12a–d**) having other alkyl substituents on the allenyl moiety were submitted to the reaction conditions (Table 3). The methylallene derivative **12a** smoothly under-

Table 3: [{RhCl(CO)dppp}$_2$]-catalyzed HPKTR of 2-cyanohexa-4,5-dienenitriles (**12**).



Entry	Substrate	R	*t* [h]	Yield [%]
1	**12a**	Me	0.25	**13a**: 54
2	**12b**	*i*Pr	1	**13b**: 62
3	**12c**	*t*Bu	4	**13c**: 58
4	**12d**	CH_2OTBS	1	**13d**: 39

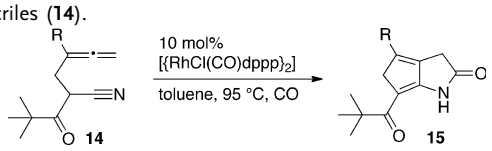
TBS = *tert*-butylsilyl.

went the carbonylative [2+2+1] ring-closing reaction (entry 1), but the yield of the product **13a** (54%) was lower than that of the *n*-butyl derivative **11b** (see Table 2, entry 2). The sterically more-hindered isopropyl (**12b**) and *tert*-butylallenes (**12c**) produced the corresponding azabicyclo[3.3.0] derivatives **13b** and **13c** in acceptable yields (62% and 58%), which are similar to that of **11b** (Table 2, entry 2). The functionalized siloxymethyl derivative **12d** provided the desired product **13d** in a slightly lower yield (entry 4).

The pivaloyl substituent provided the highest yield in a series of the *n*-butylallene substrates **10** (Table 2, entry 5). However, this was not the case for the 4-alkyl-2-pivaloyl derivatives **14a–c**, in which the yields widely varied in the range of 19 to 52% as shown in Table 4. Presumably, the fairly bulkier pivaloyl group might decrease their reactivity.[20]

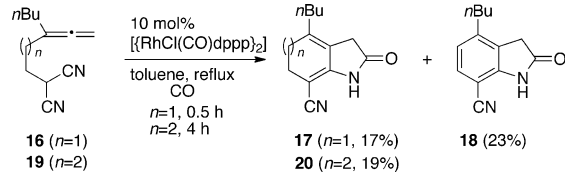
To further extend the scope of this method, the one-carbon homologated malononitrile **16** was reacted with the rhodium(I) catalyst to furnish two carbonylative azabicyclo-[4.3.0] derivatives in a total 40% of yield (Scheme 7): 5-butyl-6,7-dihydrooxyindole (**17**, 17%) and 5-butyloxyindole (**18**, 23%).[21] The azabicyclo[5.3.0]decadienone **20** could also be formed from **19** using the procedure described above, although the chemical yield was lower.

Table 4: [{RhCl(CO)dppp}$_2$]-catalyzed HPKTR of 2-pivaloylhexa-4,5-dienenitriles (**14**).



Entry	Substrate	R	*t* [h]	Yield [%]
1	**14a**	Me	10	**15a**: 28[a]
2	**14b**	*i*Pr	21	**15b**: 19[b]
3	**14c**[c]	*t*Bu	1	**15c**: 52

[a] The compound **14a** was recovered in 4% yield. [b] The compound **14b** was recovered in 55% yield. [c] 20 mol% [{RhCl(CO)dppp}$_2$] was used at refluxing temperature.



Scheme 7. Rhodium(I)-catalyzed ring-closing reaction of **16** and **19**.

In summary, we developed the novel [{RhCl(CO)dppp}$_2$]-catalyzed intramolecular carbonylative [2+2+1] cycloaddition of 2-(1,2-propadienyl)phenylacetonitrile derivatives under mild reaction conditions, thus leading to the facile formation of benzo[*f*]oxyindole derivatives. Application of this newly developed aza-Pauson–Khand-type reaction was extended to aliphatic substrates. Namely, the 4-alkylhexa-4,5-dienenitriles having an electron-withdrawing group at the α position to the nitrile produced 2-azabicyclo[3.3.0]octa-1(8),5-dien-3-ones in moderate yields. Thus, we could demonstrate the usefulness of the nitrile functionality in the carbonylative [2+2+1] cycloaddition reaction. The scope and limitations of this method as well as application to the synthesis of the natural products are now in progress.

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[9] a) F. Inagaki, K. Sugikubo, Y. Miyashita, C. Mukai, *Angew. Chem.* **2010**, *122*, 2252 – 2256; *Angew. Chem. Int. Ed.* **2010**, *49*, 2206 – 2210; b) F. Inagaki, K. Sugikubo, Y. Oura, C. Mukai, *Chem. Eur. J.* **2011**, *17*, 9062 – 9065; c) C. Mukai, Y. Ohta, Y. Oura, Y. Kawaguchi, F. Inagaki, *J. Am. Chem. Soc.* **2012**, *134*, 19580 – 19583.

[10] Similar reaction conditions with $AgBF_4$ afforded **1a** in a rather lower yield (17%). The cationic [{Rh(CO)dppp}$_2$]Cl, which was very effective in some cases of our PKTR of allenynes or allenenes,[8] also furnished **2a** in a low yield (22%). Neither [RhCl(CO)(PPh$_3$)$_2$] nor [Mo(CO)$_6$] was shown to be effective for our purpose and only a complex mixture was formed. It has already been shown that the rhodium(I)-catalyzed PKTR of enynes under a low CO pressure occasionally provides better results (see F. Inagaki, N. Itoh, Y. Hayashi, Y. Matsui, C. Mukai,

Beilstein J. Org. Chem. **2011**, *7*, 404 – 409). Thus, we next examined the effect of the CO pressure, but a yield better than 60% yield could not be achieved.

[11] The ring-closing reaction of **1a** was performed under an atmosphere consisting of 0.1 atm of CO and 0.9 atm of Ar which unexpectedly produced **2a** in a low yield (16%). Increasing the CO pressure to 5 atm also led to a decrease in the chemical yield (23%). When the reaction was carried out under an atmosphere of CO with 5 mol% [{RhCl(CO)dppp}$_2$], the chemical yield of **2a** decreased to 28%.

[12] The isomerization of nitrile to ketenimine species might be accelerated by addition of base. Thus, the rhodium(I)-catalyzed [2+2+1] cycloaddition of **1a** was performed in the presence of one equivalent of K_2CO_3 or *i*Pr$_2$NEt. However, no significant improvement could be attained (yield of **2a**: 24–40%).

[13] It was shown that 20 mol% of the rhodium(I) catalyst afforded a better yield, but we used 10 mol% of the catalyst for the following experiment.

[14] C. Nahera, M. Yus, *Tetrahedron* **1999**, *55*, 10547 – 10658.

[15] a) S. Kitagaki, K. Ohdachi, K. Katoh, C. Mukai, *Org. Lett.* **2006**, *8*, 95 – 98; b) S. Kitagaki, Y. Okumura, C. Mukai, *Tetrahedron Lett.* **2006**, *47*, 1849 – 1852; c) S. Kitagaki, K. Katoh, K. Ohdachi, Y. Takahashi, D. Shibata, C. Mukai, *J. Org. Chem.* **2006**, *71*, 6908 – 6914; d) S. Kitagaki, Y. Okumura, C. Mukai, *Tetrahedron* **2006**, *62*, 10311 – 10320.

[16] The compound **6** was converted into the corresponding tosylate **26** in 55% yield by conventional means (TsCl, *i*Pr$_2$NEt and DMAP in CH_2Cl_2). The structures of both **26** (CCDC 939923) and **7** (CCDC 939921) were unambiguously confirmed by their X-ray crystallographic analyses; see the Supporting information.

[17] The formation of **6** and **7** was rationalized based on the mechanism proposed by Padwa and Yeske, and Martín, Ruano, and co-workers. See: a) A. Padwa, P. E. Yeske, *J. Am. Chem. Soc.* **1988**, *110*, 1617 – 1618; b) A. Padwa, P. E. Yeske, *J. Org. Chem.* **1991**, *56*, 6386 – 6390; c) A. Núñez, Jr., M. R. Martín, A. Fraile, J. L. G. Ruano, *Chem. Eur. J.* **2010**, *16*, 5443 – 5453.

[18] The reaction conditions, such as the rhodium(I) catalyst, solvent, and addition of acid or base, were examined again using **10b** in anticipation of an easy isomerization to the ketimine form, but all efforts were fruitless.

[19] CCDC 939922 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] The pivaloyl derivative **10e** produced the 6-butyl-8-pivaloyl-2-azabicylo[3.3.0] compound **11e** in the highest yield. It is uncertain about the reason so far, but other pivaloyl derivatives **14** having methyl, isopropyl, and *tert*-butyl groups tend to produce the corresponding 6-alkyl-8-pivaloyl-2-azabicylo[3.3.0] compound **15** in rather low yields compared to those of the 6-alkyl-8-cyano-2-azabicylo[3.3.0] compound **13**.

[21] The oxyindole derivative **18** was tentatively regarded as an over-oxidized product of **17**. Thus, the compound **17** was exposed to the rhodium(I) catalyst under the standard reaction conditions, but no conversion into **18** could be observed and **17** was recovered intact.

