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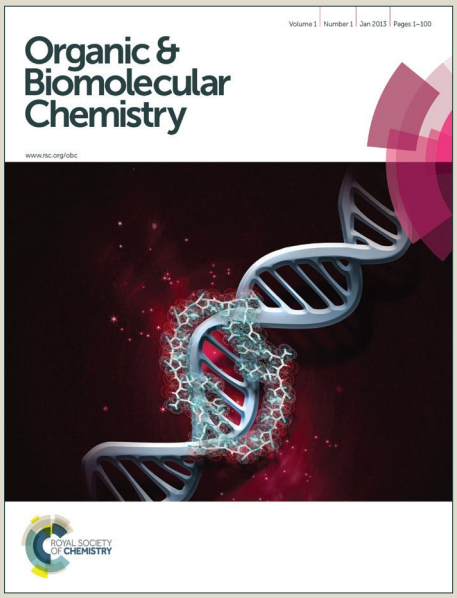

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COMMUNICATION

Rhodium(I)-catalysed intermolecular alkyne insertion into (2-pyridylmethylene)cyclobutenes†‡

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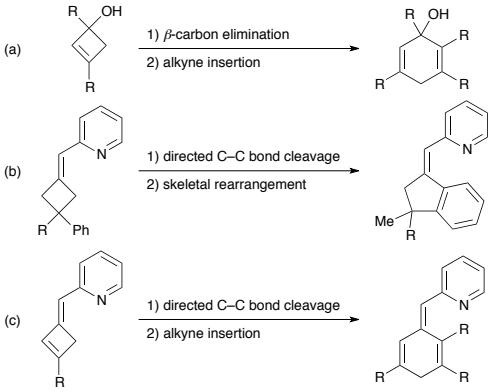
Cyclobutenes with 2-pyridylmethylene groups at the 3 position underwent an intermolecular alkyne insertion reaction in the presence of a rhodium(I) catalyst at 170 °C to afford substituted benzenes. Among the different 2-pyridylmethylene groups examined, 3-methyl-2-pyridyl derivatives showed superior activity and readily coupled with various alkynes, including sterically demanding, heteroaromatic and terminal alkynes.

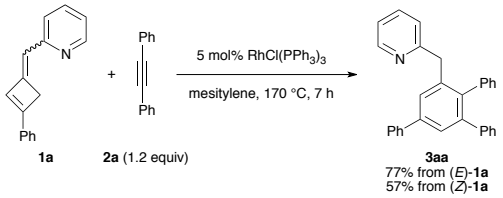
The catalytic cleavage of the carbon–carbon bond and its utilisation in organic synthesis has become one of the most intensely researched fields in recent years.[1] In particular, the cleavage of carbon–carbon bonds of small ring compounds and the subsequent migratory insertion of unsaturated molecules, such as alkynes and carbon monoxide, provide unique access to ring expansion reactions. Insertion reactions of four-membered ring ketones[2] and alcohols[3] are well established; however, there are only limited examples of successful insertions into cyclobutanes that lack heteroatom substituents.[4]

We recently reported the alkyne insertion reaction of cyclobutenols (Scheme 1, (a))[3b] and the skeletal rearrangement reaction of (2-pyridylmethylene)cyclobutanes (Scheme 1, (b)),[5] both of which are catalysed by rhodium(I). In this study, we focus on (2-pyridylmethylene)cyclobutenes. We have developed a rhodium(I)-catalysed intermolecular cyclobutene–alkyne coupling reaction, which proceeded via an alkyne insertion into the C(3)–C(4) bond of cyclobutene to form a 3-(2-pyridylmethylene)-1,4-cyclohexadiene (Scheme 1, (c)). The initial coupling product then undergoes double bond isomerisation to create a benzene ring skeleton.



Scheme 1 Our rhodium-catalysed reactions of cyclobutanes and cyclobutenes.

3-(2-Pyridylmethylene)-1-phenylcyclobutene (**1a**) was selected as the initial substrate for this study, and it was prepared by the Wittig reaction of 3-phenylcyclobut-2-enone with (2-pyridylmethylene)phosphorane.[6] The reaction gave an *E*/*Z* mixture of **1a**'s stereoisomers, which were separated by column chromatography. Mixing (*E*)-**1a** and diphenylacetylene (**2a**) in the presence of Wilkinson's catalyst at 170 °C in mesitylene led to the formation of 1,2,5-triphenyl-3-(2-pyridylmethyl)benzene **3aa** (77%) (Scheme 2). The use of the corresponding (*Z*)-isomer also gave **3aa**, but with a slight decrease in yield (57%). Based on this result, (2-pyridylmethylene)cyclobutenes **1** were used as stereoisomeric mixtures for further study.



Scheme 2 Intermolecular insertion of **2a** into (*E*)- and (*Z*)-**1a** in the presence of $RhCl(PPh_3)_3$.

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† Dedicated to Prof. Masahiro Murakami on the occasion of his 60th birthday.

‡ Electronic Supplementary Information (ESI) available: Experimental procedures and characterisation data for new compounds. See DOI: 10.1039/x0xx00000x

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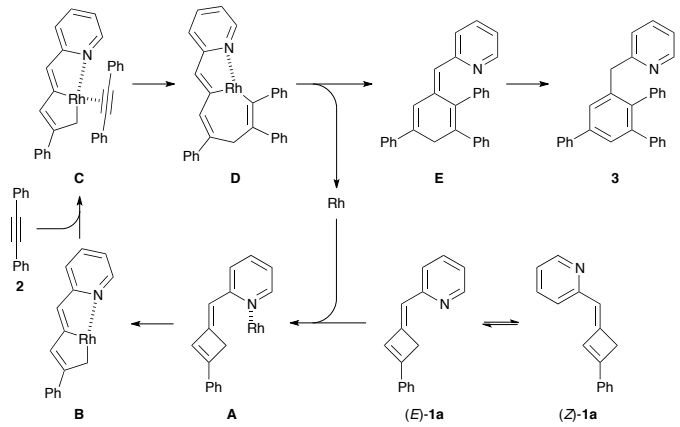
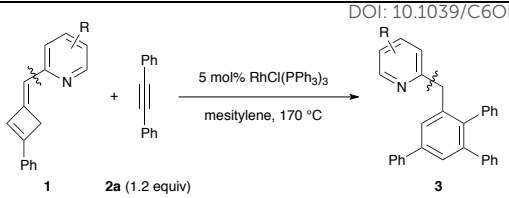
A proposed mechanism for the rhodium(I)-catalysed intermolecular alkyne insertion into cyclobutene is depicted in Scheme 3. The cyclobutenes, (*E*)- and (*Z*)-**1a**, are in equilibrium under the stipulated reaction conditions (mesitylene, 170 °C).[7] The rhodium(I) metal, guided by the pyridine nitrogen (as in **A**), would initially insert into the C(3)–C(4) bond of (*E*)-**1a** to produce the five-membered rhodacycle **B**.[8] Next, the alkyne **2a** coordinates to the rhodium metal (as in **C**) and its migratory insertion into the Rh–C(sp^3) bond results in a ring expansion to form the seven-membered rhodacycle **D**. Finally, a reductive elimination yields the (2-pyridylmethylene)cyclohexadiene **E**, which aromatises by double bond isomerisation to **3aa** under the reaction conditions used.[9]



Scheme 3 Proposed mechanism of the rhodium-catalysed reaction between **1a** and **2a**.

The rhodium(I)-catalysed alkyne insertion of **1** was then screened under various reaction parameters, and the results are summarised in Table 1. Firstly, the effect of pyridine ring substituents was evaluated. Introducing methyl substituents on the pyridine ring of **1** increased the yield of the insertion products **3** (entries 1–3) and the highest yield was achieved with 3-methyl-2-pyridyl **1d** (entry 3). While 2-quinolyl **1e** gave a satisfactory result (entry 4), the reaction was far less efficient with 2-pyrazyl **1f** (entry 5). More importantly, compound **1g**, which lacks a nitrogen atom, failed to react, hence implying that the reaction is initiated by pyridine-directed C–C bond cleavage rather than cyclobutene ring opening[10] and subsequent oxidative cyclisation with the rhodium(I) complex.[11] The effect of reaction temperature was obvious, with the yields decreasing with the reaction temperature (entries 7–9).[12] Among the rhodium catalysts tested, $RhCl(PPh_3)_3$ exhibited the highest catalytic activity (entries 10 and 11), and a 73% yield of **3da** was obtained with a catalyst loading of 2.5 mol% $RhCl(PPh_3)_3$ (entry 12). Unsurprisingly, no reaction was observed in the absence of the rhodium catalyst (entry 13).

Table 1 Insertion of diphenylacetylene (**2a**) into cyclobutenes **1**

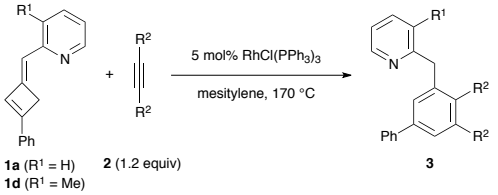


Entry	1	Deviation from the standard conditions	Time (h)	3	Yield (%)[a]
1	**1b**		6	**3ba**	77
2	**1c**		5	**3ca**	83
3	**1d**		4	**3da**	93
4	**1e**		3	**3ea**	86
5	**1f**		5	**3fa**	27
6	**1g**		11	**3ga**	NR[b]
7	**1d**	*p*-xylene, 150 °C	5	**3da**	84
8	**1d**	PhCl, 130 °C	16	**3da**	45
9	**1d**	toluene, 110 °C	6	**3da**	38
10	**1d**	$[RhCl(cod)]_2$[c]	8	**3da**	53
11	**1d**	$RhCl(CO)(PPh_3)_2$	8	**3da**	56
12	**1d**	2.5 mol% $RhCl(PPh_3)_3$	6	**3da**	73
13	**1d**	without Rh catalyst	5	**3da**	NR[b]

[a] Isolated yield. [b] No reaction. [c] 2.5 mol% of dimer (5 mol% Rh) was used.

Next, various symmetrical alkynes **2** were subjected to the alkyne insertion reaction with (2-pyridylmethylene)cyclobutene **1a** and (3-methyl-2-pyridylmethylene)cyclobutene **1d** (Table 2). In all cases examined, 3-methyl-2-pyridyl **1d** produced the six-membered ring products **3** in higher yields than 2-pyridyl **1a**. Cyclobutenes **1a** and **1d** reacted with the diphenylacetylene derivatives **2b**–**2f** to afford the 1,2,5-triaryl-3-(2-pyridylmethyl)benzenes **3ab**–**af** in 42–62% and **3db**–**3df** in 61–86% yields, respectively (entries 1–5). The insertion of sterically demanding alkynes (**2g** and **2h**) to **1d** was also possible (entries 6 and 7). We also established that heteroaromatic and aliphatic alkynes (**2i** and **2j**) reacted with **1a** and **1d** to afford the corresponding coupling products (entries 8 and 9).

Table 2 Insertion of various symmetrical internal alkynes **2** into **1a** and **1d**[a]



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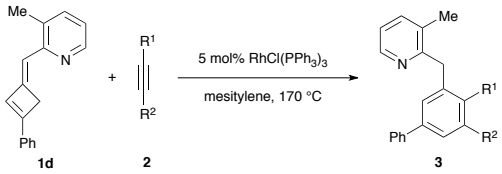
Entry	2 (R^2)	R^1 = H 3 (%Yield[b])	R^1 = Me 3 (%Yield[b])
1	**2b** (4-MeC_6H_4)	**3ab** (57)	**3db** (74)
2	**2c** (4-$MeOC_6H_4$)	**3ac** (42)	**3dc** (61)
3	**2d** (4-ClC_6H_4)	**3ad** (47)	**3dd** (83)
4	**2e** (4-$CF_3C_6H_4$)	**3ae** (62)	**3de** (86)
5	**2f** (3,5-$Me_2C_6H_3$)	**3af** (59)	**3df** (84)
6	**2g** (2-MeC_6H_4)	**3ag** (–[c])	**3dg** (61)
7	**2h** (1-naphthyl)	**3ah** (–[c])	**3dh** (75)
8	**2i** (2-thienyl)	**3ai** (46)	**3di** (87)
9	**2j** (Bu)	**3aj** (57)	**3dj** (82)

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol, 1.2 equiv), $RhCl(PPh_3)_3$ (5.0 µmol, 5 mol%), mesitylene (0.50 mL, 0.2 M), 170 °C for 4–16 h. [b] Isolated yield. [c] Not examined.

Results of the reaction with unsymmetrical alkynes are shown in Table 3. To our surprise, the reaction of **1d** and phenylacetylene (**2k**) was efficient, and gave the 1,4-diphenyl derivative **3dk** in 80% yield, with no other possible isomer being found in the crude reaction mixture (entry 1).[13] However, the reaction with the aliphatic terminal alkyne **2l** gave **3dl** in 53% yield as a 3.2:1 isomeric mixture of products (entry 2). Mixtures of isomers were also obtained from the reaction of unsymmetrical internal alkynes **2m** and **2n** (entries 3 and 4).

Table 3 Reaction of **1d** with unsymmetrical alkynes **2k–n**[a]

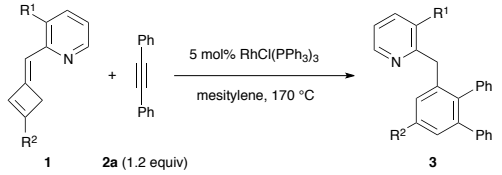


Entry	2 (R^1, R^2), Equiv	3 (%Yield[b])	Ratio[c]
1	**2k** (Ph, H), 3.0	**3dk** (80)	>20:1
2	**2l** (Oct, H), 1.5	**3dl** (53)	3.2:1
3	**2m** (Ph, Me), 1.2	**3dm** (50)	2.2:1
4	**2n** (isopropenyl, Et), 3.0	**3dn** (78)	5.8:1

[a] Reaction conditions: **1d** (0.10 mmol), **2** (0.12–0.30 mmol), $RhCl(PPh_3)_3$ (5.0 µmol, 5 mol%), mesitylene (0.50 mL, 0.2 M), 170 °C for 6–7 h. [b] Isolated yield. [c] Determined by ^1H NMR.

Cyclobutenes with substituted phenyl and 1-naphthyl groups at the 1 position of cyclobutene (**1h–n**) reacted with **2a** to produce 1,2,5-triaryl-3-(2-pyridylmethyl)benzenes **3ha–3na** (Table 4).

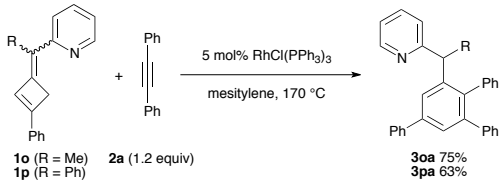
Table 4 Reaction of **1h–n** with **2a**[a]



Entry	1 (R^1, R^2)	3 (%Yield[b])
1	**1h** (H, 4-MeC_6H_4)	**3ha** (69)
2	**1i** (Me, 4-MeC_6H_4)	**3ia** (87)
3	**1j** (H, 4-$MeOC_6H_4$)	**3ja** (58)
4	**1k** (Me, 4-$MeOC_6H_4$)	**3ka** (85)
5	**1l** (H, 4-ClC_6H_4)	**3la** (52)
6	**1m** (Me, 4-ClC_6H_4)	**3ma** (86)
7	**1n** (H, 1-naphthyl)	**3na** (69)

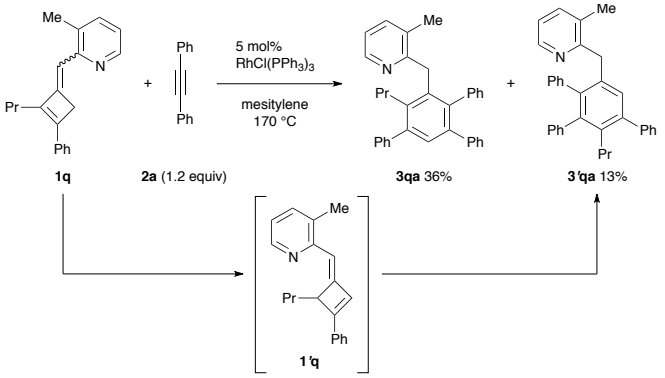
[a] Reaction conditions: **1**, **2a** (1.2 equiv), $RhCl(PPh_3)_3$ (5 mol%), mesitylene, 170 °C, 5–24 h. [b] Isolated yield.

The reaction between cyclobutenes **1o** and **1p** (*i.e.* compounds with tetrasubstituted alkene moieties) and **2a** afforded **3oa** and **3pa**, both of which have substituents at the benzylic position (Scheme 4).



Scheme 4 Reaction of **1o** and **1p** with **2a**.

In the case of **1q**, another cyclobutene with a tetrasubstituted alkene moiety, two isomeric pentasubstituted benzenes **3qa** and **3'qa** were obtained in 49% combined yield via the insertion reaction (Scheme 5).[14] The major product **3qa** was formed by a normal alkyne insertion into the C(3)–C(4) bond of **1q**. Conversely, the formation of **3'qa** was likely a result of double bond isomerisation of **1q** to **1'q** under the reaction conditions used. The insertion of **2a** into the original C(2)–C(3) bond of **1'q** led to the isomer **3'qa**.



Scheme 5 Reaction of **1q** with **2a**.

In this cyclobutene–alkyne coupling reaction, the directing pyridylmethylene groups are retained in the products as pyridylmethyl groups. Thus, we studied the derivatisation of functionality that is present in the products. The copper-catalysed aerobic oxidation of the methylene group belonging to **3da** and **3dj** afforded the ketones **4a** and **4b**, respectively.[15] The resulting 3-methylpicolinoyl group of **4b** was removed

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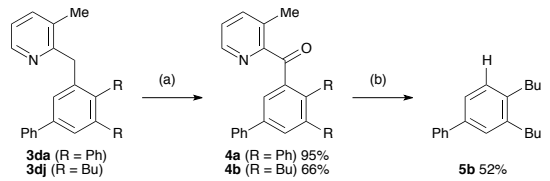
upon treatment with *t*-BuOK to furnish 1,2,4-trisubstituted benzene **5b**.[16]



Scheme 6 Derivatisation of **3**: (a) 10 mol% CuI, AcOH, DMSO, 100 °C, O_2; (b) 3.1 equiv *t*-BuOK, 1.2 equiv H_2O, 1,4-dioxane, 100 °C.

In conclusion, we have developed a rhodium(I)-catalysed reaction that affords tetra- and pentasubstituted benzenes, involving an alkyne insertion into the C–C bond of cyclobutene. Sterically demanding, heteroaromatic and terminal alkynes are all effectively coupled to 3-(2-pyridylmethylene)-1-phenylcyclobutenes. The 2-pyridylmethyl groups of the products can be removed using established procedures.

Acknowledgements

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6 See the Supporting Information for the preparation of **1**.

7 Heating (*E*)- and (*Z*)-**1a** at 170 °C in mesitylene for 24 h in the absence of $RhCl(PPh_3)_3$ induced the E/Z isomerisation, resulting in the formation of 2:1 and 1:3 mixtures of the isomers, respectively.

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