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Rhodium/Phosphine/Amine·HBr Catalyst System for Highly Selective Cross-Cyclodimerization of Aryl- and Alkylalkynes: Efficient Access to Multisubstituted Naphthalene Derivatives

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Various polysubstituted aromatic compounds have long been of great significance in the chemical and pharmaceutical industries. In particular, those with polycyclic π-conjugated structures have recently become increasingly important in the area of organic electronics.[1] The transition-metal-mediated annulative benzene ring homologation with alkynes or their equivalents[2–6] is one of the modern potential synthetic strategies to prepare naphthalenes and higher fused aromatics. As one of the early examples, Sakakibara[2a] and Heck[2b] independently reported the palladium-catalyzed annulation reaction of aryl halide with two acetylenedicarboxylate or diphenylacetylene molecules to construct the naphthalene skeletons. Takahashi described the homologation reaction with *o*-dihalobenzenes and zirconacyclopentadienes.[3] Our groups also focused on this methodology and succeeded in the formation of polysubstituted naphthalenes and anthracenes from internal alkynes and benzoyl chlorides or benzoic acids accompanied by decarbonylation or decarboxylation.[4] In addition, the recent advances of benzyne chemistry provide an efficient route to fused aromatics involving anthracenes and phenanthrenes by using *o*-dibromobenzene or *o*-trimethylsilylphenyl triflates as the starting materials.[5] However, the processes mentioned above require the leaving groups on the benzene rings so that the inevitable wastes, such as the metal salts, are produced simultaneously. Recently, we reported the rhodium-catalyzed oxidative homologation of directing-group-containing arenes with alkynes through two sp^2 C–H bond cleavages.[7] Wu also has described the palladium-catalyzed similar type of transformation with electron-rich arenes, such as *p*-xylene, under oxidative conditions.[8] While these procedures are useful because preactivation of the arene moieties could be eliminated, a stoichiometric amount of oxidant, $Cu(OAc)_2$ or AgOAc, is required. From the viewpoint of atom economy, further development of different protocols for the synthesis of the multisubstituted aromatics from relatively simple hydrocarbons is strongly desired.

In 1998, Kisch reported the rhodium-catalyzed cyclodimerization of diarylacetylenes to give multisubstituted naphthalenes with the aid of HCl.[9] Although the catalytic dimerization is an ideal waste-free process, it is restricted in scope and generality; one of the possible reasons for this may be the use of the relatively strong acid. Moreover, the cross-cyclodimerization of diaryl- and dialkylacetylenes encounters difficulty in controlling chemoselectivity of the reaction due to the competitive homo-cyclodimerization of diarylacetylenes.[10] Nevertheless, the elegant pioneering work appears to be quite attractive and encourages us to explore a more efficient rhodium-based catalyst for this type of direct alkyne coupling. In this communication, we report the rhodium/phosphine/amine·HBr catalyst system directed toward the highly chemoselective synthesis of multisubstituted naphthalene derivatives from two different internal alkynes. Under the catalytic conditions, a variety of alkynes are tolerant, and the cross-dimerization predominates over the conceivable homo-dimerization. Furthermore, the catalyst system allows the cross-cyclodimerization event of diarylalkynes with some cyclic alkenes leading to the corresponding dihydronaphthalenes.

We initially investigated the effect of various Brønsted acids using diphenylacetylene (**1a**, 0.50 mmol) and 4-octyne (**2a**, 1.0 mmol) as model substrates in the presence of

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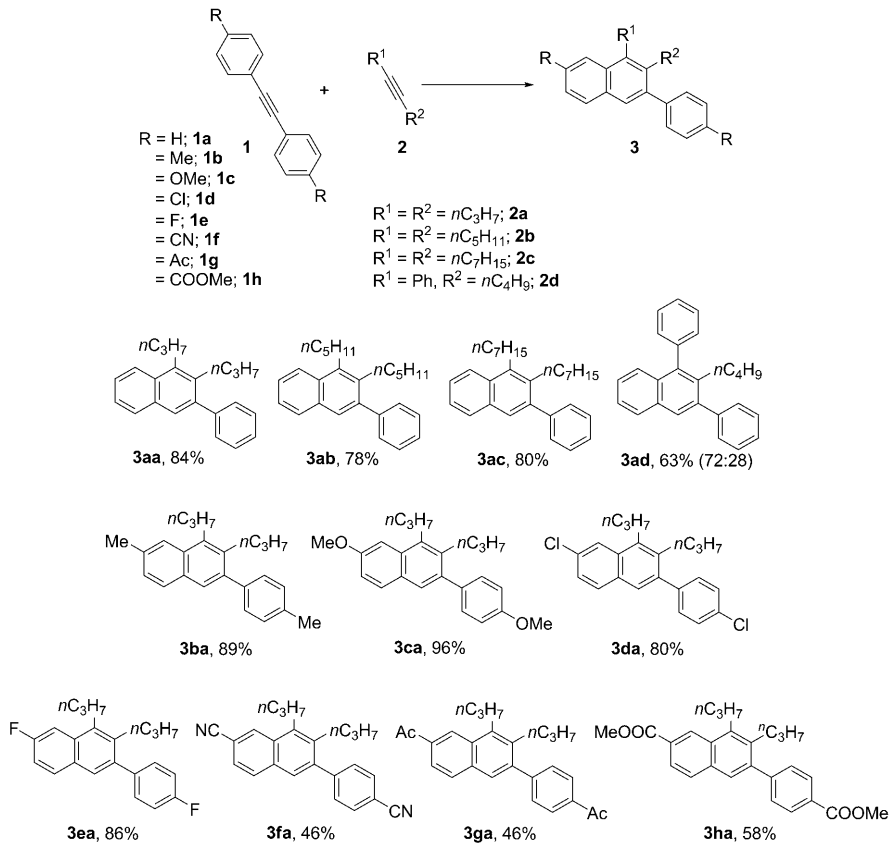
1.5 mol% of [{RhCl(cod)}$_2$] (3 mol% Rh) and 6 mol% of PPh_3 in refluxing *o*-xylene (Table 1). As shown previously,[9] no reaction took place without any acid, and the starting materials were recovered intact (entry 1). Addition of PhCOOH or *p*-TsOH·H_2O (20 mol%) led to the formation of the desired product **3aa**, albeit with low yield and chemoselectivity (entries 2 and 3). In contrast, use of amine salts was found to change the selectivity in the reaction (entries 4–7). Especially, with Py·HBr (Py = pyridine), the cross-dimer **3aa** was obtained in 84% isolated yield (entry 7). Although we also screened other monodentate triarylphosphine ligands in the presence of Py·HBr, the effect on the yield and ratio (**3aa**:**4aa**) was almost negligible as far as we examined. However, without PPh_3, no product was formed even in the presence of Py·HBr.

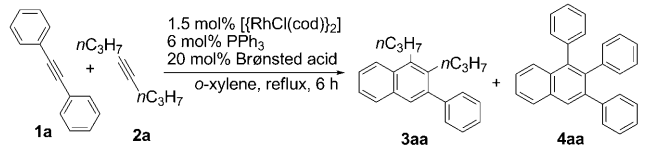
With the optimized reaction conditions in hand, the cross-cyclodimerization of various diarylacetylenes **1** was carried out (Scheme 1). Longer alkyl side chains could be introduced to the 1- and 2-positions of naphthalene without any difficulties (**3ab** and **3ac**): Note that introduction of such alkyl chains is known to generally improve the solubility of condensed aromatics. Unsymmetric alkyne **2d** also reacted with diphenylacetylene (**1a**) to furnish the corresponding condensed cross-dimer **3ad** in 63% yield, although the regioselectivity was moderate. On the other hand, activated alkynes such as 3-phenyl-2-propyn-1-ol and ethyl phenylpropiolate did not couple with **1a**, a large amount of which remained unchanged. Subsequently, the substitution effect on the benzene ring of diphenylacetylene was examined. The substrates bearing electron-donating as well as electron-withdrawing substituents were effectively transformed to the expected 1,2,3,7-tetrasubstituted naphthalenes in good to high yields (**3ba**–**ea**). Notably, the acid-labile functional groups CN, Ac, and COOMe were tolerant under the reaction conditions to give rise to **3fa**–**ha** with substantial yields. It is worth noting that the reaction of **1a** with **2a** on a five-fold larger scale was successfully produced **3aa** in a 94% yield.

Our catalyst system could be applied to the cross-dimerization with thienylacetylenes (Scheme 2). Dithienylacetylene **5** underwent the cross-dimerization with 4-octyne (**2a**) to construct the benzothiophene core **6** in 95% yield (top).



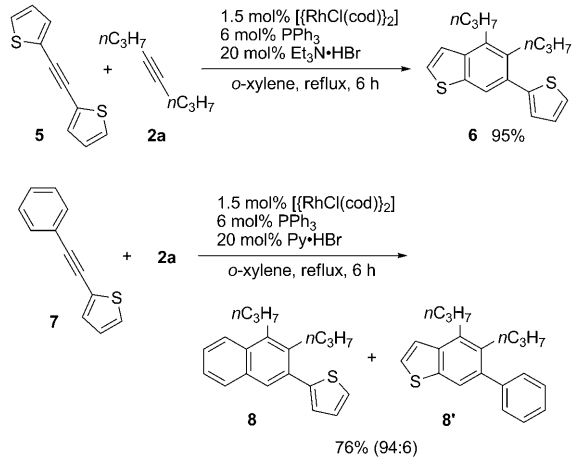
Scheme 1. The rhodium-catalyzed cross-cyclodimerization of various diarylacetylenes **1** with aliphatic alkynes **2**. Reaction conditions: A mixture of [{RhCl(cod)}$_2$] (0.0075 mmol, 3 mol% Rh), PPh_3 (0.030 mmol), Py·HBr (0.10 mmol), **1** (0.50 mmol), and **2** (1.0 mmol) in *o*-xylene (2.5 mL) was heated at 160°C (bath temp.) for 6 h under N_2. Isolated yields [%] are given and the regioisomeric ratio is given in parentheses where appropriate. For **3aa** a reaction on a five times larger scale in *o*-xylene (10 mL) led to a yield of 94%.

Table 1. Effect of various Brønsted acids in rhodium-catalyzed cross-cyclodimerization of diphenylacetylene (**1a**) with 4-octyne (**1b**).[a]



Entry	Brønsted acid	Yield [%][b] **3aa**	**4aa**	**3aa**:**4aa**
1	none	0	0	–
2	PhCOOH	12	16	43:57
3	*p*-TsOH·H_2O	2	5	29:71
4	Et_3N·HCl	23	5	82:18
5	Et_3N·HBr	63 (47)	8	89:11
6	Py·HCl	46	6	88:12
7	Py·HBr	93 (84)	3	97:3

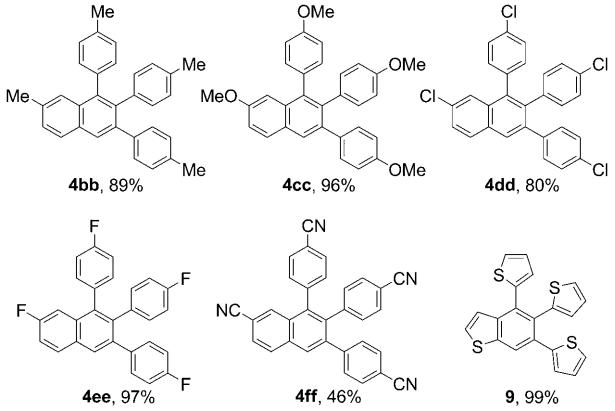
[a] A mixture of [RhCl(cod)]$_2$ (0.0075 mmol, 3 mol% Rh), PPh_3 (0.030 mmol), Brønsted acid (0.10 mmol), **1a** (0.50 mmol), and **2a** (1.0 mmol) in *o*-xylene (2.5 mL) was heated at 160°C (bath temp.) for 6 h under N_2. [b] GC yield. Isolated yield is in parentheses. The yield of **4aa** was based on a half amount of **1a** employed.



Scheme 2. Reactions of thienylacetylenes **5** and **7**.

In this case, the use of Et_3N·HBr instead of Py·HBr gave the better result. It is worth noting that the reaction of 2-(phenylethynyl)thiophene (**7**) with **2a** proceeded regioselectively to provide 3-thienyl-1,2-dipropylnaphthalene (**8**) predominantly (bottom).

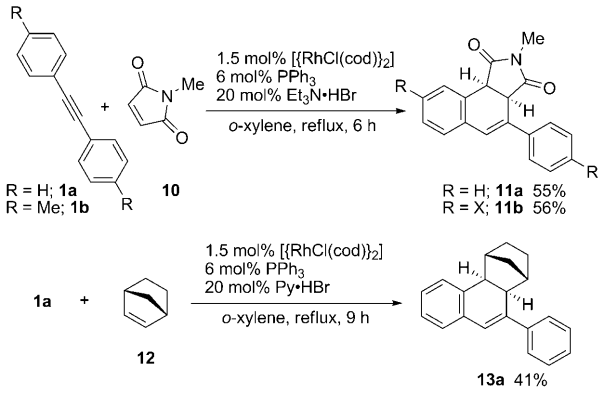
The [{RhCl(cod)}$_2$]/PPh_3/Py·HBr catalyst system also improved the efficiency of homo-dimerization with diarylacetylenes (Scheme 3).[9] Not only electron-rich diary-



Scheme 3. Products of the rhodium-catalyzed homo-cyclodimerization of various diarylacetylenes **1** and **5**. Reaction conditions: A mixture of [{RhCl(cod)}$_2$] (0.0075 mmol, 3 mol% Rh), PPh_3 (0.030 mmol), Py·HBr (0.10 mmol), **1** or **5** (0.50 mmol), and **2** (1.0 mmol) in *o*-xylene (2.5 mL) was heated at 160 °C (bath temp.) for 6 h under N_2. The isolated yield based on the half amount of **1** or **5** employed. In the case of **9** Et_3N·HBr was used in place of Py·HBr.

lacetylenes, but also electron-deficient ones readily homo-dimerized under the standard conditions. In addition, dithienylacetylene **5** could also participate in the reaction to furnish **9** in excellent yield.[10] In contrast, the dimerization of aryl(alkyl)acetylene such as 1-phenyl-1-hexyne was unsuccessful. This is probably due to the diminished reactivity toward the insertion to the rhodium hydride species in the catalytic cycle (vide infra).

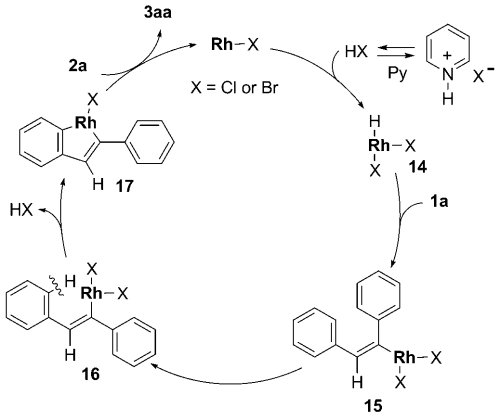
Next, we tried to apply the catalyst system to the cross-dimerization of diarylacetylenes with alkenes. The preliminary results are shown in Scheme 4. On exposure of diphenylacetylene (**1a**) and *N*-methylmaleimide (**10**) to the Et_3N·HBr-



Scheme 4. Cross-cyclodimerization with alkenes.

promoted conditions, the corresponding dihydronaphthalene **11a** was obtained in 55% yield (top). Methyl-substituted acetylene **1b** was also available for use. It is worth noting that norbornene (**12**) coupled with **1a** to give the tetracyclic framework **13a** (bottom).

We are tempted to assume the reaction mechanism of the cross-cyclodimerization as illustrated in Scheme 5 with diphenylacetylene (**1a**) and 4-octyne (**2a**) as the representa-

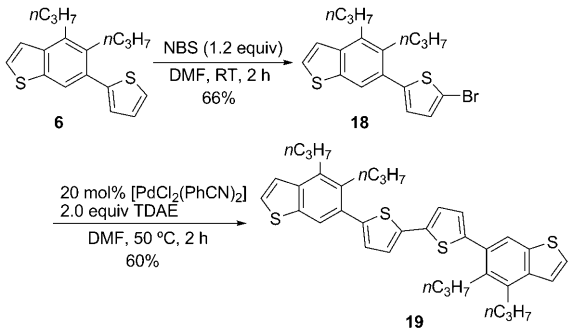


Scheme 5. Plausible reaction mechanism.

tive substrates.[9] Initial oxidative addition of HX to Rh^I gives the rhodium hydride species **14**.[11] The subsequent insertion of **1a** to the Rh–H bond[12] and geometrical isomerization via a zwitterionic form[13] would afford the intermediate **16**. The rhodium complex undergoes *ortho*-metalation[14] with the liberation of HX to furnish rhodacycle **17**, and the selective insertion of **2a** to the rhodium–aryl or –alkenyl bond followed by productive reductive elimination produces the cross-dimer **3aa** along with the starting Rh^I complex to complete the catalytic cycle. Although the reason for the

preferable insertion of 4-octyne (**2a**) rather than diphenylacetylene (**1a**) to the rhodacycle **17** is not clear at this stage, the free pyridine generated in situ may coordinate to the rhodium center of **17** to cause the unusual chemoselectivity.[15] Moreover, the possibility that the bromide ligand on Rh of **17** enhances the selectivity could not be excluded (Table 1, entry 4 vs. 5 and 6 vs. 7).

Finally, in order to demonstrate the synthetic utility of the catalytic reaction, we performed the derivatization of the cross-dimer **6** (Scheme 6). The regioselective mono-bromi-



Scheme 6. Derivatization of **6** to thiophene core π system **19**. TDAE = tetraxis(dimethylamino)ethylene.

nation of **6** was possible upon treatment with *N*-bromosuccinimide (NBS) in DMF. The brominated **18** obtained was subjected to the dimerization conditions under palladium catalysis[16] to form the structurally interesting thiophene-containing π system **19** in an acceptable yield.[17]

In summary, we have developed the efficient rhodium/phosphine/amine·HBr catalyst system for highly selective cross-cyclodimerization as well as homo-dimerization of diarylacetylenes leading to the multisubstituted naphthalenes. In addition, the catalyst enabled the use of alkenes as the coupling components, providing the dihydronaphthalenes. Thus, the catalytic reactions appear to be powerful synthetic tools for the construction of naphthalene core from the simple and readily accessible unsaturated molecules.

Experimental Section

Rhodium-catalyzed cross-cyclodimerization of diphenylacetylene (1a) with 4-octyne (2a): Under N_2 atmosphere, [{RhCl(cod)}$_2$] (3.7 mg, 0.0075 mmol), PPh_3 (8.0 mg, 0.030 mmol), Py·HBr (16 mg, 0.10 mmol), **1a** (89 mg, 0.50 mmol), **2a** (110 mg, 1.0 mmol), *o*-xylene (2.5 mL), and 1-methylnaphthalene (ca. 50 mg, internal standard) were placed in a 20 mL two-necked reaction flask equipped with a reflux condenser. After the mixture was heated at 160 °C for 6 h, the consumption of **1a** was checked by GC analysis. The resulting mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel with hexane as an eluent to give 3-phenyl-1,2-dipropylnaphthalene (**3aa**, 121 mg, 0.42 mmol) in 84% yield.

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Keywords: alkynes · cross-cyclodimerization · dihydronaphthalenes · naphthalenes · rhodium

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