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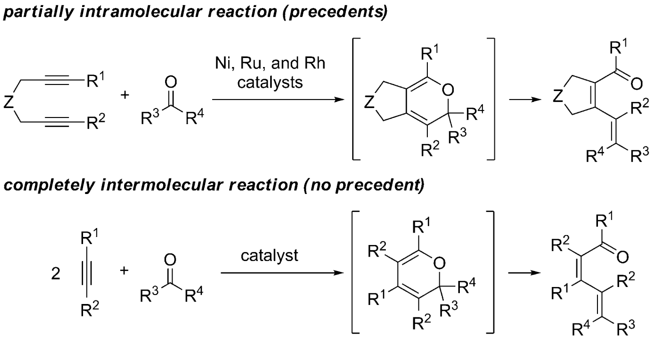
Rhodium-Catalyzed Intermolecular [2+2+2] Cross-Trimerization of Aryl Ethynyl Ethers and Carbonyl Compounds To Produce Dienyl Esters**

*Yuta Miyauchi, Masayuki Kobayashi, and Ken Tanaka**

Transition-metal-catalyzed [2+2+2] cycloaddition reactions of alkynes and C_{sp}–heteroatom multiple bonds, such as nitriles and heterocumulenes, are valuable methods for the synthesis of substituted heterocycles in a highly atom economical manner.[1] However, the analogous transition-metal-catalyzed [2+2+2] cycloaddition of alkynes and C_{sp^2}–heteroatom multiple bonds, such as ketones and aldehydes, have been reported in a limited number of examples.[2–6] The pioneering example of such a catalysis was the nickel(0)/monophosphine complex catalyzed cycloaddition of diynes and aldehydes.[2] After this initial report, the [Cp*Ru(cod)Cl]-catalyzed cycloaddition of diynes and electron-deficient ketones,[3] the nickel(0)/imidazolylidene complex catalyzed cycloaddition of diynes and electron-rich aldehydes and ketones,[4] and the neutral rhodium(I) complex catalyzed cycloaddition of diynals were reported.[5] However, a catalyst that can be used for both electron-deficient and electron-rich carbonyl compounds has not been developed. Our research group discovered that a cationic rhodium(I)/H_8-binap complex is able to catalyze the [2+2+2] cycloaddition of diynes and both electron-deficient and electron-rich carbonyl compounds at room temperature.[6] Unfortunately, these examples are strictly limited to partially or completely intramolecular reactions between tethered diynes and carbonyl compounds. The development of the transition-metal-catalyzed completely intermolecular [2+2+2] cycloaddition of two untethered alkynes and a carbonyl compound[7,8] is one of the most challenging targets (Scheme 1).[9]

Our research group recently reported that the cationic rhodium(I)/H_8-binap complex is able to catalyze the completely intermolecular [2+2+2] cycloaddition of two aryl ethynyl ethers with nitriles,[10] isocyanates,[10] and alkynylesters.[11] Interestingly, although aryl ethynyl ethers[12] reacted with unsymmetrical electron-deficient unsaturated compounds (nitriles,[10] isocyanates,[10] and ethyl 2-butynoate)[11] in high yields, they reacted with symmetrical electron-deficient alkynes (diethyl acetylenedicarboxylates) in very low yields.[10] Aryl ethynyl ethers showed high reactivity towards polar unsaturated compounds, so we anticipated that aryl ethynyl ethers would show high reactivity towards the polar C–O double bonds of carbonyl compounds. Herein, we report the rhodium-catalyzed chemo-, regio-, and stereoselective completely intermolecular [2+2+2] cross-trimerization of two aryl ethynyl ethers and carbonyl compounds at room temperature.



Scheme 1. Transition-metal-catalyzed [2+2+2] cycloaddition reactions of alkynes and carbonyl compounds.

We first investigated the reaction of ethynyl 2-naphthyl ether (**1a**) and α-ketoester **2a** in the presence of various $[Rh(cod)_2]BF_4$/bisphosphine complexes (Table 1). After screening a range of bisphosphine ligands (Scheme 2; Table 1, entries 1–7;), we found that H_8-binap is the best ligand, as when using this ligand dienyl ester **3aa** was obtained in the highest yield with complete regio- and stereoselectivity (Table 1, entry 1). The catalyst loading could be reduced to 0.025 equiv with only a slight erosion of the product yield (Table 1, entry 8).[13]

With the optimized reaction conditions established, we explored the scope of the ketones in reactions with **1a** (Scheme 3).[13] Not only α-ketoester **2a** but also α-ketoester **2b**, α-ketoamide **2c**, acylphosphonate **2d**, and 1,2-diketones **2e** and **2f** reacted with **1a** to give the corresponding dienyl esters in moderate to good yields. In the previously reported [2+2+2] cross-trimerization of tethered diynes with carbonyl compounds catalyzed by the cationic rhodium(I)/H_8-binap complex, electron-rich ketones showed lower reactivity than electron-deficient ketones.[6a,c] However, interestingly, **1a** reacted with acetone (**2g**) to give the product in a yield of 88 %, which is significantly higher than the yield of the reaction of a 1,6-diyne with acetone (51 %).[6a,c] Not only

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[*] Y. Miyauchi, M. Kobayashi, Prof. Dr. K. Tanaka
Department of Applied Chemistry, Graduate School of Engineering
Tokyo University of Agriculture and Technology
Koganei, Tokyo 184-8588 (Japan)
E-mail: tanaka-k@cc.tuat.ac.jp
Homepage: http://www.tuat.ac.jp/~tanaka-k/

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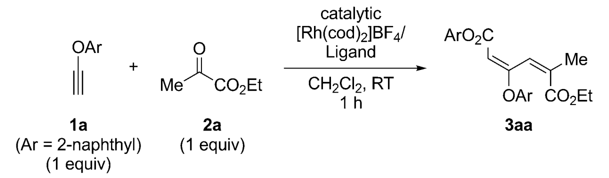
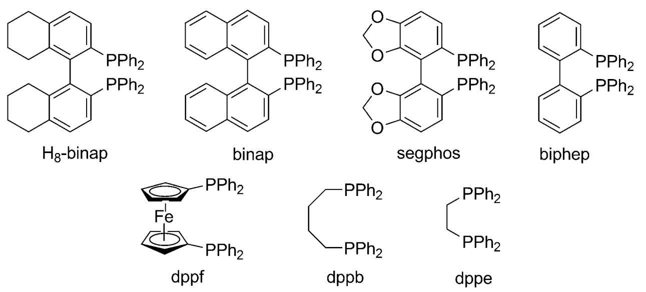
Table 1: Optimization of reaction conditions for the rhodium-catalyzed [2+2+2] cross-trimerization reaction of **1a** and **2a**.[a]



Entry	Ligand	Catalyst [equiv]	Yield [%][b]	*E*/*Z*
1	H_8-binap	0.05	44	1:>99
2	binap	0.05	30	7:93
3	segphos	0.05	19	1:>99
4	biphep	0.05	20	7:93
5[c]	dppf	0.05	24	1:>99
6	dppb	0.05	21	1:>99
7[d]	dppe	0.05	17	10:90
8[e]	H_8-binap	0.025	41	1:>99

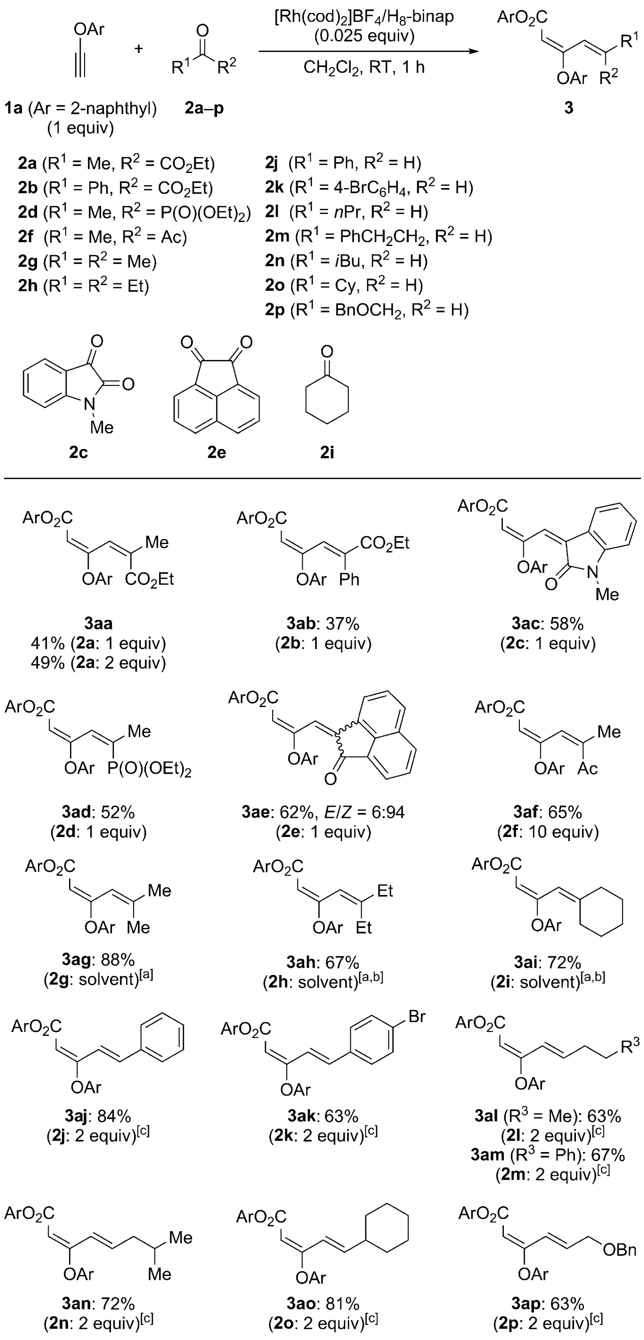
[a] $[Rh(cod)_2]BF_4$ (0.0075 mmol), ligand (0.0075 mmol), **1a** (0.15 mmol), **2a** (0.15 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Yield of the isolated products. [c] For 3 h. [d] $[Rh(nbd)_2]BF_4$ was used. [e] **1a** (0.30 mmol) and **2a** (0.30 mmol) were used.



Scheme 2. Structures of bisphosphine ligands.

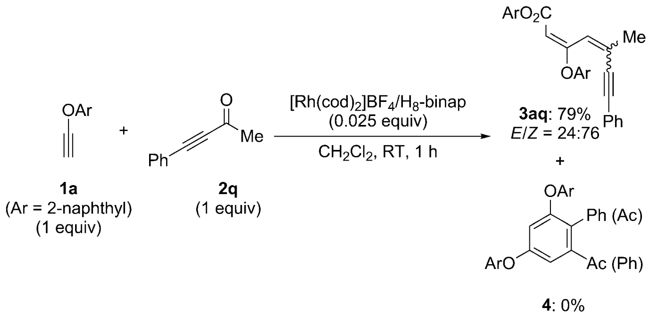
acetone but also 3-pentanone (**2h**) and cyclohexanone (**2i**) reacted with **1a** in good yields. Next, the use of aldehydes instead of ketones was examined. A variety of aromatic and aliphatic aldehydes **2j–p** were able to react with **1a** to give the corresponding dienyl esters in good to high yields. It is noteworthy that all reactions in Scheme 3 proceeded to completion at room temperature in only 1 hour, and complete regioselectivity and excellent stereoselectivity were observed.

This exceptionally high reactivity of the aryl ethynyl ether **1a** towards the C–O double bonds prompted our investigation into the chemoselectivity in the reactions of aryl ethynyl ethers and carbonyl compounds, bearing an additional reaction site.[14] Cationic rhodium(I)/biaryl bisphosphine complexes are highly effective catalysts for the [2+2+2] cycloaddition of 1,6-diynes and electron-deficient alkynes,[15] and thus the reaction of 1,6-diyne and alkynyl ketone **2q** using the cationic rhodium(I)/H_8-binap complex as a catalyst exclusively furnished the corresponding substituted benzene.[6a,c] In contrast, **1a** exclusively reacted with the C–O double bond of **2q** using the same rhodium catalyst to give not benzene **4**, but the corresponding dienyne ester **3aq** in high yield (Scheme 4).[13]



Scheme 3. Rhodium-catalyzed [2+2+2] cross-trimerization reactions of ethynyl 2-naphthyl ether (**1a**) and carbonyl compounds **2a–p**. $[Rh(cod)_2]BF_4$ (0.0075 mmol), H_8-binap (0.0075 mmol), **1a** (0.30 mmol), **2a–p** (0.30–3.0 mmol), and CH_2Cl_2 (2.0 mL) were used. Cited yields are of the isolated products. [a] **2g–i** were used as a solvent instead of CH_2Cl_2. [b] $[Rh(cod)_2]BF_4$ (0.015 mmol) and H_8-binap (0.015 mmol) were used. [c] $(CH_2Cl)_2$ was used as the solvent.

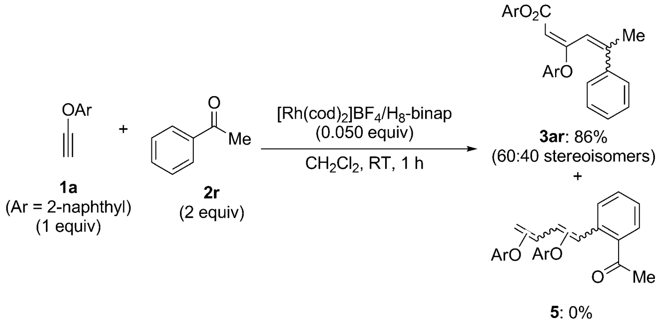
We have also reported that the reaction of 1,6-diynes and aryl ketones in the presence of a cationic rhodium(I)/biaryl bisphosphine complex, as the catalyst, exclusively furnished the corresponding dienylation products through carbonyl-directed aromatic C–H bond activation.[16] In contrast, **1a** exclusively reacted with the C–O double bond of acetophe-



Scheme 4. Chemoselectivity between the ketone carbonyl group and alkyne triple bond.

none (**2r**) to give not diene **5**, but the corresponding dienyl ester **3ar** in high yield (Scheme 5).[13]

Next, we explored the scope of aryl ethynyl ethers in the reaction with acetone (**2g**; Table 2).[13] Electronically and sterically different aryl ethynyl ethers **1a–d** could be employed in this process (Table 2, entries 1–4). Interestingly, electron-rich ethynyl 4-methoxyphenyl ether (**1b**) showed excellent reactivity (Table 2, entry 2). Importantly, a direct connection between the aryloxy group and the triple bond is essential to promote this reaction. Phenyl and methyl propargyl ether (**1e** and **1f**, respectively), benzyl acetylene (**1g**), and phenyl acetylene (**1h**) failed to react with **2g**, and the homo-cyclotrimerization products of **1e–h** were generated (Table 2, entries 5–8).

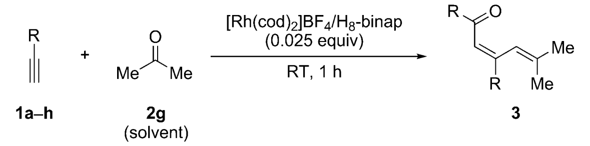


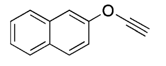
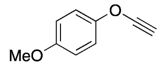
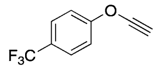
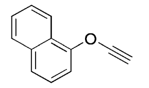
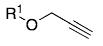
Scheme 5. Chemoselectivity between the [2+2+2] cross-trimerization and C–H bond functionalization.

Finally, the reaction of **1a** and **2g** was examined in the presence of an excess of **1f** (Scheme 6). The yield of the cross-trimerization product **3ag** from two molecules of **1a**, and one molecule **2g** was decreased to 22%, and the cross-trimerization product **3afg** from **1a**, **1f**, and **2g** was generated in only 7% yield, even though excess **1f** was employed.[17]

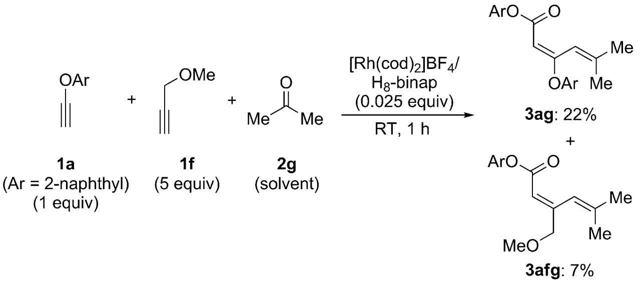
Scheme 7 depicts a mechanistic proposal for this rhodium-catalyzed chemo-, regio-, and stereoselective [2+2+2] cross-trimerization of aryl ethynyl ethers and carbonyl compounds. Two molecules of aryl ethynyl ether **1** react with rhodium to generate rhodacyclopentadiene intermediate **A**.[13] Insertion of the carbonyl compound **2** into intermediate **A** generates intermediate **B**.[18] Reductive elimination of rhodium to

Table 2: Rhodium-catalyzed [2+2+2] cross-trimerization reactions of terminal alkynes **1a–h** and acetone (**2g**).[a]

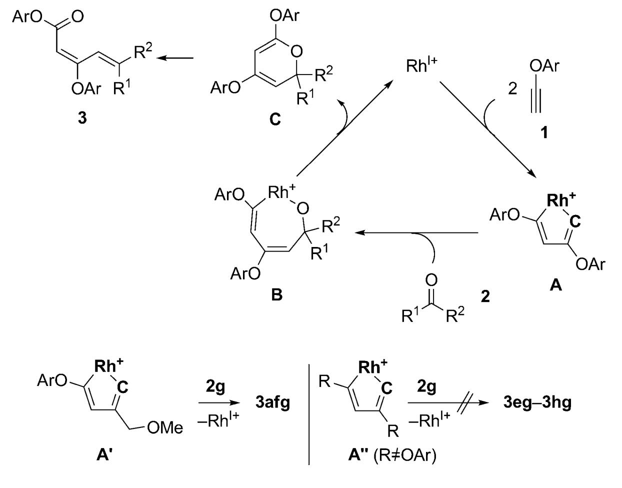


Entry	1	R—≡	3	Yield [%][b]
1	**1a**		**3ag**	88
2	**1b**		**3bg**	98
3	**1c**		**3cg**	76
4	**1d**		**3dg**	74
5	**1e** (R^1 = Ph)		**3eg**	0
6	**1f** (R^1 = Me)		**3fg**	0
7	**1g** (R^2 = Ph)	R^2—≡	**3gg**	0
8	**1h** (R^2 = Bn)		**3hg**	0

[a] [Rh(cod)$_2$]BF$_4$ (0.0075 mmol), H$_8$-binap (0.0075 mmol), **1a–h** (0.30 mmol), and **2g** (2.0 mL) were used. [b] Yields of the isolated products.



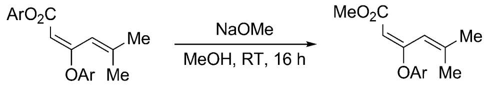
Scheme 6. Rhodium-catalyzed reaction of **1a**, **1f**, and **2g**.



Scheme 7. A mechanistic proposal.

generate pyrane **C** followed by electrocyclic ring opening furnishes dienone **3**. The olefin geometry of dienone **3** may be determined by the thermodynamically controlled electrocyclic ring-opening reaction[19] and the subsequent *E*/*Z* isomerization catalyzed by a cationic rhodium(I) complex.[20] In intermediate **A**, the highly polarized Rh–C bond (highlighted in bold) may facilitate the carbonyl insertion. Indeed, the electronic nature of the aromatic substituents of **1a–c**, which would affect the polarity of the Rh–C bond of intermediate **A**, had an appreciable impact on the product yields (electron density of alkyne: **1b** > **1a** > **1c**, product yield: **3bg** > **3ag** > **3cg**; Table 2, entries 1–3). The cross-trimerization reaction of **1a**, **1f**, and **2g** could proceed through moderately electron-rich intermediate **A′**, bearing one aryloxy group, to afford **3afg** in low yield, while the less electron-rich intermediate **A″**, bearing no aryloxy group, would not react with **2g**.[17]

With regard to the synthetic utility of the present [2+2+2] cross-trimerization reactions, it is important to note that 3-alkoxy-6-oxo-2,4-hexadienoates show biological activity for various pharmacological targets.[21] The present method enables the preparation of interesting new analogues. Although alkyl ethynyl ethers cannot be employed in this reaction owing to their instability towards the Lewis acidic cationic rhodium(I) catalyst, 2-naphthyl ester **3ag** can be converted almost quantitatively into the corresponding methyl ester **6** by treatment with NaOMe in MeOH (Scheme 8).



3ag (Ar = 2-naphthyl) **6**: 99%

Scheme 8. Transesterification of 2-naphthyl ester **3ag** leading to methyl ester **6**.

In conclusion, the chemo-, regio-, and stereoselective completely intermolecular [2+2+2] cross-trimerization of two aryl ethynyl ethers with both electron-deficient and electron-rich carbonyl compounds, leading to aryloxy-substituted dienyl esters, has been achieved at room temperature by using a cationic rhodium(I)/H_8-binap complex as a catalyst. Further utilization of aryl ethynyl ethers in rhodium-catalyzed reactions is underway in our laboratory.

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Keywords: alkynes · carbonyl compounds · dienyl esters · homogeneous catalysis · rhodium

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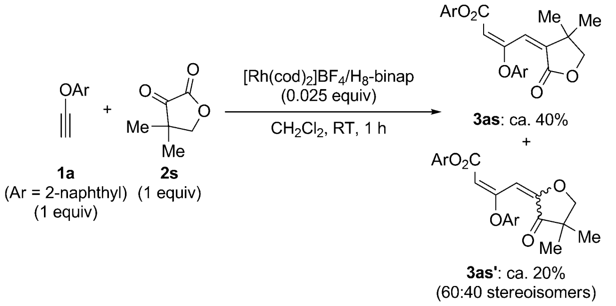
[13] In the reactions of aryl ethynyl ethers **1a–d** and carbonyl compounds **2a–r** (Tables 1–2 and Scheme 3–5), homo-cyclotrimerization products of **1a–d** were generated as by-products. These by-products are generated via intermediates **A**, and therefore their formation supports the formation of **3** via intermediates **A** (Scheme 7).

[14] We have reported that the cationic rhodium(I)/H_8-binap complex catalyzes the reaction of a 1,6-diyne with the ketone carbonyl group and not the ester carbonyl group of α-ketoester **2s** (see: Ref. [6c]). However, interestingly, **1a** reacted with not only the ketone carbonyl group but also the ester carbonyl group of **2s**, although products **3as** and **3as′** were isolated as an inseparable mixture.



[15] For an account, see: a) Ref. [1m]; for examples, see: b) K. Tanaka, K. Takeishi, K. Noguchi, *J. Am. Chem. Soc.* **2006**, *128*, 4586; c) G. Nishida, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2007**, *119*, 4025; *Angew. Chem. Int. Ed.* **2007**, *46*, 3951; d) G. Nishida, K. Noguchi, M. Hirano, K. Tanaka, *Angew. Chem.* **2008**, *120*, 3458; *Angew. Chem. Int. Ed.* **2008**, *47*, 3410; e) T. Suda, K. Noguchi, M. Hirano, K. Tanaka, *Chem. Eur. J.* **2008**, *14*, 6593; f) G. Nishida, S. Ogaki, Y. Yusa, T. Yokozawa, K. Noguchi, K. Tanaka, *Org. Lett.* **2008**, *10*, 2849; g) N. Sakiyama, D. Hojo, K. Noguchi, K. Tanaka, *Chem. Eur. J.* **2011**, *16*, 1428; h) S. Ogaki, Y. Shibata, K. Noguchi, K. Tanaka, *J. Org. Chem.* **2011**, *76*, 1926.

[16] a) See Ref. [6a,e]. Another research group also reported a similar reaction, see: b) K. Tsuchikama, Y. Kuwata, Y. Tahara, Y. Yoshinami, T. Shibata, *Org. Lett.* **2007**, *9*, 3097.

[17] The reaction shown in Scheme 6 furnished cross-cyclotrimerization products of **1a** and **1f** [ca. 50% yield (**1a**/**1f** = 2:1) and ca. 20% yield (**1a**/**1f** = 1:2)] as major products. Possible pathways for the formation of these products may involve intermediates **A** and **A′**, which would support the formation of **3ag** and **3afg** via intermediates **A** and **A′**, respectively (see Scheme 7).

[18] For carbonyl insertion into a Rh−C bond, see: C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1674.

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