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Rhodium(I)-Catalyzed Synthesis of Indoles: Amino-Claisen Rearrangement of *N*-Propargylanilines

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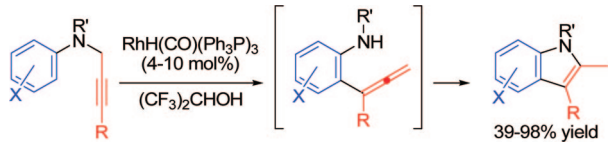

Mild and facile preparations of 2-substituted or 2,3-disubstituted indole compounds were achieved by $RhH(CO)(Ph_3P)_3$ (4−10 mol %)-catalyzed reaction of *N*-propargylanilines in hexafluoroisopropyl alcohol (HFIP). The formation of indoles was proven to be derived from an *o*-allenylaniline intermediate, which was generated by the Rh(I)-catalyzed amino-Claisen rearrangement of *N*-propargylanilines. The catalytic system is also available for the one-pot synthesis of indoles by reacting *N*-alkylaniline (1 equiv) with propargyl bromide (1.3 equiv) in the presence of K_2CO_3 (3 equiv) in HFIP. The active catalyst was proven to be $[Rh(CO)(Ph_3P)_2]OCH(CF_3)_2$ generated in situ from $RhH(CO)(Ph_3P)_3$ and HFIP. The structure of $[Rh(CO)(Ph_3P)_2]OCH(CF_3)_2$ was confirmed by single-crystal X-ray crystallographic analysis.

Introduction

Transition-metal-catalyzed synthesis of heterocycles has received considerable attention, and novel and efficient synthetic methods have been developed for the creation of the core structure of biologically attractive molecules.[1] In particular, the metal-catalyzed preparation of indole skeletons, which is prevalent in a wide variety of biologically and medicinally important compounds,[2] has been well studied by many research groups.[3,4] Intramolecular cyclization of *o*-alkynylaniline derivatives is the method of choice for the synthesis of 2-substituted indoles, and thus, Pd-catalyzed cyclization of *o*-alkynylanilines in the presence of alkyl, vinyl, or aryl halides has been reported to give various 2,3-disubstituted indoles.[5−7] Recently, Pt-catalyzed cyclization of *N*-allyl- or *N*-acyl-*o*-alkynylanilines,[8] Au-catalyzed formation of 2,3-disubstituted indoles from *o*-alkynylanilines and α,β-unsaturated carbonyl compounds,[9] and Rh-catalyzed reaction of *o*-alkynylaniline to 2,3-unsubstituted

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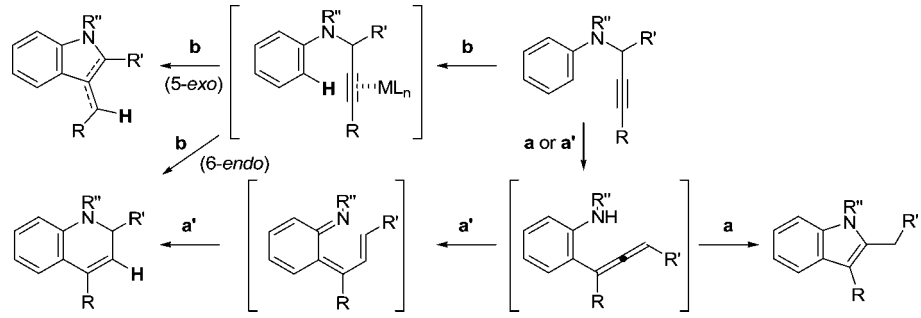
SCHEME 1



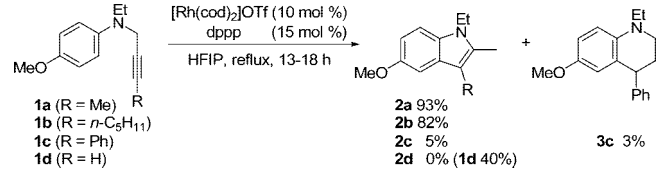
indoles have been reported.[10] The synthesis of 2,3-disubstituted indoles through the intermolecular Pd-catalyzed Heck reactions of *o*-iodoanilines with alkynes has also been reported.[11,12] In the described reactions, however, the procedures have been met with the drawback of the scope and limitations on the substituent of the substrate and/or poor regioselectivity.[11b]

N-Propargylanilines are alternative candidates for the preparation of heterocycles, since regioselective intramolecular hydroarylation reactions of *N*-propargylanilines are considered to be divergent methods for the preparation of quinoline or indole frameworks (6-*endo* or 5-*exo*). Intramolecular hydroarylation reactions have been achieved by various metal catalysts,[13,14] and the reactions of *N*-propargylanilines have been known to proceed via the 6-*endo* mode to give 1,2-dihydroquinolines (path **b**, Scheme 1).[15,16] On the other hand, amino-Claisen rearrangements[17,18] of *N*-propargylaniline derivatives, which could be considered to be an alternative route to the quinoline ring system, have been reported to proceed through *o*-allenylaniline under the thermal[19] or Cu-promoted conditions[20,21] (path **a′**). Although a few examples of the thermal rearrangements of *N*-propargylanilines brought about the formation of indoles (path **a**), the reactions required extremely high temperatures (240−260 °C) and the products were obtained in low yields.[19a] Recently, we reported on the mild synthesis of 2,3-substituted indole derivatives through amino-Claisen rearrangement of *N*-propargylaniline derivatives (path **a**) catalyzed by $[Rh(cod)_2]OTf$ in hexafluoroisopropyl alcohol (HFIP).[22,23] In the reaction, however, there still remains a main drawback in terms of the limitation on the substrate. In this full account, we describe that further search for an efficient Rh(I) catalyst led to $RhH(CO)(Ph_3P)_3$ and its use for the one-pot preparation of indoles from a mixture of anilines and propargyl halides in the presence of a base. Besides the synthetic work on indoles, we elucidated that the real catalyst of the indole formation was derived from $RhH(CO)(Ph_3P)_3$ with HFIP and the structure was confirmed by single-crystal X-ray crystallographic analysis.

Results and Discussion

Formation of Indole Derivatives from *N*-Propargylanilines. Initial studies focused on extending the limited scope of our previous synthetic method[22] of indoles from *N*-propargylanilines. In the presence of 10 mol % of $[Rh(cod)_2]OTf$ and 15 mol % of 1,3-diphenylphosphinopropane (dppp), the reaction of *N*-propargylaniline **1a** or **1b** proceeded in HFIP to give the corresponding indole **2a** or **2b** in high yield (Scheme 2). In the

SCHEME 2



reaction of Ph derivative **1c** or terminal alkyne **1d**, however, the product (**2c** or **2d**) was obtained in a low yield or was not detected. Thus, we examined miscellaneous rhodium(I) catalysts (10 mol %) in the reaction of *N*-propargylaniline **1c**, and the

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TABLE 1. Rh(I) Catalysts for the Reaction of 1c[a]

entry	Rh(I)	ligand (mol%)	time (h)	**2c** yield (%)[b]
1	$[Rh(cod)_2]OTf$	dppp (15)	18	5 (**3c** 3)
2	$[Rh(cod)_2]OTf$	dppe (15)	18	34 (**3c** 26)
3	$RhH(Ph_3P)_4$		5	− (**1c** 92)
4	$RhH(CO)(Ph_3P)_3$		2	43 (**3c** 4)
5	$RhH(CO)(Ph_3P)_3$	Ph_3P (20)	5	77
6	$RhH(CO)(Ph_3P)_3$	Cy_3P (20)	5	87 (85)[c]
7[d]	$RhH(CO)(Ph_3P)_3$	Cy_3P (20)	5	0 (**1c** 82)
8[e]	$RhH(CO)(Ph_3P)_3$	Cy_3P (20)	5	83
9[f]	$RhH(CO)(Ph_3P)_3$	Cy_3P (20)	5	45
10[g]	$RhH(CO)(Ph_3P)_3$	Cy_3P (20)	5	18
11	$[RhCl(CO)_2]_2$	Ph_3P (30)	5	65
12	$[RhCl(CO)_2]_2$	Ph_3P (30), Cy_3P (20)	5	72

[a] In HFIP at 80 °C with 10 mol % of Rh(I) catalyst. Cy = cyclohexyl. [b] Yields were determined by ^1H NMR analysis. [c] Yield in parentheses is the isolated yield. [d] Solvent: DCE. [e] Solvent: HFIP−DCE (3:2). [f] Solvent: HFIP−DCE (2:3). [g] Solvent: HFIP−DCE (1:4).

results are shown in Table 1. Although the use of $[Rh(cod)_2]OTf$ gave a considerable amount of tetrahydoroquinoline **3c** as a byproduct (entries 1 and 2),[24,25] $RhH(CO)(Ph_3P)_3$ in refluxing HFIP suppressed the formation of **3c**, and indole **2c** was obtained in 43% yield (entry 4). It turned out that the addition of a monodentate phosphine ligand to the Rh catalyst was an effective way to improve the formation of **2c** (entries 5 and 6). Thus, the addition of tricyclohexylphosphine (Cy_3P, 20 mol %) improved the yield of **2c** to 87% (entry 6). 1,2-Dichloroethane (DCE) and other solvents (trifluoroethanol, 2-propanol, THF) instead of HFIP, however, did not promote the formation of the indole product at all, and the reactions ended with the recovery of **1c** (57−82%, entry 7). A mixture of HFIP−DCE (3:2) as a solvent was found to be identical to that of the sole use of HFIP (entries 6 and 8−10). Thus, the presence of HFIP for the present reaction is indispensable. It should be mentioned that the use of $[RhCl(CO)_2]_2$ in the presence of Ph_3P (30 mol %)/Cy_3P (20 mol %) in HFIP brought about a good result (**2c**: 72%, entry 12).

For the formation of indole compounds **2** from various *N*-propargylaniline derivatives **1**, $RhH(CO)(Ph_3P)_3$ exerted superior activity compared to the $[Rh(cod)_2]OTf$ catalyst (Table 2). Terminal alkyne **1d**, which was not converted into indole **2d** by $[Rh(cod)_2]OTf$-dppp (entry 1), gave **2d** in 65% yield within 3 h (entry 2). In the case of methyl or pentyl compound **1a** or **1b**, even 4−6 mol % of $RhH(CO)(Ph_3P)_3$ brought about the formation of indole **2a** or **2b** in high yields in a short period (5 h), respectively (entries 4 and 6).

The substituent effect on the nitrogen atom or the aromatic ring of substrates was examined under conditions A ($[Rh(cod)_2]OTf$−dppp: 10 mol %), B ($RhH(CO)(Ph_3P)_3$: 10 mol %), or C ($RhH(CO)(Ph_3P)_3$: 4 mol %) as shown in Table 3. As well as the reaction of **1a**, 4 mol % of $RhH(CO)(Ph_3P)_3$ in refluxing HFIP (condition C) worked well for the reaction of *N*-Bn derivatives **1e** giving rise to the corresponding indole **2e**, quantitatively (entry 1). It is noteworthy that **1f** (R = H), which has been reported to afford quinoline **3f** as a main product under the thermal rearrangement,[19] preferentially yielded indole **2f**, albeit in fair yield (**2f**: 37%, **3f**: 9%, entry 2). The reaction of amide compounds (R = Ms, BOC) did not proceed under identical conditions, and the starting materials were recovered. Regarding the substituent on the aromatic ring, regardless of *o*-, *m*-, and *p*-MeO-substituted anilines (**4**, **6**, and **1e**), Rh catalysts under conditions A, B, or C could be applied to the reaction of these substrates, and the corresponding indole products were obtained in good yields, respectively (entries 1, 3, and 4). In the case of *meta*-substituted aniline **6**, the attack at the *para*-position to MeO group is preferable to that at the *ortho*-position, and the use of $RhH(CO)(Ph_3P)_3$ (condition B) led to the formation of the indole as a sole product in 87% yield (entry 4). Not only aniline and naphthylamine derivatives (**8a** and **13**) but also substrates **8b**−**d**, which have electron-withdrawing halogen or CF_3 substituents, brought about good results under conditions B or C (entries 5−8 and 10). $RhH(CO)(Ph_3P)_3$ (condition B) was also an effective catalyst in the reaction of difluorinated compounds **10**, and 4,6-difluoro-2,3-dimethylindole (**11**) was obtained in 68% yield without the detection of tetrahydoroquinoline compound **12** (entry 9).

TABLE 2. Rh(I)-Catalyzed Reaction of 1a,b,d[a]

entry	**1**	Rh(I)−ligand (mol %)	time (h)	**2**[b] (%)
1	**1d**	$[Rh(cod)_2]OTf$ (10)−dppp (15)	21	0
2	**1d**	$RhH(CO)(Ph_3P)_3$ (10)	3	65
3	**1a**	$[Rh(cod)_2]OTf$ (10)−dppp (15)	18	93
4	**1a**	$RhH(CO)(Ph_3P)_3$ (4)	5	99
5	**1b**	$[Rh(cod)_2]OTf$ (10)−dppp (15)	13	82
6	**1b**	$RhH(CO)(Ph_3P)_3$ (6)	5	86

[a] In HFIP at 80 °C with 4−10 mol % of Rh(I) catalyst. [b] Isolated yield.

One-Pot Synthesis of Indole Derivatives from Propargyl Bromide Compounds and Anilines. The efficiency of $RhH(CO)(Ph_3P)_3$ in HFIP encouraged us to examine the one-pot synthesis of indole compounds directly from propargyl halides and anilines (Table 4). In the beginning, we examined the reaction of 1-bromo-2-butyne (**15**) and aniline **16** under Rh(I)-catalyzed conditions. Thus, the reaction was carried out by (i) stirring a mixture of **15** (1 equiv) and **16** (3 equiv) at room temperature for 30 min, (ii) followed by the addition of the Rh(I)-catalyst, and the mixture was heated to reflux for 2−20 h (entries 1−3). To our delight, the target indole **2a** was obtained in 64−78% yields. In the sense of catalytic activity, $RhH(CO)(Ph_3P)_3$ catalyst showed high efficiency in the one-pot procedure. It should be mentioned that an equal ratio of **15** and **16** did not give satisfactory results (entries 4 and 5). The addition of an inorganic or organic base to a 1.3:1 mixture of **15** and **16** and subsequent treatment with the Rh catalyst significantly improved the yield of **2a** (entry 6). Among the bases examined, K_2CO_3 (3 equiv) exerted a preferable effect (**2a**: 70%).[26] As shown in Table 5, the one-pot procedure could be applied to the synthesis of indole derivatives from **19** and anilines **17**−**20** by the method D (**19**/aniline = 1:3) or by the method E (**19**/aniline = 1.3:1, K_2CO_3 as an additive).

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(24) The formation of **3c** or **12** may be due to the hydrogenation of 3,4-dihydroquinoline derivative formed through possible routes from **1c** or **10** as shown in Scheme 1. Thus, regardless of the presence of Rh(I) catalyst, the hydrogenation of 3,4-dihydro-1-methylquinoline proceeded in HFIP to give 1-methyl-tetrahydroquinoline and 3,4-dihydro-1-methylquinolin-2(1*H*)-one. Since the corresponding tetrahydroquinoline deuterated at the 3-position was obtained in both cases of $(CF_3)_2CHOD$ and $(CF_3)_2CDOD$, hydrogen at the 2-position of HFIP did not take part in the hydrogenation reaction. See: (a) Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* **2004**, *45*, 3215.

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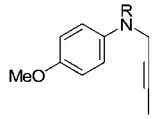
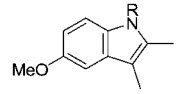
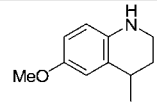
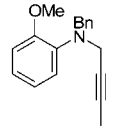
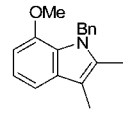
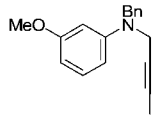
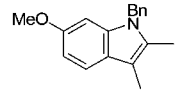
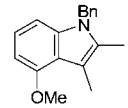
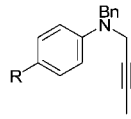
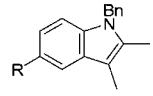
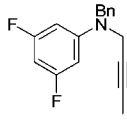
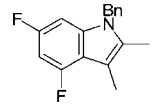
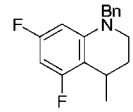
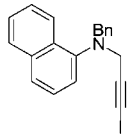
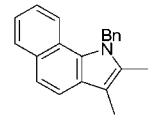
TABLE 3. Effect of Substituent on the Nitrogen Atom or the Aromatic Ring[a]

entry	substrate		product		condition /yield (%)[b]
1		**1e**: R=Bn			A / **2e** 87
					C / **2e** 99
2		**1f**: R=H			A[c] / **2f** 37 **3f** 17
			2e: R=Bn, **2f**: R=H	**3f**	B / **2f** 39 **3f** 9
3		**4**		**5**	A / 92
					B / 96
4		**6**			A / 69 (*p*:*o*=50:19)
					B / 87 (*p*:*o*=87:0)
			***p*-7**	***o*-7**	
5		**8a**: R=H		**9a**: R=H	A / 93 C / 98
6		**8b**: R=Br		**9b**: R=Br	A / 92 C / 90
7		**8c**: R=F		**9c**: R=F	A / 89 C / 91
8		**8d**: R=CF_3		**9d**: R=CF_3	A / 20 B / 85
9		**10**			A / **11** 25 **12** 25
					B / **11** 68 **12** 0
			11	**12**	
10		**13**		**14**	A / 89 C / 89

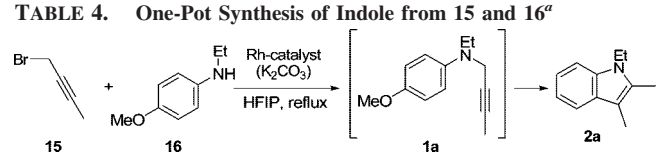
[a] Conditions A: $[Rh(cod)_2]OTf$ (10 mol %), dppp (10 mol %), refluxing HFIP for 2−5 h. Conditions B: $RhH(CO)(Ph_3P)_3$ (10 mol %)/refluxing HFIP for 3−9 h. Conditions C: $RhH(CO)(Ph_3P)_3$ (4 mol %)/refluxing HFIP for 1−6 h. [b] Isolated yield. [c] $[Rh(cod)_2]OTf$: 20 mol %, dppp: 20 mol %.

Mechanistic Considerations. Under $[Rh(cod)_2]OTf$−dppp-catalyzed conditions (conditions A′), **1g** was converted into conjugated diene **21** (Scheme 3). This result suggests that the primarily formed *o*-allenylaniline **22g** through amino-Claisen rearrangement of **1g** was isomerized to form a 1,3-dienyl chain in the *ortho*-position. A similar observation has been reported in Brønsted acid-catalyzed rearrangement of *N*-propargylanilines.[19c] On the other hand, the use of $RhH(CO)(Ph_3P)_3$−Cy_3P (conditions B′) led to the formation of indole **2g** (30%) in addition to **21** (40%). It should be mentioned that the prolonged reaction of **1g** did not increase the yield of **2g**. Furthermore, the reaction of **1h**, which has no migrating hydrogen in the assumed phenyl allene intermediate **22h**, gave indole **2h** under both Rh-catalyzed conditions A′ and B′. These results indicate that the amino-Claisen rearrangement takes part in the present formation of indole derivatives. Thus, the regiospecific intramolecular hydroamination of *o*-allenylaniline intermediate **22** gave indole **2**.

The cyclization of *o*-allenylaniline **24** (Scheme 4), which was independently generated in 84% yield by the treatment of **23**

(27) It is instructive to note that a small amount of **9a** has already been generated under MeMgBr/Cu(I) conditions.

TABLE 4. One-Pot Synthesis of Indole from 15 and 16[a]

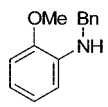
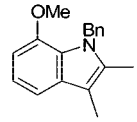
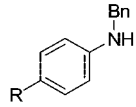
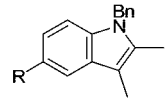
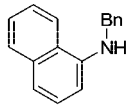
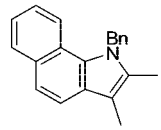


15 **16** **1a** **2a**

entry	**15**:**16**	conditions	base (equiv)	time (h)	**2a** (%)[b]
1	1:3	A′		20	64
2	1:3	B′		4	78
3	1:3	B		2	73
4	1.3:1	A′		5	(**1a** 72)[c]
5	1.3:1	B′		24	26[c]
6	1.3:1	B′	K_2CO_3 (3)	4	70[c]
7	1.3:1	B	K_2CO_3 (3)	2	37[c]

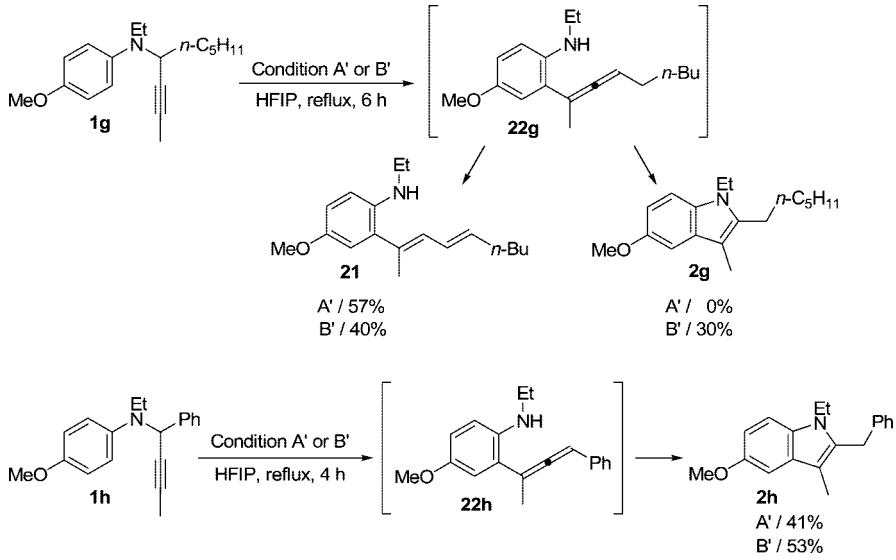
[a] Conditions A′: $[Rh(cod)_2]OTf$ (10 mol %), dppp (15 mol %). Conditions B′: $RhH(CO)(Ph_3P)_3$ (10 mol %), Cy_3P (20 mol %). Conditions B: $RhH(CO)(Ph_3P)_3$ (10 mol %). [b] Isolated yield based on **15**. [c] Isolated yield based on **16**.

TABLE 5. One-Pot Synthesis of Indole from 15 and Various Anilines 17−20[a]

entry	substrate		product		method / yield (%)[b]	
1		**17**		**5**	D / 73	E / 57[c]
2		**18**: R=OMe		**2e**: R=OMe	D / 62	E / 81[c]
3		**19a**: R=H		**9a**: R=H	D / 55	E / 89[c]
4		**19b**: R=Br		**9b**: R=Br	D / 38	E / 66[c]
5		**19c**: R=F		**9c**: R=F	D / 41	E / 70[c]
6		**20**		**14**	D / 72	E / 62[c]

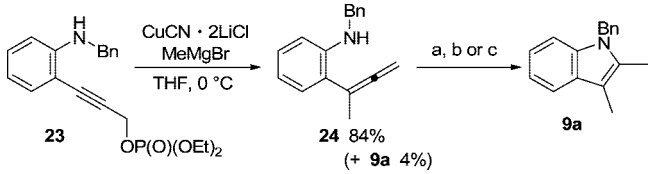
[a] In refluxing HFIP with 10 mol % of $RhH(CO)(Ph_3P)_3$ and 20 mol % of Cy_3P. Method D: **19**/aniline = 1:3. Method E: **19**/aniline = 1.3:1, K_2CO_3 as an additive. [b] Isolated yield based on **15**. [c] Isolated yield based on aniline **17−20**.

SCHEME 3[a]



[a] Conditions A′: $[Rh(cod)_2]OTf$ (10 mol %), dppp (15 mol %). Conditions B′: $RhH(CO)(Ph_3P)_3$ (10 mol %), Cy_3P (20 mol %).

SCHEME 4[a]



[a] Key: (a) $[Rh(cod)_2]OTf$ (10 mol %), dppp (10 mol %)/HFIP, reflux 3 h; 74%; (b) no catalyst/HFIP, reflux 3 h; 51%; (c) no catalyst/DCE, reflux 3 h; 53%.

with CuCN·2LiCl and MeMgBr at 0 °C for 15 min,[27] brought about the formation of **9a** in 74% yield (from **23**) under conditions similar to those for **8a** (condition A, entry 5, Table 3). Taking into consideration the formation of diene **21** and indoles (**2g**,**h**), we believe that the present process consists of (i) Rh-catalyzed amino-Claisen rearrangement of *N*-propargylaniline and (ii) the cyclization of the *o*-allenylaniline via path **a** as shown in Scheme 1. Since the thermal reaction of **24** gave **9a** in HFIP or DCE in moderate yield, the cyclization of *o*-allenylaniline intermediate would be induced not only by Rh-catalyst but also by thermal reaction.

Structure of Rh(I) Catalyst Derived from $RhH(CO)(Ph_3P)_3$ and HFIP. To gain a better understanding about the Rh(I)/HFIP catalytic system in the present reaction, we focused on the determination of the actual structure of the Rh catalyst in HFIP. It has been reported that $RhH(CO)(Ph_3P)_3$ reacts with Brønsted acids such as trifluoromethanesulfonic acid (TfOH) and carboxylic acid (RCOOH) to afford Rh complexes $[Rh(CO)(Ph_3P)_2]X$ (X = OTf and OCOR), respectively,[28] while the treatment of $RhH(Ph_3P)_4$ with a large excess of HFIP (pK_a = 9.3[29]) has been reported to afford $[Rh(Ph_3P)_3]OCH(CF_3)_2$ with

(28) (a) Jardine, F. H. *Polyhedron* **1982**, *1*, 569, and references cited therein. (b) Trzeciak, A. M.; Olejnik, Z.; Ziolkowski, J. J.; Lis, T. *Inorg. Chim. Acta* **2003**, *350*, 339.

(29) Donghi, D.; Beringhelli, T.; D'Alfonso, G.; Mondini, M. *Chem.—Eur. J.* **2006**, *12*, 1016.

SCHEME 5

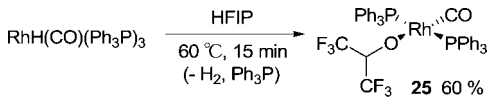
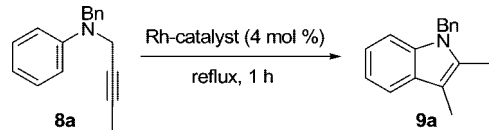


TABLE 6. Reactivities of [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ (25)



entry	Rh catalyst	solvent	**9a**[a] (%)
1	RhH(CO)(Ph$_3$P)$_3$	HFIP	97
2	RhH(CO)(Ph$_3$P)$_3$	HFIP−CHCl$_3$ (3:2)	97
3	**25**	HFIP	99
4	**25**	*i*PrOH	(**8a**, 67)
5	**25**	CHCl$_3$	(**8a**, 98)
6	**25**	benzene	(**8a**, 99)

[a] Yields were determined by ^{1}H NMR analysis.

evolution of a stoichiometric amount of hydrogen gas.[30] Thus, it is reasonable to postulate the in situ formation of [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ (**25**) from RhH(CO)(Ph$_3$P)$_3$ and HFIP (Scheme 5) under the present conditions. Treatment of RhH(CO)(Ph$_3$P)$_3$ with HFIP at 60 °C for 15 min and evaporation to dryness gave crystals, which were recrystallized from hexane−Et$_2$O to afford pale yellow crystals (Scheme 5). ^{1}H NMR analysis of the crystals in C$_6$D$_6$ indicated the −OCH(CF$_3$)$_2$ group and Ph$_3$P in a 1:2 ratio. In the ^{31}P NMR spectrum, only one doublet signal due to Rh−P coupling was observed. Thus, we assumed the structure of the crystals to be [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ (**25**). The structure of **25** was finally confirmed by single-crystal X-ray crystallographic analysis (see the Supporting Information).[31]

As shown in Table 6, the catalytic activity of the isolated Rh−alkoxide complex **25** was confirmed by quantitative formation of indole **9a** from *N*-propargylaniline **8a** within 1 h (entry 3). Thus, it is suggested that rhodium alkoxide **25** formed from RhH(CO)(Ph$_3$P)$_3$ and HFIP is the actual catalyst for the formation of indole compounds from *N*-propargylaniline derivatives. *On the other hand,* **25** in 2-propanol or CHCl$_3$ *did not catalyze the formation of indole* **9a** (entries 4 and 5), and decomposition of the alkoxide complex was observed. This solvent dependence on the catalytic activity of **25** is in good accord with the results obtained by RhH(CO)(Ph$_3$P)$_3$. By ^{31}P NMR studies of **25** in CDCl$_3$, signal ***a*** gradually changed into new signals ***b*** (δ: 29.6 ppm, J_{Rh-P} = 126 Hz) and ***c*** (δ: 32.2 ppm) on standing at ambient temperature for 80 h. It turned out that signals ***b*** and ***c*** corresponded to RhCl(CO)(Ph$_3$P)$_2$ and Ph$_3$P(O) by comparison with authentic samples, respectively (Figure 1).[32] In contrast to a solution of **25** in isopropanol or CHCl$_3$, **25** in benzene was stable at 60 °C for 2 h. The indole compound, however, was not obtained under conditions using

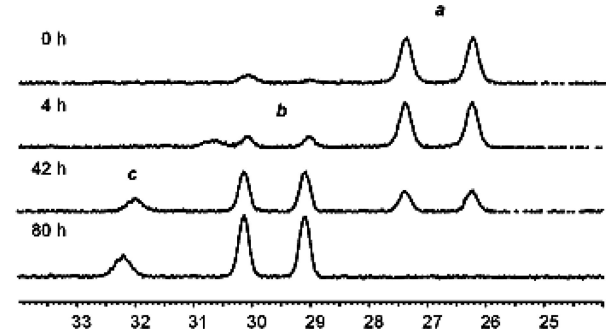


FIGURE 1. ^{31}P NMR spectroscopic analysis for the sequential change of [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ (a) into RhCl(CO)(Ph$_3$P)$_2$ (b) and Ph$_3$P(O) (c) in CDCl$_3$ at room temperature.

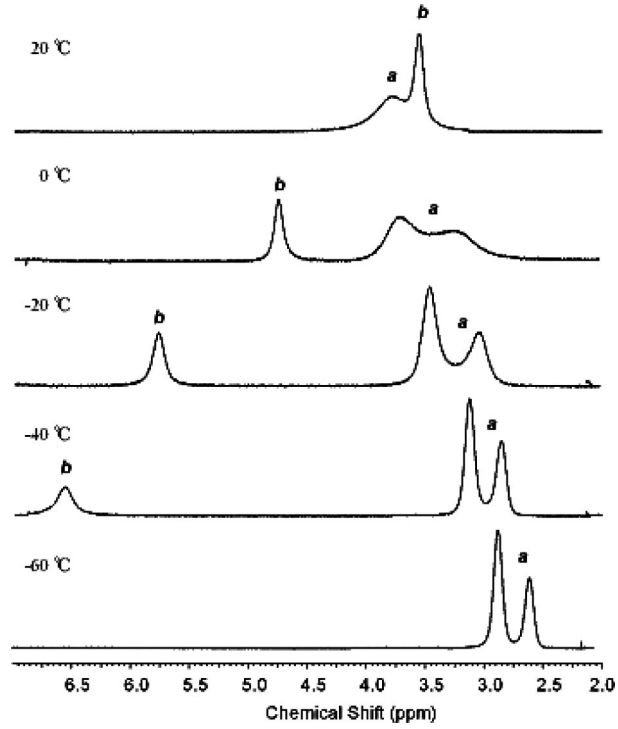


FIGURE 2. Variable-temperature ^{1}H NMR spectrum of [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ with 1 equiv of HFIP in CDCl$_3$.

the solution of **25** in benzene (entrys 6). Thus, the importance of HFIP is apparent not only for the generation of alkoxide **25** but also for the catalytic formation of indoles.

Behavior of [Rh(CO)(Ph$_3$P)$_2$]OCH(CF$_3$)$_2$ (25) with 1 equiv of HFIP. The Rh−O bond of (R$_3$P)$_3$RhOR′ (R = Me, Ph, R′ = aryl, fluorinated alkyl) has been known to be strongly polarized, having an excessively negative charge at oxygen and an excessively charge at the metal, and this is supported by the strong hydrogen-bonding (O−H−O) between the rhodium alkoxide complex with 1 equiv of alcohol (H−OR).[33,34] As part of our studies on the rhodium alkoxide complex, we carried out the NMR studies of alkoxide **25** with 1 equiv of HFIP (Figure 2). The addition of 1 equiv of HFIP to **25** in CDCl$_3$ at 20 °C showed broad signals ***a*** and ***b*** in the ^{1}H NMR spectrum. Since signal ***b*** disappeared in the case of DOCH(CF$_3$)$_2$ in place of HFIP, signal ***b*** was confirmed to be the OH hydrogen of HFIP. At low temperature (−60 °C), peak ***a*** split into two

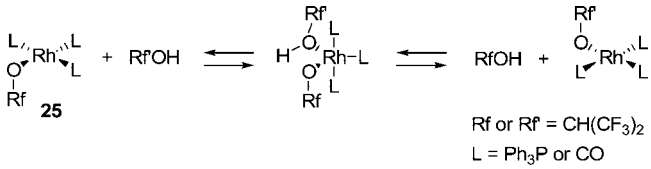
(30) Hayashi, Y.; Komiya, S.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1984**, 1363.

(31) CCDC 696799 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.

(32) RhCl(CO)(Ph$_3$P)$_2$ may be generated by (i) β-hydrogen elimination from Rh-alkoxide **25**, (ii) conversion of Rh−hydride complex into [Rh(μ-CO)(Ph$_3$P)$_2$]$_2$, and (iii) reaction [Rh(μ-CO)(Ph$_3$P)$_2$]$_2$ with CDCl$_3$. Each route i, ii, or iii has been previously reported; see: (a) Kung, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674. (b) Booth, B. L.; Casey, G. C.; Haszeldine, R. N. *J. Organomet. Chem. Soc.* **1982**, *224*, 197.

(33) Kegley, S. E.; Schaverien, C. J.; Freudenberger, J. H.; Bergman, R. G.; Nolan, S. P.; Hoff, C. D. *J. Am. Chem. Soc.* **1987**, *109*, 6563.

SCHEME 6



signals at 2.70 and 2.86 ppm, and signal ***a*** (3.54 ppm) at 20 °C could be observed as an average of both $-OC(CF_3)_2H$ of the fluorinated alkoxide ligand (3.36 ppm) of **25** and HFIP (4.37 ppm). Thus, Rh−alkoxide **25** with HFIP at 20 °C is in an equilibrium between the fluorinated alkoxide ligand of **25** and free HFIP. A similar observation has been reported in the exchange reaction of the Rh- or Pd-fluorinated alkoxide complex with fluorinated alcohol, and the exchange reaction was suggested to occur via a hydrogen bond formed between metal alkoxide and free alcohol.[33,34] Signal ***b*** at 20 °C was observed at higher field (3.54 ppm) than the reported chemical shift (9−14 ppm) of hydrogen-bonded species [Rh−O(R′)···H−OR′],[33] and FT-IR spectrum of **25** with 1 equiv HFIP did not show a significant absorption band corresponding to the hydrogen-bonding. From these results, we assume that the coordination of the oxygen atom of HFIP to Rh metal in **25** (O···Rh) rather than O···H−O-type hydrogen bonding between **25** and HFIP would take part in the exchange reaction of the Rh−alkoxide **25** with HFIP (Scheme 6). Such a coordination mode has been reported in cases of cationic Rh(I) complex and carbonyl Rh(I) complex with alcohol ligands.[35,36]

Activation of Substrate by the Rh(I)/HFIP Catalytic System. Since the reaction of **8a** by $RhH(CO)(Ph_3P)_3$ in HFIP−$CHCl_3$ (3:2) proceeded as well as the Rh-catalyzed conditions in HFIP (entries 1 and 2, Table 6), we carried out NMR studies using *N,N*-dibenzyl-2-butynylamine as a model compound with $RhH(CO)(Ph_3P)_3$ in HFIP−$CDCl_3$ (3:2) (Figure 3).[37] The addition of $RhH(CO)(Ph_3P)_3$ (20, 40, 60, 80, or 100 mol %) to the model compound resulted in significant shifts of alkyne signals (***a*** and ***b***) in the ^{13}C NMR spectrum. With use of

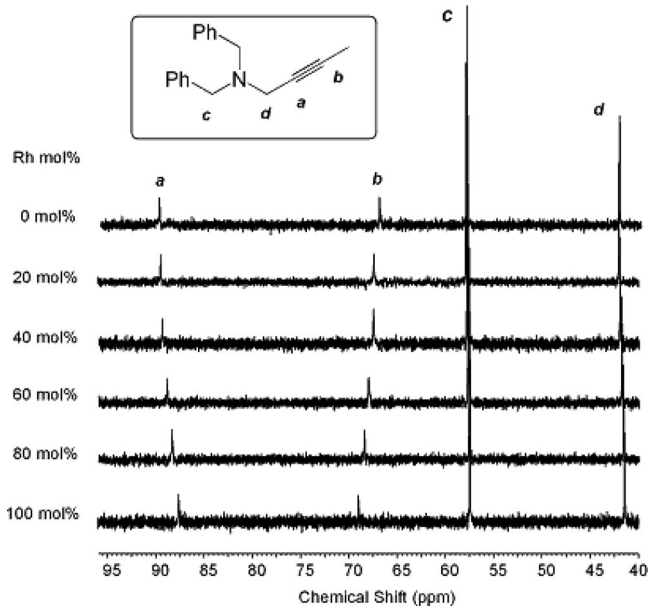


FIGURE 3. Difference ^{13}C NMR spectra of *N,N*-dibenzyl-2-butynylamine in the presence of various amounts of $RhH(CO)(Ph_3P)_3$ in HFIP−$CDCl_3$ (3:2) at room temperature. Peaks of HFIP and $CDCl_3$ were subtracted from these spectra.

100 mol % of $RhH(CO)(Ph_3P)_3$, the signal of ***a*** shifted to a higher field ($\Delta = -2.26$ ppm) and the signal of ***b*** shifted to a lower field ($\Delta = 1.65$ ppm). On the other hand, both chemical shifts at the benzyl (***c***) and propargyl (***d***) positions remained in smaller shifts (***b***: $\Delta = -0.79$ ppm, ***c***: $\Delta = -0.53$ ppm). These observations would indicate that the interaction of the alkyne unit with the present catalytic systems would be involved rather than that of the N···Rh interaction. This observation agrees with the activation mechanism reported in the Cu-promoted amino-Claisen rearrangement.[38]

Conclusions

For the purpose of extending the synthetic scope of indole compounds through the aromatic amino-Claisen rearrangement of *N*-propargylaniline derivatives, $RhH(CO)(Ph_3P)_3$ in HFIP was found to be very efficient. The Rh(I)/HFIP system could be applied to the one-pot synthesis of indoles from propargyl bromide derivatives and aniline compounds. The present formation of indoles was proven to consist of (i) Rh-catalyzed amino-Claisen rearrangement of *N*-propargylaniline and (ii) the cyclization of *o*-allenylaniline intermediate under the Rh(I)-catalyzed conditions and/or thermal conditions. We concluded from the NMR studies that the Rh catalyst would activate alkyne unit of *N*-propargylaniline at the amino-Claisen rearrangement step. Moreover, rhodium complex $[Rh(CO)(Ph_3P)_2]OCH(CF_3)_2$ formed from $RhH(CO)(Ph_3P)_3$ and HFIP was elucidated to be an active catalyst whose structure was confirmed by single-crystal X-ray crystallographic analysis. We believe that the present reaction provides an attractive procedure for the formation of 2,3-disubstituted indole compounds under mild conditions and a detailed mechanism. Further studies on the present system and synthetic applications to natural products are under way.

Experimental Section

General Information. For details, see the Supporting Information.

General Procedure 1 for the Aromatic Amino-Claisen Rearrangement of *N*-Propargylaniline Derivatives Catalyzed by $[Rh(cod)_2]OTf$−dppp (Condition A or A′). Under an argon atmosphere, to a solution of bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate (40 μmol) and 1,3-diphenylphosphinopropane (40−60 μmol) in HFIP (1 mL) was added *N*-propargylaniline (0.4 mmol) in HFIP (1.5 mL), and the mixture was refluxed until the consumption of the substrate by TLC analysis. The mixture was diluted with ether and filtered through a Celite pad. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave an indole compound.

(34) Pd-fluorinated alkoxide complex with 1 equiv of fluorinated alcohol led to the formation of analogue hydrogen-bonded species; see: (a) Kim, Y.-J.; Osakada, K.; Takenaka, A.; Yamamoto, A. *J. Am. Chem. Soc.* **1990**, *112*, 1096. (b) Kapteijn, G. M.; Spee, M. P. R.; Grove, D. M.; Kooijman, H.; Spek, A.; van Koten, G. *Organometallics* **1996**, *15*, 1405.

(35) (a) Heaton, B. T.; Jacob, C.; Sampanthar, J. T. *J. Chem. Soc., Dalton Trans.* **1998**, 1403. (b) Bassetti, M.; Capone, A.; Mastrofrancesco, L.; Salamone, M. *Organometallics* **2003**, *22*, 2535. (c) Tsuruta, H.; Imamoto, T.; Yamaguchi, K.; Gridnev, I. D. *Tetrahedron Lett.* **2005**, *46*, 2879. (d) Ezhova, M. B.; Patrick, B. O.; James, B. R. *Organometallics* **2005**, *24*, 3753.

(36) The proton of MeOH coordinated with the Rh-complex appeared at 3.74 ppm, which agreed with signal **b** of **25** and HFIP mixture. See ref 32b.

(37) It is impossible for us to use **8a** for NMR study since the rapid formation of **9a** disturbed the NMR study.

(38) See, refs 17a, 20, and 21.

(39) Swenton, J. S.; Shih, C.; Chen, C. P.; Chou, C. T. *J. Org. Chem.* **1990**, *55*, 2019.

General Procedure 2 for the Aromatic Amino-Claisen Rearrangement of *N*-Propargylaniline Derivatives Catalyzed by $RhH(CO)(Ph_3P)_3$ (Condition B or C). Under an argon atmosphere, to a solution of carbonylhydridetris(triphenylphosphine)rhodium(I) (16−40 μmol) in HFIP (1 mL) was added *N*-propargylaniline (0.4 mmol) in HFIP (1.5 mL) at an ambient temperature, and the mixture was refluxed until the consumption of the substrate by TLC analysis. The mixture was diluted with ether and filtered through a Celite pad. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave an indole compound.

General Procedure 3 for the Aromatic Amino-Claisen Rearrangement of *N*-Propargylaniline Derivatives Catalyzed by $RhH(CO)(Ph_3P)_3-Cy_3P$ (Condition B′). Under an argon atmosphere, to a solution of carbonylhydridetris(triphenylphosphine)rhodium(I) (16−40 μmol) and tricyclohexylphosphine (80 μmol) in HFIP (1 mL) for 10 min at ambient temperature was added *N*-propargylaniline (0.4 mmol) in HFIP (1.5 mL) at an ambient temperature, and the mixture was refluxed until the consumption of the substrate by TLC analysis. The mixture was diluted with ether and filtered through a Celite pad. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave an indole compound.

General Procedure 1 for the Formation of Indole Compounds from 1-Bromo-2-butyne (19) and Aniline Derivatives (Method D). Under an argon atmosphere, to a solution of 1-bromo-2-butyne (0.4 mmol) pretreated with aniline (1.2 mmol) in HFIP (2.5 mL) for 30 min at ambient temperature were added carbonylhydridetris(triphenylphosphine)rhodium(I) (40 μmol) and tricyclohexylphosphine (80 μmol) in turn, and the mixture was refluxed until consumption of the substrate by TLC analysis. The mixture was quenched with satd $NaHCO_3$, extracted with ether, and dried over $MgSO_4$. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave an indole compound.

General Procedure 2 for the Formation of Indole Compounds from 1-Bromo-2-butyne (19) and Aniline Derivatives (Method E). Under an argon atmosphere, to a mixture of aniline (0.4 mmol) and 1-bromo-2-butyn (0.52 mmol) pretreated with K_2CO_3 (1.2 mmol) in HFIP (2.5 mL) for 30 min at ambient temperature were added carbonylhydridetris(triphenylphosphine)rhodium(I) (40 μmol) and tricyclohexylphosphine (80 μmol) in turn, and the mixture was refluxed until the consumption of the substrate by TLC analysis. The mixture was quenched with satd $NaHCO_3$, extracted with ether, and dried over $MgSO_4$. After concentration of the filtrate to dryness, purification by silica gel column chromatography (hexane/AcOEt = 25:1) gave an indole compound.

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Supporting Information Available: Experimental procedures and physical data. Crystallographic data of **25** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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