Heterocycle Synthesis

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Synthesis of 2,3-Disubstituted Indoles by a Rhodium-Catalyzed Aromatic Amino-Claisen Rearrangement of *N*-Propargyl Anilines**

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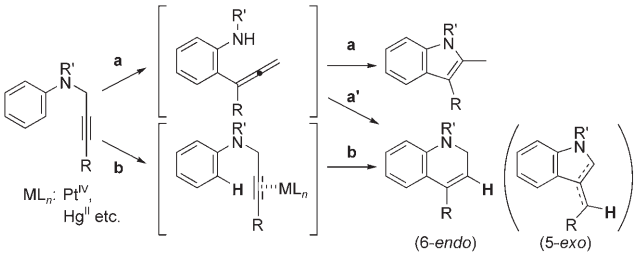
Transition-metal-catalyzed intramolecular reactions of heteroatom-tethered substrates are attractive methods for the synthesis of heterocyclic compounds.[1] In particular, regioselective annulations of *N*-propargyl aniline derivatives by intramolecular hydroarylation are diverse methods for preparing quinoline or indole ring systems (6-*endo* or 5-*exo*). Intramolecular hydroarylation is catalyzed by various metal-containing catalysts,[2] and the reactions of *N*-propargyl anilines give 1,2-dihydroquinolines in a 6-*endo* manner (path b, Scheme 1).[3] Amino-Claisen rearrangements[4,5] of



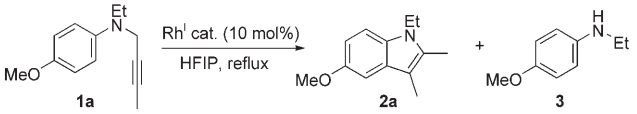
Scheme 1. Possible routes for the cyclization of *N*-propargyl anilines (see text for details).

N-propargyl aniline derivatives, which open up an alternative route to quinoline ring systems, proceed via *o*-allenylaniline under thermal[6] or copper-promoted condition[7,8] (path a′, Scheme 1). Although a few indoles have been synthesized by the thermal rearrangement of *N*-propargyl anilines, these procedures require extremely high temperatures (240–260 °C) and products were only obtained in low yields.[6a] Herein, we describe the mild formation of indoles by an amino-Claisen rearrangement of *N*-propargyl anilines catalyzed by cationic Rh^{I} complexes.[9]

Evaluation of the rhodium catalysts was conducted for the reaction with *N*-propargyl aniline (**1a**). It turns out that phosphine ligands are very important for the formation of **2a** (entries 1–5, Table 1); no cyclized product was obtained in the absence of such a ligand (entry 6, Table 1). Thus, in the presence of 10 mol% [Rh(cod)$_2$]OTf (cod = 1,5-cyclooctadiene; Tf = trifluoromethanesulfonyl) and 10 mol% 1,3-bis(diphenylphosphanyl)propane (dppp) in hexafluoro-2-propanol (HFIP), **1a** was consumed within five hours at reflux (80 °C) to give indole **2a** in 90% yield. Although the use of 15 mol% dppp required a prolonged reaction time, the yield of **2a** increased up to 97% (entry 2, Table 1). Other cationic Rh^{I} complexes, such as [Rh(cod)$_2$]BF$_4$ and [{Rh(cod)Cl}$_2$]/AgSbF$_6$,[10] and the use of trifluoroethanol as solvent were not effective (entries 7–9, Table 1). The reaction in other solvents (2-propanol, 1,2-dichloroethane, toluene, THF, acetone, and acetonitrile) gave no cyclized product. Although Lewis acids (AlCl$_3$, ZnCl$_2$, and BF$_3$·OEt$_2$)[11] and CuCl[7] have often been employed in the aromatic amino-Claisen rearrangement, these reagents did not promote the formation of the indole product here. The Brønsted acid that might be generated during the reaction does not take part in the reaction (entry 10, Table 1), and the absence of the catalyst leads to the complete recovery of **1a** (entry 11, Table 1).

The efficiency of [Rh(cod)$_2$]OTf encouraged us to examine the effect of the alkyne substituent of the substrate. It turned out that the present catalytic system can also be applied to the reaction of compounds containing an internal alkyne (Table 2). Thus, the *n*-pentyl compound **1b** gives rise

Table 1: Rh^{I} catalysts investigated for the cyclization of **1a**.



Entry	Catalyst	Ligand[a]	*t* [h]	Yield [%][b]		
				2a	**3**	**1a**
1	[Rh(cod)$_2$]OTf	dppp (10)	5	90	–	–
2	[Rh(cod)$_2$]OTf	dppp (15)	18	97	–	–
3	[Rh(cod)$_2$]OTf	dppe (10)	5	32	–	65
4	[Rh(cod)$_2$]OTf	dppb (10)	5	25	6	58
5	[Rh(cod)$_2$]OTf	PCy$_3$[c] (20)	5	60	10	–
6	[Rh(cod)$_2$]OTf	–	5	–	12	64
7	[Rh(cod)$_2$]BF$_4$	dppp (10)	5	8	-	77
8	[{Rh(cod)Cl}$_2$]/AgSbF$_6$[d]	dppp (10)	1	12	34	8
9[e]	[Rh(cod)$_2$]OTf	dppp (10)	5	26	19	–
10	HOTf[f]	–	5	–	–	99
11[g]	–	–	5	–	–	94

[a] Amount used [mol%] given in parentheses. [b] The yield was determined by ^{1}H NMR analysis using toluene as internal standard. [c] Cy = cyclohexyl. [d] 5 mol% [{Rh(cod)Cl}$_2$] and 13 mol% AgSbF$_6$. [e] The reaction mixture was refluxed in trifluoroethanol. [f] 20 mol% CF$_3$SO$_3$H. [g] The reaction mixture was refluxed in HFIP in the absence of Rh^{I} and ligand.

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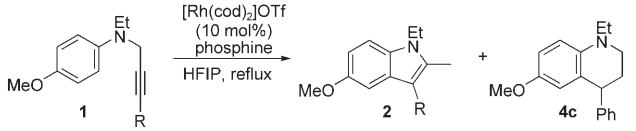
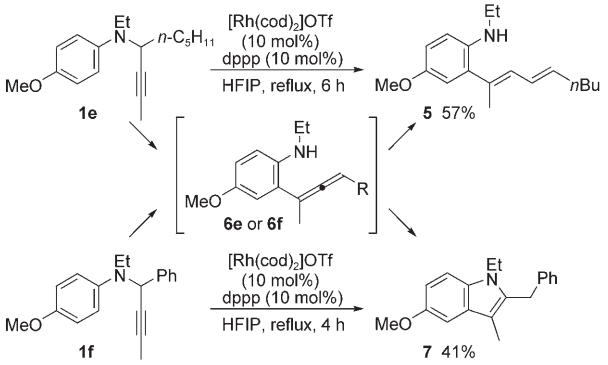
Table 2: Rh^{I}-catalyzed reaction of various alkynes.



Entry	1	R	Phosphane[a]	t [h]	Yield [%][b] 2	4
1	**1a**	Me	dppp (10)	5	87	–
2	**1a**	Me	dppp (15)	18	93	–
3	**1b**	n-C_5H_{11}	dppp (15)	13	82	–
4	**1c**	Ph	dppp (15)	18	5[c]	3
5	**1c**	Ph	dppe (15)	18	34[d]	26
6	**1d**	H	dppp (15)	21	0[e]	–

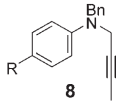
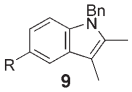
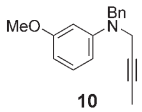
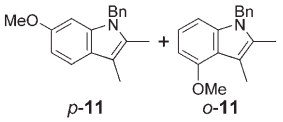
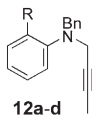
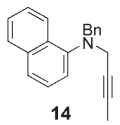
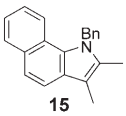
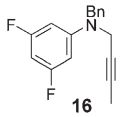
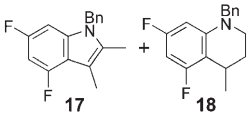
[a] Amount used [mol%] given in parentheses. [b] Yield of isolated product. [c] Yield of **3**: 22%. [d] Yield of **3**: 9%. [e] Yield of **3**: 19%; **1d** recovered: 40%.

to the corresponding indole **2b** in 82% yield in refluxing HFIP in the presence of $[Rh(cod)_2]OTf$ and dppp (entry 3, Table 2). In the case of phenyl derivative **1c**, 1,2-bis(diphenylphosphanyl)ethane (dppe) was superior to dppp, with indole **3c** being obtained in 34% yield along with tetrahydroquinoline **4c** in 26% yield (entry 5, Table 2).[12] It is noteworthy that aniline **1e** leads to the formation of conjugated diene **5** (Scheme 2). This result suggests that



Scheme 2. Formation of a diene or an indole.

Table 3: Rh^{I}-catalyzed reaction of various arenes.[a]

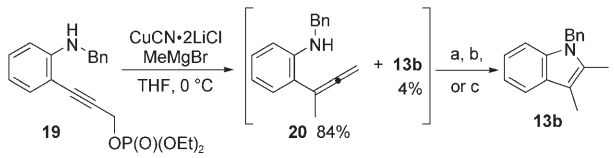
Entry	Substrate	Product	Yield [%][b]
1	 **8**	 **9**	92
2	 **10**	 *p*-**11** + *o*-**11**	50 (*p*-**11**) + 19 (*o*-**11**)
3[c]	**10**	*p*-**11** + *o*-**11**	55 (*p*-**11**) + 26 (*o*-**11**)
4	 **12a–d**	**12a** (R=OMe)	87 (**13a**)
5		**12b** (R=H)	93 (**13b**)
6		**12c** (R=Br)	92 (**13c**)
7		**12d** (R=F)	89 (**13d**)
8	 **14**	 **15**	89
9	 **16**	 **17** + **18**	25 (**17**) + 25 (**18**)

[a] All reactions were carried out in the presence of 10 mol% $[Rh(cod)_2]OTf$ and 10 mol% dppp in refluxing HFIP for 2–5 h. [b] Yield of isolated product. [c] 15 mol% dppp. [d] Yield of *N*-benzyl-3,5-difluoroaniline: 26%.

the initially formed *o*-allenylaniline **6e** isomerizes to form a 1,3-dienyl side chain.[13] Support for this assumption comes from the reaction of **1f**, which has no migrating hydrogen in the assumed phenyl allene intermediate **6f** and therefore gives indole **7** under the present conditions (Scheme 2).[14]

The effect of the substituent on the arene ring is shown in Table 3. Regardless of whether an *o*-, *m*-, or *p*-OMe-substituted aniline derivative (**12a**, **10**, and **8**, respectively) is used, the reaction in the presence of $[Rh(cod)_2]OTf$ and dppp gives the corresponding indole products in good yields (entries 1–4, Table 3). In the case of *meta*-substituted aniline **10**, attack at the position *para* to the OMe group is preferable to that at the *ortho* position (entries 2 and 3, Table 3). Substrates **12c** and **12d**, both of which have electron-withdrawing halogen substituents, also gave good results (entries 6 and 7, Table 3). The reaction of difluorinated compounds **16**, however, afforded a 1:1 mixture of indole **17** and the tetrahydroquinoline compound **18** (entry 9).[12]

To gain a better understanding of how the aromatic amino-Claisen rearrangement occurs under these conditions, we attempted the cyclization of *o*-allenylaniline **20** (Scheme 3), which was considered to be an intermediate in the reaction with **12b**. Thus, **20** was generated independently by treatment of **19** with CuCN·2 LiCl and MeMgBr at 0 °C for 15 min (yield of **20**: 84%; **13b**: 4%). Since **20** is sensitive to air and proved to be difficult to separate from **13b**, it was used as a mixture with **13b** after being passed through a short chromatography column packed with silica gel. Under similar conditions to those used previously for the reaction with **12b** (entry 5, Table 3), the cyclization of **20** gave **13b** in 74% yield (with respect to **19**). Thus, taking into consideration the formation of diene **5** and indole **7** from **1e** and **1f**,



Scheme 3. Cyclization of *o*-allenylaniline. a) $[Rh(cod)_2]OTf$ (10 mol%), dppp (10 mol%), HFIP, reflux, 3 h, 74% yield. b) No catalyst, HFIP, reflux, 3 h, 51% yield. c) No catalyst, 1,2-dichloroethane, reflux, 3 h, 53% yield.

respectively, we believe that the present process would consist of an initial Rh-catalyzed amino-Claisen rearrangement of *N*-propargyl aniline[15] and the subsequent cyclization of *o*-allenylaniline by path a in Scheme 1. Since heating **20** in HFIP or 1,2-dichloroethane gave **13b** in moderate yield, cyclization of the *o*-allenylaniline intermediate is induced by both the Rh catalyst and by heating.

In summary, we have reported the facile formation of indoles by an aromatic amino-Claisen rearrangement of *N*-propargyl aniline derivatives in the presence of a $[Rh(cod)_2]OTf$/dppp catalyst in HFIP. We believe that these findings raise new possibilities for the formation of 2,3-disubstituted indoles under mild conditions. Investigation of the synthetic applications and detailed mechanistic studies of this reaction are underway.

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[12] Although the formation mechanism of **4c** and **18** remains unclear at present, it may involve the hydrogenation of a 1,2-dihydroquinoline derivative formed from **1c** or **16** according to Scheme 1. However, the corresponding quinoline compounds, which are considered to be oxidized products, were not detected. See also: T. P. Forrest, G. A. Dauphinee, S. A. Deraniyagala, *Can. J. Chem.* **1985**, *63*, 412–417 and references [4a] and [16].

[13] A similar observation has been reported in the Brønsted acid-catalyzed rearrangement of *N*-propargyl anilines. See reference [5c].

[14] The authors acknowledge the referees for their suggestion to examine the reaction of **1f**.

[15] Although it has been reported that the activation mechanism in a transition-metal-promoted amino-Claisen rearrangement probably involves activation of the alkyne unit, as in metal-catalyzed hydroarylation, the amine unit can also be activated by the metal. See references [4a], [7], and [8], and Y. Yamamoto, J. Seta, H. Murooka, X.-H. Han, *Inorg. Chem. Commun.* **2003**, *6*, 202–205.

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