Vinylidenes

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Rhodium-Catalyzed Cycloisomerization: Formation of Indoles, Benzofurans, and Enol Lactones**

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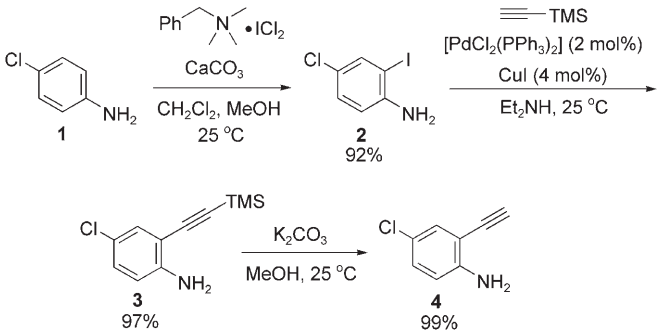
The development of atom-economical reactions is one of the primary challenges for synthetic chemists.[1] Accordingly, our research group has developed addition and isomerization reactions in which all of the reactant atoms are expressed in the product.[2] The involvement of vinylidenes in catalytic cycles represents a relatively new and attractive approach towards such reactions.[3] The precursor alkynes are readily available, and the unique reactivity of these intermediates opens the door to the discovery and invention of new reactions. Herein we present our results on one such reaction: the rhodium-catalyzed cycloisomerization of alkynyl anilines, phenols, and carboxylic acids to give indoles, benzofurans, and enol lactones, respectively.

The first use of vinylidenes to form C–C bonds in a catalytic reaction was reported by our research group some years ago.[4] Subsequently, we extended the use of vinylidene intermediates to the formation of C–O bonds in the cycloisomerization of homopropargyl and bis-homopropargyl alcohols to give dihydrofurans and dihydropyrans, respectively.[5] Earlier studies by MacDonald et al. investigated similar transformations.[6] We then hypothesized that nitrogen and less-nucleophilic oxygen (for example, phenol and carboxylic acid) substrates could be used. Herein we report the results of our studies.

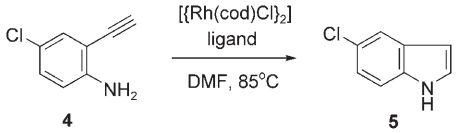
The synthesis of the substrates for cycloisomerization was straightforward (Scheme 1). For example, 4-chloroaniline (**1**) was iodinated in high yield,[7] and a Sonogashira cross-coupling of **2** with trimethylsilylacetylene, followed by protodesilylation, provided the desired substrate **4** in an overall yield of 88% for the three steps.

The rhodium-catalyzed cycloisomerization reaction was optimized by systematically changing the reaction parameters (Table 1). The initial conditions, derived from the cycloisomerization of homopropargyl and bis-homopropargyl alcohols,[5b] provided the product indole **5** in good yield (entry 1, Table 1). Lowering the ligand to metal ratio (entries 2 and 3), as well as the overall loading (entry 4), provided the product in similar yields. Control experiments showed that both ligand and metal were essential (entries 5 and 6). The use of a more electron rich ligand was detrimental to the reaction (entry 7), while use of the less expensive triphenylphosphine gave a similar yield of product (entry 8). Lowering the metal and ligand loadings further did not diminish the yield (entries 9 and 10); however, an increase in the concentration proved detrimental (entries 11 and 12), and



Scheme 1. Representative synthesis of the substrates. TMS = trimethylsilyl.

Table 1: Optimization of the internal cycloisomerization of alkynyl aniline **4**.



Entry	Conc. of **4** [M]	[{Rh(cod)Cl}$_2$] [mol%]	Ligand	[mol%]	*t* [min]	Yield [%]
1	0.20	5.0	(4-FC$_6$H$_4$)$_3$P	60	120	84
2	0.20	5.0	(4-FC$_6$H$_4$)$_3$P	45	120	89
3	0.20	5.0	(4-FC$_6$H$_4$)$_3$P	30	120	87
4	0.20	2.5	(4-FC$_6$H$_4$)$_3$P	15	120	89
5	0.20	2.5	–	–	120	11
6	0.20	–	(4-FC$_6$H$_4$)$_3$P	15	120	n.r.
7	0.20	2.5	(4-MeOC$_6$H$_4$)$_3$P	15	120	53
8	0.20	2.5	Ph$_3$P	15	120	80
9	0.20	2.5	Ph$_3$P	10	120	80
10	0.20	1.0	Ph$_3$P	4	120	77
11	0.50	1.0	Ph$_3$P	4	120	69
12	1.0	1.0	Ph$_3$P	4	120	59
13	0.20	1.0	Ph$_3$P	4	30	49[a]
14	0.20	1.0	Ph$_3$P	4	60	61[b]

[a] 29% of substrate **4** was recovered. [b] 16% of substrate **4** was recovered. DMF = *N*,*N*-dimethylformamide, cod = cycloocta-l,5-diene, n.r. = no reaction.

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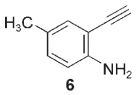
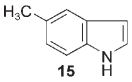
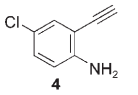
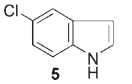
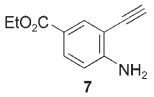
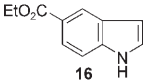
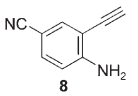
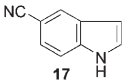
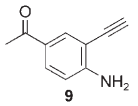
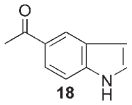
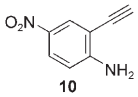
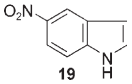
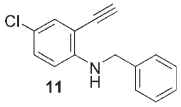
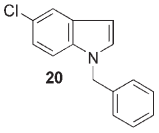
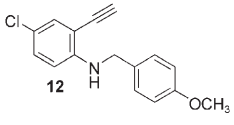
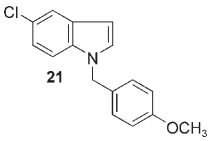
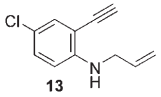
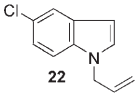
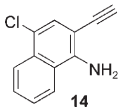
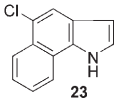
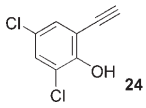
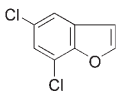
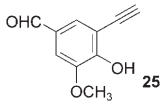
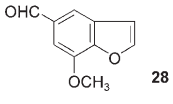
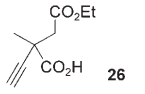
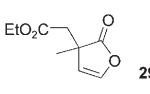
Table 2: Cycloisomerization of alkynyl anilines into indoles.

Entry	Substrate	Product	Conditions A yield [%][a]	B yield [%][b]	C yield [%][c]
1	 6	 15	52[d]	79	72
2	 4	 5	77	84	88
3	 7	 16	84	98	92
4	 8	 17	90	98	89
5	 9	 18	77	93	85
6	 10	 19	81	79	80
7	 11	 20	61	88	73
8	 12	 21	52[e]	94	74
9	 13	 22	decomp	decomp	decomp
10	 14	 23	59	83	73

[a] 1% [{Rh(cod)Cl}$_2$], 4% Ph_3P, DMF, 85°C, 2 h. [b] 5% [{Rh(cod)Cl}$_2$], 60% (4-FC_6H_4)$_3$P, DMF, 85°C, 2 h. [c] 1% [{Rh(cod)Cl}$_2$], 4% (4-FC_6H_4)$_3$P, DMF, 85°C, 2 h. [d] 15% of the substrate was recovered. [e] 5% of the substrate was recovered. decomp = decomposed.

Table 3: Cycloisomerization of alkynyl phenols and carboxylic acids.

Entry	Substrate	Product	Conditions A yield [%][a]	B yield [%][b]	C yield [%][c]
1	 24	 27	n.r.[d]	77	12
2	 25	 28	n.r.[d]	75	52
3	 26	 29	n.r.[d]	81	n.r.[d]

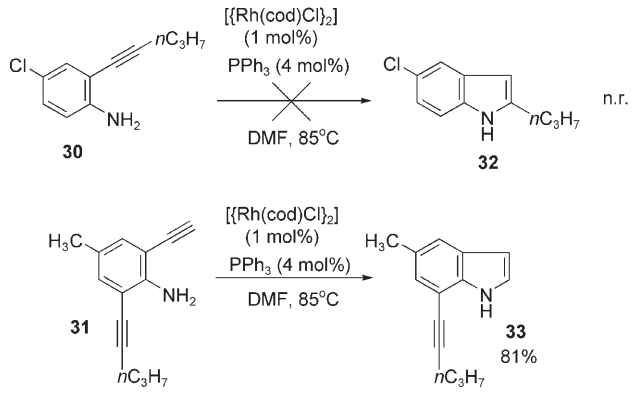
[a] 1% [{Rh(cod)Cl}$_2$], 4% Ph_3P, DMF, 85°C, 2 h. [b] 5% [{Rh(cod)Cl}$_2$], 60% (4-FC_6H_4)$_3$P, DMF, 85°C, 2 h. [c] 1% [{Rh(cod)Cl}$_2$], 4% (4-FC_6H_4)$_3$P, DMF, 85°C, 2 h. [d] Partial decomposition.

shortening the reaction time led to incomplete conversion (entries 13 and 14). Thus the initial optimal conditions for indole formation were seen to be those used in entry 10, because the least expensive phosphine was used.

A variety of alkynyl anilines were converted into the corresponding indole products in synthetically useful yields using the initial optimized conditions (column A, Table 2). The chemoselectivity of the process was excellent, with a wide range of functional groups (for example, chloro, ester, nitrile, ketone, nitro, and ether) being compatible. The higher yields obtained with tris(4-fluorophenyl)phosphine (Table 1) led us to return to this ligand, and as a result, the yields increased invariably (column B, Table 2). When the catalyst loading was lowered to that of the conditions in column A, but with this ligand, we achieved results that were comparable to those with the higher catalyst loading (column C, Table 2). Benzyl- and paramethoxybenzyl-protected anilines could serve as substrates (entries 7 and 8), although the use of a more strongly electron-withdrawing ligand was required to provide similar yields as those achieved with the parent system (entry 2). The failure of an allyl-protected aniline may be explained by the proclivity of such groups to undergo isomerization to the enamine,[8] which then could lead to various undesired products.

As we had established that anilines were viable nucleophiles, we reasoned that the formation of benzofurans and enol lactones from alkynyl phenols and carboxylic acids, respectively, would be feasible. As shown in Table 3, this proved to be the case. Use of triphenylphosphine as a ligand in this reaction failed; however, higher loadings of the metal and use of the more strongly electron-withdrawing ligand were sufficient to promote the reaction. This may be because of the reduced nucleophilicity of the oxygen atom compared to nitrogen atom.

Substrates **30** and **31** were subjected to the reaction conditions to probe the reaction mechanism (Scheme 2). We reasoned that if a vinylidene mechanism were operational, then only terminal alkynes could serve as substrates for indole formation. Thus, substrate **30** bearing an internal alkyne should not react, whereas **31** should react exclusively through the terminal alkyne to give indole **33**. In the event, these predictions were borne out experimentally.

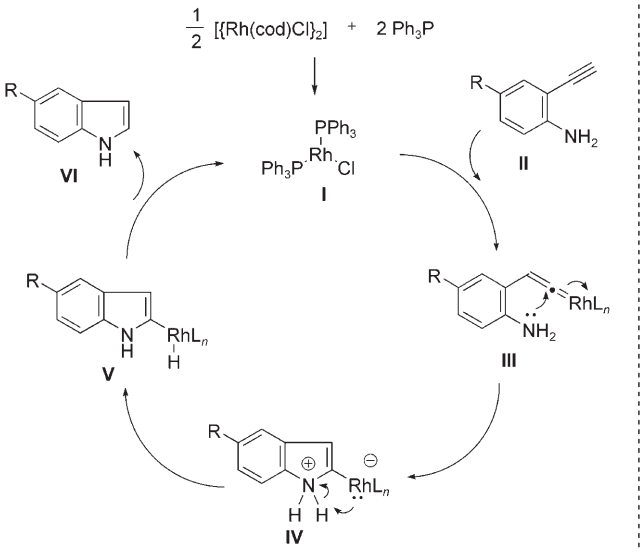


Scheme 2. Studies into the mechanism.

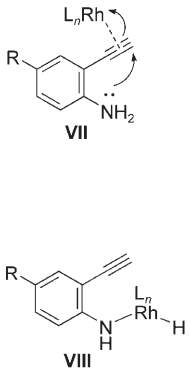
These results may be interpreted according to the proposed mechanism shown in Scheme 3. The dimeric rhodium precursor [{Rh(cod)Cl}$_2$] may react with the phosphine ligand to form the coordinatively unsaturated monomeric species **I**.[9] Coordination of the alkyne substrate **II**, followed by rearrangement, leads to vinylidene intermediate **III**.[10] This process has good precedent for terminal alkynes but is unknown for internal alkynes, and is also consistent with the results in Scheme 2. This key intermediate may undergo nucleophilic capture by the pendant amine to give **IV**. Finally, proton transfer from the nitrogen atom to the rhodium center, followed by reductive elimination, could provide indole product **VI**, and regenerate the active catalyst. The fact that electron-withdrawing phosphine ligands perform best in the reactions suggest that either nucleophilic attack or reductive elimination may be the rate-determining steps of the catalytic cycle, as these processes would be facilitated by such ligands.

One alternative mechanism involves coordination of the catalyst to the alkyne to induce nucleophilic attack (**VII**, Scheme 3), followed by proton transfer from the nitrogen atom to the rhodium center, and subsequent reductive elimination. Complexes of palladium(II),[11] gold(III),[11a,12] and indium(III)[13] catalyze the reaction of internal alkynes and free amines in this manner, while complexes of palladium(II),[11a,14] gold(III),[11a] and copper(II)[15] catalyze the reaction of internal alkynes and amines that contain electron-withdrawing groups. There are limited examples that involve terminal alkynes and free amines.[12,15a,b] This mechanism is consistent with the observation that anilines were superior to phenols in the reaction, as the former are better nucleophiles. Another possible mechanism involves insertion of the metal into the N–H bond (**VIII**, Scheme 3), followed by coordination/insertion into the pendant alkyne and reductive elimination. Ruthenium catalyzes hydroamination reactions of alkynyl amines in this manner.[16] The fact that anilines reacted more readily than phenols, despite the similar strength of N–H and O–H bonds,[17] is inconsistent with a mechanism involving oxidative addition of the metal into these bonds. Neither of these alternative mechanisms explains the lack of reactivity of internal alkynes.

In summary, a chemoselective cycloisomerization reaction has been reported for the formation of indoles, benzofurans, and enol lactones. Substrates are readily available and functional-group tolerance is high for this atom-economical reaction. In the case of alkynyl aniline substrates, low loadings of metal and triphenylphosphine make for a very practical method of forming indoles.[18] The synthesis of parent indoles from the cyclization of unprotected anilines and terminal alkynes distinguishes this process from other metal-catalyzed cyclization methods. Collectively, these reactions further increase the scope of known nucleophiles that react with metal vinylidene intermediates in catalytic processes.[5,6,19]



Scheme 3. Proposed mechanism of the cycloisomerization.



Experimental Section

Typical experimental procedure (Method A): *N*,*N*-dimethylformamide (2.50 mL) was degassed (Ar balloon) for 20 min and then added through a cannula to a mixture of **4** (76 mg, 0.500 mmol), [{Rh(cod)Cl}$_2$] (2.5 mg, 0.005 mmol), and triphenylphosphine (5.2 mg, 0.020 mmol). The solution was stirred for 2 h at 85 °C under Ar. The reaction mixture was then cooled to 25 °C and extracted from saturated aq $NaHCO_3$ (50 mL) with diethyl ether (3 × 10 mL). The combined organic extracts were washed with saturated aq $NaHCO_3$ (10 mL), dried with anhydrous $MgSO_4$, filtered, and evaporated in vacuo. Purification by flash column chromatography through silica gel (petroleum ether/diethyl ether/triethylamine 90:10:3→50:50:3→25:75:3) gave the product **5** (58 mg, 77 %) as pale tan crystals; mp: 71.5–72.0 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3476, 2252, 1721, 1569, 1458, 1447, 1413, 1338, 1315, 1265, 1242, 1196, 1094, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):

$\delta = 8.06$ (br s, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 8.6$ Hz, 1H), 7.17 (t, $J = 2.9$ Hz, 1H), 7.13 (dd, $J = 2.0$, 8.6 Hz, 1H), 6.48–6.47 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 134.0, 128.8, 125.5, 125.3, 122.2, 120.0, 112.0, 102.3 ppm; HRMS (EI) *m/z* calcd for C_8H_6ClN [M^+]: 151.0189, found: 151.0183.

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