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Cobalt-Catalyzed Intramolecular Olefin Hydroarylation Leading to Dihydropyrroloindoles and Tetrahydropyridoindoles**

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Fused tricyclic indoles with dihydropyrroloindole and tetrahydropyridoindole core skeletons are present in pharmaceutically relevant small molecules, such as L-888,607, Ro 32-0432, and MK-7246 (Figure 1).[1] The latter skeleton is also relevant to indole alkaloids, such as strychnine, brucine, and vincamine. Consequently, efficient and selective reactions allowing construction of such fused cyclic systems could be useful synthetic methods. As a notable example, the group of Bergman and Ellman achieved the synthesis of biologically active dihydropyrroloindole derivatives, including a chiral non-racemic derivative, through rhodium-catalyzed, aldimine-directed C–H activation/intramolecular hydroarylation of *N*-allylindoles (Scheme 1a).[2] Along with this particular example, they have extensively developed rhodium-catalyzed C–H activation reactions of aromatic, heteroaromatic, and olefinic substrates bearing alkene tethers[3–6] and demonstrated their utility in target-oriented synthesis of carbo- and heterocycles,[7] while the Murai group earlier reported seminal studies on rhodium- and ruthenium-catalyzed intramolecular cyclization of 1,5- and 1,6-diene derivatives through chelation-assisted olefinic C–H activation.[8]

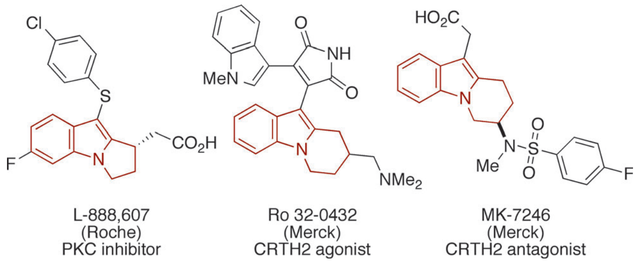
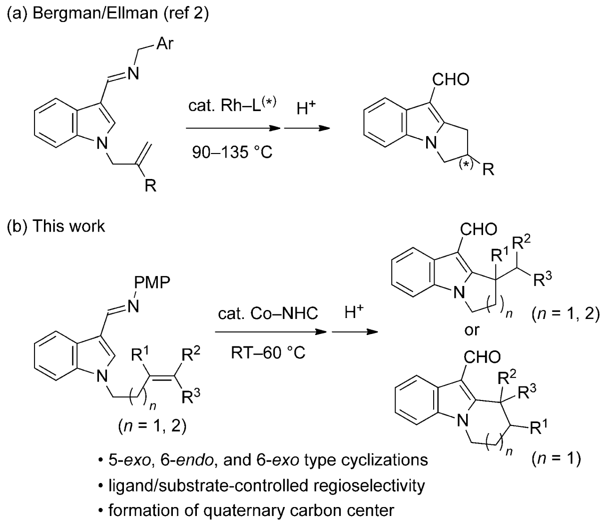


Figure 1. Biologically active compounds containing dihydropyrroloindole or tetrahydropyridoindole moieties.



Scheme 1. Intramolecular hydroarylation leading to dihydropyrroloindole and tetrahydropyridoindole.

As shown in Scheme 1a, the rhodium catalysis works most efficiently for 5-*endo*-type cyclization with substrates bearing allylic tethers. On the other hand, homoallylic tethers pose a regioselectivity issue because of the two intrinsically feasible modes of cyclization (that is, 5-*exo* vs. 6-*endo*) as well as facile olefin isomerization prior to hydroarylation, and have not been employed on the indole platform. Alkene tethers that are longer than a homoallyl group have not been used on any aromatic or heteroaromatic platforms.[9] We report herein on our development of cobalt-N-heterocyclic carbene (NHC)-catalyzed intramolecular olefin hydroarylation of indole substrates bearing homoallyl or bishomoallyl tethers. Complementing the scope of the rhodium catalysis, the present catalytic systems allow 5-*exo*-, 6-*endo*-, and 6-*exo*-type cyclization to afford a series of dihydropyrroloindole and tetrahydropyridoindole derivatives under mild reaction conditions. The present study has led to a couple of notable findings, namely, 1) regiodivergent formation of five- and six-membered rings by the choice of the NHC ligand and 2) formation of a quaternary carbon center, which have been hitherto unknown for olefin hydroarylation through chelation-assisted C–H activation.

Our study began with intramolecular cyclization of indole **1a** bearing an aldimine moiety on the C3 position and a homoallyl group on the N atom (Table 1). In light of our recent study on cobalt-catalyzed, chelation-assisted intermolecular olefin hydroarylation,[10,11] screening of reaction conditions was performed using 10 mol% of $CoBr_2$, 10–20 mol%

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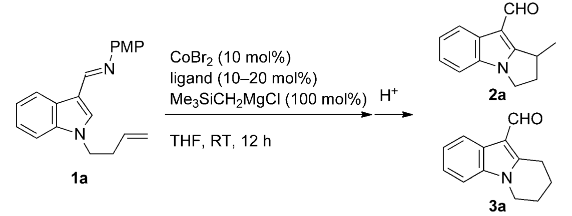
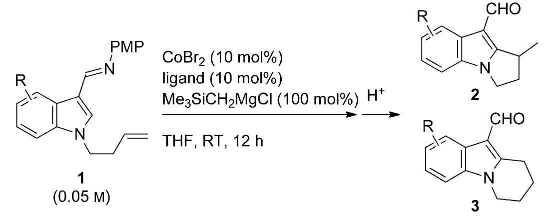
Table 1: Screening of reaction conditions.[a]



Entry	Conc. [M]	Ligand [mol %]	Yield [%] (**2a**:**3a**)[b]
1	0.2	SIMes·HCl (10)	39 (4:1)
2	0.2	PPh$_3$ (20)	9 (1:1)
3	0.2	dppe (10)	0
4	0.2	DPEphos (10)	6 (1:5)
5	0.2	phen (10)	4 (< 1:20)
6	0.05	SIMes·HCl (10)	84 (8:1)[c]
7	0.05	IMes·HCl (10)	45 (2:1)
8	0.05	SIPr·HCl (10)	46 (1:5)
9	0.05	IPr·HCl (10)	63 (1:5)[c]
10[d]	0.05	[RhCl(PPh$_3$)$_3$] (10)	37 (1:2)
11[e]	0.05	[{RhCl(coe)$_2$}$_2$]/PCy$_3$ (10)	8 (1:2)

[a] The reaction was performed on a 0.3 mmol scale. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Yield and selectivity are based on isolated product. [d] The reaction was performed using [RhCl(PPh$_3$)$_3$] (10 mol %) at 150 °C in toluene. [e] The reaction was performed using [{RhCl(coe)$_2$}$_2$] (10 mol %) and PCy$_3$ (10 mol %) at 150 °C in toluene.

Table 2: Regiodivergent cyclization of *N*-homoallylindoles.[a]



Entry	R	Ligand	Yield [%] (**2**:**3**)[b]
1	H (**1a**)	SIMes·HCl (10)	84 (8:1)
2	H (**1a**)	IPr·HCl (10)	63 (1:5)
3	5-OMe (**1b**)	SIMes·HCl (10)	56 (5.2:1)
4	5-OMe (**1b**)	IPr·HCl (10)	45 (1:2.2)
5[c]	5-Cl (**1c**)	SIMes·HCl (10)	55 (4.5:1)
6[c]	5-Cl (**1c**)	IPr·HCl (10)	51 (1:2.3)
7	6-F (**1d**)	SIMes·HCl (10)	82 (9:1)
8[c]	6-F (**1d**)	IPr·HCl (10)	71 (1:2.5)
9[c]	7-Me (**1e**)	SIMes·HCl (10)	62 (4.1:1)
10[c]	7-Me (**1e**)	IPr·HCl (10)	59 (1:2.3)

[a] Reaction was performed on a 0.3 mmol scale. [b] Yield and regioisomer ratio are based on isolated product. [c] The reaction temperature was 40 °C.

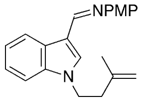
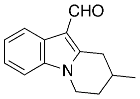
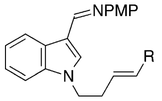
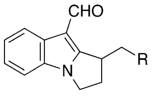
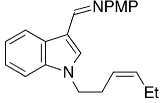
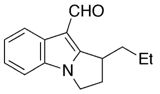
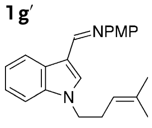
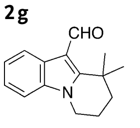
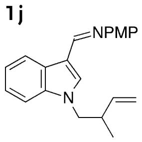
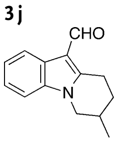
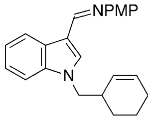
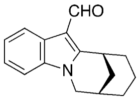
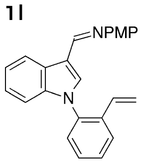
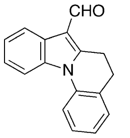
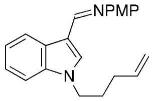
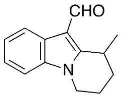
of ligand, and 100 mol % of Me$_3$SiCH$_2$MgCl at room temperature. In preliminary experiments performed at the relatively high concentration of 0.2 M, SIMes·HCl was identified as a promising pre-ligand, affording the expected five- and six-membered cyclization products **2a** and **3a** with a ratio of 4:1 in 39 % overall yield (entry 1). Reactions using other types of ligands, such as mono- and bidentate phosphines (PPh$_3$, dppe, DPEphos) and phenanthroline, were much more sluggish (entries 2–5).

Lowering the concentration to 0.05 M significantly improved the reaction using the SIMes ligand to afford **2a** and **3a**, which were separable by routine chromatography, with an 8:1 ratio in 84 % overall yield (entry 6). Upon examination of other NHC pre-ligands, we noted significant effects of their saturation/unsaturation and N-substituents on the catalytic activity and regioselectivity. The use of IMes·HCl resulted in a decrease in the product yield and regioselectivity, but it still gave **2a** as the major product (entry 7). In contrast, sterically more congested SIPr·HCl and IPr·HCl reversed the regioselectivity, the latter affording **2a** and **3a** with a 1:5 ratio in 63 % overall yield (entries 8 and 9). In our hands, the reaction of **1a** using a rhodium(I) catalyst, such as [RhCl(PPh$_3$)$_3$] or [{RhCl(coe)}$_2$]/PCy$_3$, was sluggish at an elevated temperature of 150 °C, exhibiting regioselectivity of 1:2 (entries 10 and 11).[12]

With the effective Co-SIMes and Co-IPr catalytic systems in hand, we first examined the reaction of *N*-homoallylindoles bearing different substituents on the indole nucleus (Table 2). As a result, regiodivergent cyclization was achieved in moderate to good yields for the substrates **1b–e** bearing 5-methoxy, 5-chloro, 6-fluoro, and 7-methyl substituents, respectively (entries 3–10). For some of the substrates, gentle warming at 40 °C was necessary for the desired cyclization (entries 5, 6, and 8–10). At room temperature, they cyclized rather sluggishly or underwent undesirable isomerization of the homoallyl group to an unreactive allylic group (see below). Five-membered ring formation with the Co-SIMes catalytic system was achieved with a reasonable level of regioselectivity (4:1 or greater; entries 3, 5, 7, and 9), while the selectivity toward six-membered ring formation with the Co-IPr catalyst was generally modest (ca. 1:2; entries 4, 6, 8, and 10).

We next explored cyclization of indole substrates bearing substituted homoallyl or other olefin tethers on the nitrogen atom (Table 3). The substrate **1f** with a *gem*-disubstituted olefin moiety smoothly underwent cyclization under Co-IPr catalysis to afford the six-membered ring **3f** with near complete regioselectivity (entry 1), presumably because formation of a quaternary carbon center through five-membered ring formation is unfavorable.[4,5] Even with this steric bias, consistent with the regioselectivity trend observed with **1a**, the reaction of **1f** with the Co-SIMes catalyst afforded a substantial amount of the five-membered ring isomer **2f** (**3f**:**2f** = 1.2:1; entry 2). An alkyl substituent on the homoallylic terminus directed the reaction to give the five-membered cyclic product (**2g–i**) in preference to the six-membered isomer regardless of the ligand used (entries 3–6).[13] Both the *E*- and *Z*-olefin moieties smoothly participated in the reaction (entries 3 and 6), showing a relatively minor effect of the double-bond geometry on the reactivity and the regioselectivity. Given these results, it was rather surprising that the substrate **1j**, which bears two methyl groups on the homoallylic terminus, cyclized exclusively to the six-membered ring product **3j** under Co-IPr catalysis, albeit in a modest yield (entry 7). Note that the same selectivity was also observed with the Co-SIMes catalyst. To our knowledge, this and the formation of **2f** (entry 2) are the first examples of

Table 3: Cyclization of indoles with various olefin tethers.[a]

Entry	Substrate	Ligand	Major product	Yield [%] (r.r)[b]
1		IPr		99 (48:1)[c]
2	**1f**	SIMes	**3f**	75 (1.2:1)[c]
3	 **1g** (R = Et)	SIMes	 **2g**	78 (9:1)[d]
4	**1h** (R = $(CH_2)_2Ph$)	IPr	**2h**	51 (9:1)[d]
5	**1i** (R = c-C_6H_{11})	SIMes	**2i**	51
6	 **1g′**	SIMes IPr	 **2g**	70 (3:1)[d] 65 (8:1)[d]
7[e]	 **1j**	IPr	 **3j**	40
8	 **1k**	IPr	 **3k**	43
9[f]	 **1l**	IPr	 **3l**	43
10[e]	 **1m**	IPr	 **3m**	63
11	 **1n**	IPr	 **3n**	73 (9:1)[g]

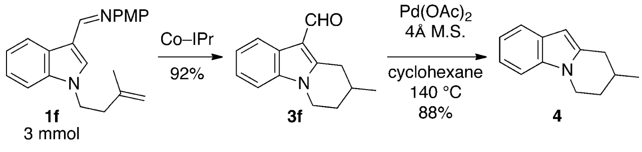
[a] Unless otherwise noted, the reaction was performed on a 0.2 mmol scale under conditions described in Table 2. [b] Yield of isolated product, except for entry 6 (yield from GC). The regioisomer ratio (r.r.) was determined by ^1H NMR except for entries 2 and 11 (each isomer separated) and entry 6 (determined by GC). [c] The minor isomer was a five-membered ring. [d] The minor isomer was a six-membered ring. [e] The reaction was performed at 60 °C. [f] The reaction was performed at 40 °C. [g] The minor isomer was a seven-membered ring.

formation of a quaternary carbon center by olefin hydroarylation through chelation-assisted C–H activation. Exclusive six-membered ring formation was also observed with the substrate **1k** bearing a substituent at the allylic position (entry 8). Likewise, the geometrically more constrained substrate **1l** with a cyclohexenyl moiety afforded the tetracyclic product **3l** with a bicyclo[3.3.1] skeleton (entry 9).[13]

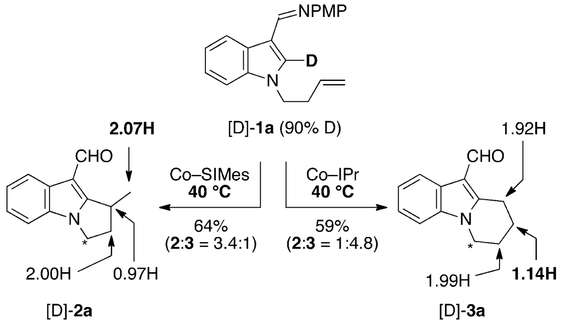
Along with the *N*-homoallylindole substrates, the substrate **1m** with a 2-vinylphenyl group also participated in six-membered ring formation to afford the angularly fused tetracyclic product **3m** in 63 % yield (entry 10). Furthermore, the substrate **1n** with a bis(homoallyl) group smoothly underwent six-membered ring formation to afford tetrahydropyridoindole **3n**, notably along with a minor seven-membered ring isomer (entry 11; ratio 9:1). Note that, in contrast to the rhodium catalysis,[2–6] *N*-allylindole and *N*-methallylindole derivatives did not cyclize to the corresponding five-membered ring products under either Co-IPr or Co-SIMes catalysis. The Co-IPr catalyst caused isomerization of the allyl group of *N*-allylindole to a 1-propenyl group, while in other cases the starting material was simply recovered. These observations indicate that five-membered ring formation from the *N*-homoallylindole substrates (for example, Table 2, odd-number entries) takes place directly through 5-*exo*-type cyclization rather than through isomerization of the olefin moiety followed by 5-*endo*-type cyclization.

The present reaction can be readily scaled up, allowing conversion of **1f** to **3f** on a 3 mmol scale in 92 % yield (average of two runs; Scheme 2). Removal of the formyl group of **3f** was achieved in a high yield using a palladium-catalyzed procedure.[14]

To gain insight into the reaction pathways, the C2-deuterated substrate [D]-**1a** was subjected to Co-SIMes and Co-IPr catalysis (Scheme 3). Unlike the parent substrate **1a**, [D]-**1a** reacted rather sluggishly at room temperature (< 10 % yield, > 70 % recovery). Both of the catalytic systems promoted the reaction at 40 °C to afford the cyclization products [D]-**2a** and [D]-**3a** in about 60 % overall yield with the same regioselectivity as was observed for **1a**. These observations suggest that the rate-limiting step of the present reaction involves cleavage of the C2–H bond, while



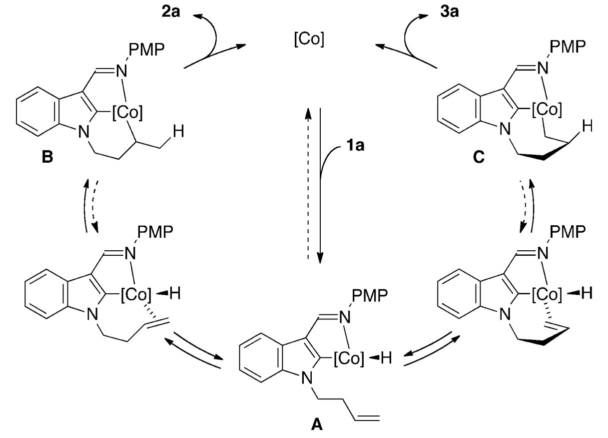
Scheme 2. Preparative-scale reaction and subsequent palladium-catalyzed decarbonylation.



Scheme 3. Deuterium-labeling experiments. The labels "*n*H" indicate the numbers of protons as determined by the ^{1}H NMR spectra (the protons on the asterisked carbon atoms are taken as the references for integration).

C–C reductive elimination has often been considered as rate-determining in the rhodium-catalyzed hydroarylation.[2–4,15] Analysis of the cyclization products showed that the deuterium atom on the C2 position of [D]-**1a** was largely transferred to the methyl moiety of [D]-**2a** and the C8-methylene moiety of [D]-**3a**, and that deuterium incorporation into the other moieties was almost negligible. These observations are also in contrast to significant H/D scrambling observed for related rhodium-catalyzed intramolecular cyclization reactions.[5a,8b]

In light of the above observations and our previous studies on cobalt-catalyzed intermolecular olefin hydroarylation,[10] we are tempted to propose the reaction pathways outlined in Scheme 4. Thus, the reaction is initiated by chelation-assisted oxidative addition of the C2–H bond to a low-valent cobalt species to give a cobaltacycle intermediate **A**. Subsequent insertion of the olefin moiety into the Co–H bond leads to either six-membered (**B**) or seven-membered (**C**) cobaltacycle intermediates,[16] which undergo reductive elimination to afford the product **2a** or **3a**, respectively. Judging from the lack of significant H/D scrambling in the deuterium-labeling experiments, we surmise that the C–H oxidative addition and olefin insertion steps are practically irreversible. Thus, the olefin insertion step is probably the regioselectivity-determining step of the present reaction.



Scheme 4. Proposed reaction pathways.

In summary, we have developed a cobalt-NHC-catalyzed intramolecular olefin hydroarylation reaction on an indole platform to afford dihydropyrroloindole and tetrahydropyridoindole derivatives under mild conditions. Construction of a quaternary carbon center and a bicyclo[3.3.1] skeleton and use of a bishomoallyl tether have been achieved for the first time in the manifold of intramolecular hydroarylation by directed C–H activation, highlighting the uniqueness of cobalt catalysis.[17] The regioselectivity of the cyclization reaction is primarily dependent on the structure of the olefin tether, but is controllable by the steric nature of the NHC ligand when the tether is a parent homoallyl group, which is an example of catalytic regiodivergent synthesis.[18,19] The origin of the substrate- and ligand-dependent regioselectivity deserves further mechanistic investigation. The development of an enantioselective variant is also among subjects of further studies.

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Keywords: alkenes · C–H activation · cobalt · indoles · intramolecular reactions

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[13] The structure of **2i** was unambiguously determined by X-ray diffraction analysis. Upon being left in hexane/EtOAc, the aldehyde **3l** was oxidized to a carboxylic acid, the structure of which was also determined by X-ray diffraction analysis (see the Supporting Information). CCDC 943911 (**2i**) and 943912 (the carboxylic acid derived from **3l**) contain 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.

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