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Enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes†

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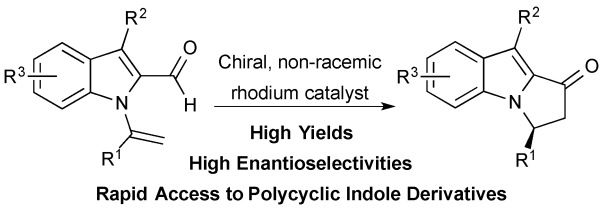
We report catalytic, enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes. These hydroacylation reactions occur in the presence of a readily accessible rhodium catalyst and form chiral, non-racemic 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones in high yields with excellent enantioselectivities.

Intramolecular hydroacylation of alkenes in the presence of transition metal catalysts is a well-known process that couples C–H bond activation with carbon–carbon bond formation to form synthetically valuable ketone products.[1] Hydroacylations of substituted 4-pentenals and 2-vinylbenzaldehydes to form cyclopentanones are common[2] and occur with high enantioselectivities in the presence of chiral, non-racemic catalysts.[3] Recent reports have also shown that six-, seven- and eight-membered carbocycles and heterocycles are accessible from intramolecular alkene hydroacylation reactions.[4] However, alkene hydroacylations to generate nitrogen-containing heterocycles are rare.[4e,5,6]

Bendorf and co-workers reported amine-directed, intramolecular hydroacylation of 2-(homoallylamino)benzaldehydes.[5a] These amine-directed hydroacylation reactions occur in the presence of 10 mol% of Wilkinson's catalyst, and the efficiency of the reactions is greatly influenced by the identity of the substituents on the nitrogen atom. Recently, Douglas reported hydroacylation of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes.[5b] These hydroacylation reactions involve *in situ* formation of imines to install chelating functionality to stabilize the resulting iminorhodium(III) hydride intermediate.[2j,7] The heterocyclic ketone products are formed in good yields, but the requirement for chelation assistance leads to poor atom economy and efforts to develop a highly enantioselective catalyst were unsuccessful. Although reports by Bendorf and Douglas provide an entry into practical alkene hydroacylation reactions to generate nitrogen containing heterocycles, the opportunity exists to form nitrogen heterocycles by alkene hydroacylations that occur (1) with high enantioselectivity and (2) without the need for strategies to stabilize the acylrhodium(III) hydride intermediate.



(1)

The potential for enantioselective intramolecular hydroacylation to create a rapid entry into dihydropyrroloindoles led us to study Rh-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehydes (eqn (1)). Dihydropyrroloindoles are core structures of a variety of indole alkaloids including yuremamine[8,9] and antimalarial bis-indoles from the *Flindersia* species, such as the isoborreverines (Fig. 1).[10] Thus, we report the synthesis of highly enantioenriched 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolones by intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes in the presence of a rhodium catalyst prepared *in situ* from commercially available precursors.

Initial studies to develop catalytic, enantioselective hydroacylations of *N*-vinylindole-2-carboxaldehydes were guided by

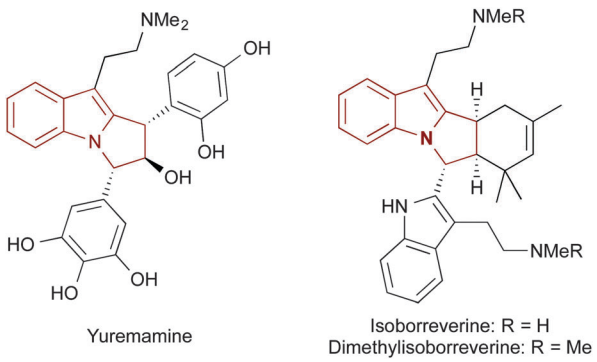


Fig. 1 Dihydropyrroloindoles as core elements of indole alkaloids.

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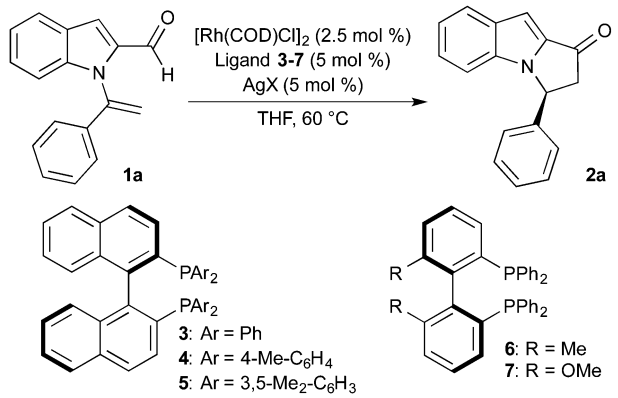
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for new compounds, and crystallographic data (CIF) for compound **3**. CCDC 976167. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00210e

Table 1 Identification of catalysts for Rh-catalyzed hydroacylation of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a**[a]



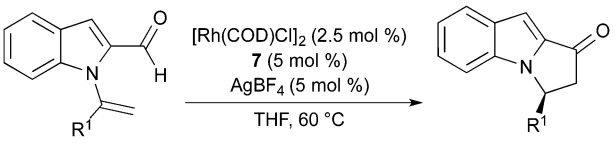
Entry	AgX	Ligand	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
1	—	**3**	0	—	—
2	$AgNO_3$	**3**	0	—	—
3	AgOMs	**3**	0	—	—
4	$AgClO_4$	**3**	96	10	ND
5	$AgBF_4$	**3**	75	54	94
6	$AgPF_6$	**3**	72	49	91
7	$AgSbF_6$	**3**	99	61	95
8	$AgBF_4$	**4**	95	75	96
9	$AgBF_4$	**5**	42	35	98
10	$AgBF_4$	**6**	80	63	97
11	$AgBF_4$	**7**	95	90	99

[a] For detailed reaction conditions, see ESI. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield of **2a**. [d] Determined by chiral HPLC analysis.

hydroacylations of 2-vinylbenzaldehydes catalyzed by a rhodium(I)–BINAP complex. To test whether hydroacylation of *N*-vinylindole-2-carboxaldehydes could occur with similar catalysts, we studied the reaction of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** catalyzed by complexes prepared *in situ* from $[Rh(COD)Cl]_2$, (*R*)-BINAP **3**, and a variety of silver salts (Table 1, entries 1–7). We found that the hydroacylation of **1a** did not occur in THF at 60 °C when the rhodium(I) catalysts contained coordinating counteranions, such as chloride, nitrate, and mesylate (entries 1–3). However, the hydroacylation of **1a** formed dihydropyrroloindolone **2a** in low to modest yield when the rhodium catalyst contained a weakly coordinating counteranion. The hydroacylation of **1a** catalyzed by a rhodium catalyst with a perchlorate counterion occurred to high conversion, but formed **2a** in low yield (entry 4). In contrast, the reaction of **1a** generated dihydropyrroloindolone **2a** in 49–61% yield in the presence of rhodium complexes with tetrafluoroborate, hexafluorophosphate, and hexafluoroantimonate counteranions (entries 5–7). Although the catalyst containing a hexafluoroantimonate counterion led to the highest yield of **2a**, this catalyst also promoted decomposition of **1a**. We chose to continue our study with rhodium catalysts containing a tetrafluoroborate counterion since we observed less decomposition of **1a** with this catalyst system.

To improve the yield and selectivity of our model reaction, we studied the hydroacylation of **1a** in the presence of catalysts prepared from $[Rh(COD)Cl]_2$, $AgBF_4$, and a selection of aromatic bisphosphine ligands **3–7** containing axial chiral backbones

Table 2 Rhodium-catalyzed enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes **1a–h**[a]



Entry	R^1 (**1**)	**2**	Yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	**2a**	90	99
2	4-MeO-C_6H_4 (**1b**)	**2b**	99	99
3	4-Cl-C_6H_4 (**1c**)	**2c**	68	98
4	4-F_3C-C_6H_4 (**1d**)	**2d**	30	99
5[d]	4-F_3C-C_6H_4 (**1d**)	**2d**	70	99
6	3-MeO-C_6H_4 (**1e**)	**2e**	92	98
7	3,4,5-$(MeO)_3$-C_6H_2 (**1f**)	**2f**	82	99
8	Me (**1g**)	**2g**	99	99
9	Cyclohexyl (**1h**)	**2h**	20	97
10[e]	Cyclohexyl (**1h**)	**2h**	45	95

[a] For detailed reaction conditions, see ESI. [b] Isolated yield of **2**. [c] Determined by chiral HPLC analysis. [d] Reaction run in the presence of 10 mol% catalyst. [e] Reaction run at 100 °C in 1,4-dioxane.

(Table 1, entries 5, 8–11). The rhodium(I) complex of (*R*)-Tol-BINAP **4** catalyzes the hydroacylation of **1a** to form **2a** in higher yield than the rhodium complex of the parent (*R*)-BINAP ligand, while the rhodium(I) complex of (*R*)-Xyl-BINAP catalyzes the formation of **2a** in lower yield (compare entries 8 and 9 with entry 5). Rhodium complexes of both (*R*)-Tol-BINAP and (*R*)-Xyl-BINAP catalyze the formation of **2a** with higher enantioselectivity. The reaction of **1a** occurred with the best combination of yield and enantioselectivity in the presence of rhodium complexes of (*S*)-Me-BIPHEP and (*S*)-MeO-BIPHEP (entries 10 and 11). The hydroacylation of **1a** catalyzed by rhodium(I) complex of (*S*)-MeO-BIPHEP formed **2a** in 90% yield with 99% ee (entry 11).

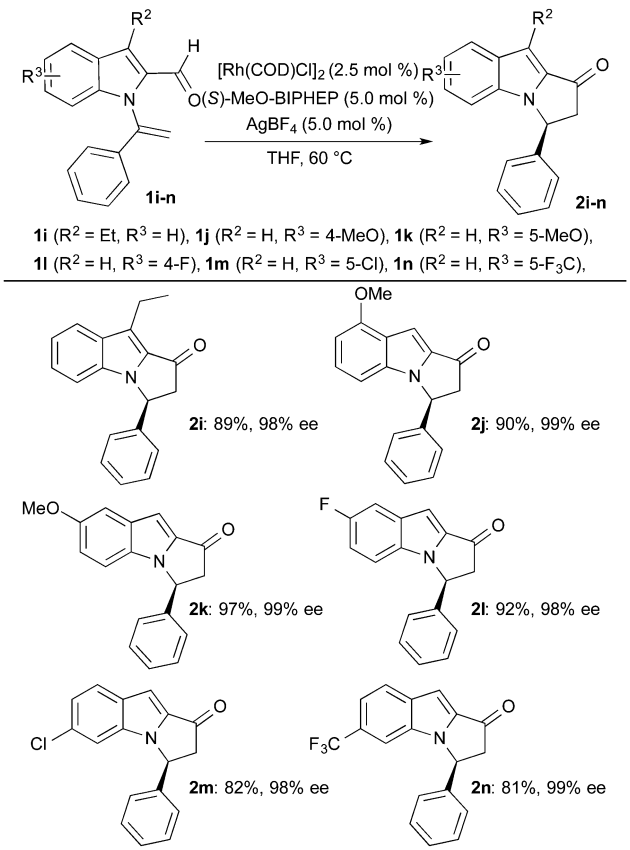
The results of intramolecular hydroacylations of *N*-vinylindole-2-carboxaldehydes containing a range of substituted vinyl units are shown in Table 2. The hydroacylations of *N*-vinylindole-2-carboxaldehydes containing electron-neutral or electron-rich aryl groups at the 1-position of the *N*-vinyl moiety gave the corresponding dihydropyrroloindolones **2a** (R^1 = Ph) and **2b** (R^1 = 4-MeO-C_6H_4) in high yields (90–99%) with 99% enantiomeric excess (entries 1 and 2). The hydroacylation of *N*-vinylindole-2-carboxaldehydes substituted with electron-deficient aryl groups at the 1-position of the vinyl group formed dihydropyrroloindolones **2c** (R^1 = 4-Cl-C_6H_4) and **2d** (R^1 = 4-F_3C-C_6H_4) in lower yield (68% and 30%, entries 3 and 4). However, these hydroacylations occurred with excellent enantioselectivity (98–99% ee), and the yield of **2d** improved to 70% when the reaction was run in the presence of 10 mol% rhodium catalyst (entry 5).

N-Vinylindole-2-carboxaldehydes containing *meta*-substituted aryl groups at the 1-position of the *N*-vinyl moiety are also excellent substrates for these intramolecular hydroacylations. *N*-Vinylindole-2-carboxaldehydes **1e** (R^1 = 3-MeO-C_6H_4) and **1f** (R^1 = 3,4,5-$(MeO)_3$-C_6H_2) reacted to form dihydropyrroloindolones **2e** and **2f** in 82–92% yield with 98–99% ee (entries 6 and 7). We were unable to generate data on hydroacylations of *N*-vinylindole-2-carboxaldehydes containing *ortho*-substituted aryl groups at the

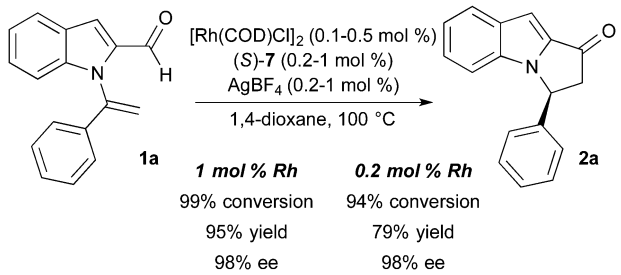
1-position of the *N*-vinyl moiety because Ullmann-type coupling of appropriately substituted indoles and α-halogenated styrenes were unproductive in our hands.

Reactions of *N*-vinylindole-2-carboxaldehydes containing alkyl groups at the 1-position of the *N*-vinyl moiety also occurred with high enantioselectivity. The reaction of **1g** (R^1 = Me) formed **2g** in nearly quantitative yield and nearly perfect enantioselectivity (entry 8). The reaction of *N*-vinylindole-2-carboxaldehyde **1h** bearing a bulky cyclohexyl group formed dihydropyrroloindole **2h** with 97% enantiomeric excess (entry 9). However, the yield of **2h** was low when the reaction was run under our standard conditions. The yield of **2h** improved to 45% with a modest decrease in enantioselectivity when the reaction was performed in 1,4-dioxane at 100 °C (entry 10).

Scheme 1 summarizes the results of hydroacylations with *N*-vinylindole-2-carboxaldehydes containing substitution at the 3-, 4-, 5-, and 6-positions on the indole moiety. A variety of *N*-vinylindole-2-carboxaldehydes containing electron-donating and electron-withdrawing substituents, as well as halogens, were excellent substrates for the intramolecular alkene hydroacylation. Alkyl substitution at the 3-position of the indole ring was well tolerated, and the hydroacylation of 3-ethyl-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1i** (R^2 = Et, R^3 = H) formed product **2i** in 89% yield with 98% ee. Hydroacylations of 4-MeO, 5-MeO, and 5-F substituted *N*-vinylindole-2-carboxaldehydes **1j–l** occurred with excellent enantioselectivity (98–99%),



Scheme 1 Rhodium-catalyzed enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes **1i–n**.



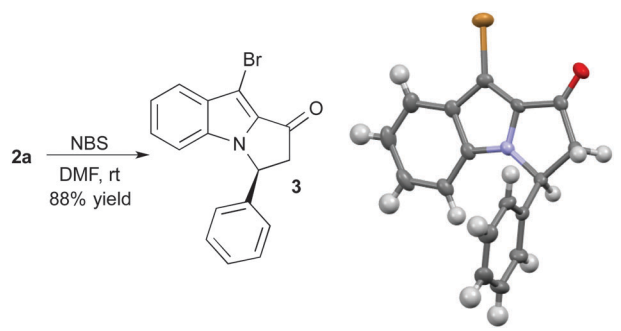
Scheme 2 Impact of catalyst loading on the enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehyde **1a**.

and dihydropyrroloindolones **2j–l** were isolated in 90–97% yield. Intramolecular hydroacylations of 6-chloro- and 6-trifluoromethyl-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehydes (**1m** and **1n**) formed **2m** and **2n** in slightly lower yield (81–82%), but the enantioselectivity remained high (98–99% ee).

Although reactions of *N*-vinylindole-2-carboxaldehydes to establish the scope of these hydroacylations are conducted in the presence of 5 mol% of the rhodium catalyst, this relatively high catalyst loading is not a requirement to achieve high isolated yields and enantioselectivities (Scheme 2). The hydroacylation of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** performed in the presence of 1 mol% of the rhodium catalyst at 100 °C in 1,4-dioxane generates dihydropyrroloindolone **2a** in 95% yield with 98% ee. Decreasing the catalyst loading to 0.2 mol% led to a lower yield (79%) of dihydropyrroloindolone **2a**, but this heterocyclic ketone was still formed with excellent enantioselectivity (98% ee).

The absolute configuration of dihydropyrroloindolone **2a** was determined after bromination (Scheme 3). Treatment of **2a** with *N*-bromosuccinimide occurred to form **3** in 88% yield. The absolute configuration of 9-bromo-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **3** was determined to be (3*S*) by X-ray crystallographic analysis. Thus, the catalyst generated from (*S*)-MeO-BIPHEP **7** leads to the formation of (*S*)-**3**.

In conclusion, we have established a method for highly enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes in the presence of a rhodium catalyst prepared *in situ* from commercially available precursors. These reactions encompass a broad range of *N*-vinylindole-2-carboxaldehydes bearing a variety of aryl and alkyl substituents on the olefin



Scheme 3 Absolute stereochemistry and structure of **3** based on X-ray diffraction data.

moiety and substitution throughout the indole core. The enantioenriched dihydropyrroloindolone products are generated with consistently high enantioselectivity (95–99% ee) even at low catalyst loadings. The use of this reaction to complete the first total synthesis of yuremamine is currently under investigation in our laboratory.

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