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Enantioselective Synthesis of Polycyclic Nitrogen Heterocycles by Rh-Catalyzed Alkene Hydroacylation: Constructing Six-Membered Rings in the Absence of Chelation Assistance

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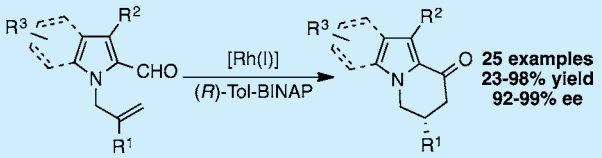
Supporting Information

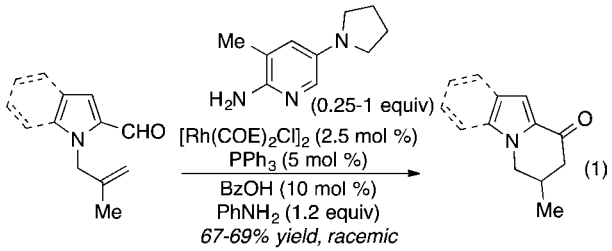
ABSTRACT: Catalytic, enantioselective hydroacylations of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes are reported. In contrast to many alkene hydroacylations that form six-membered rings, these annulative processes occur in the absence of ancillary functionality to stabilize the acylrhodium(III) hydride intermediate. The intramolecular hydroacylation reactions generate 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)ones and 6,7-dihydroindolizin-8(5*H*)-ones in moderate to high yields with excellent enantioselectivities.

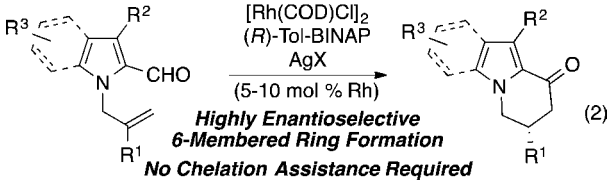


The hydroacylation of alkenes in the presence of a transition metal catalyst has been extensively investigated as a direct route to ketones from simple starting materials.[1] Despite the importance of ketones as synthetic building blocks and their potential as entry points to an array of chemical architectures, the hydroacylation of alkenes remains underdeveloped and underutilized relative to other metal-catalyzed hydrofunctionalizations of alkenes.[2]

Intramolecular hydroacylations to generate five-membered carbocycles are the most established class of alkene hydroacylations,[3] and many enantioselective hydroacylations of substituted 4-pentenals and 2-vinylbenzaldehydes form chiral, nonracemic cyclopentanones and dihydroindenones.[4] Recent strategies also enable the synthesis of six-, seven-, and eight-membered carbocycles and heterocycles through intramolecular alkene hydroacylation reactions.[5] Despite these achievements, intramolecular alkene hydroacylations to generate nitrogen heterocycles remain rare,[5a−c,6] and hydroacylation reactions to form rings of greater than five atoms are often driven by strain release[5c,e,h] or rely on heteroatom functionality contained at specific sites within the substrate molecules to stabilize acylrhodium(III) hydride intermediates and prevent catalyst decomposition.[5b,d,g,6b]

The potential to develop alkene hydroacylation as a platform for synthesis of medicinally important nitrogen heterocycles led us to study hydroacylations of indole- and pyrrole-2-carboxaldehydes containing *N*-vinyl and *N*-allyl substitution. We recently reported Rh-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehydes to form dihydropyrroloindolones in high yields with excellent enantioselectivities.[7] Hydroacylations of *N*-allylindole-2-carboxaldehydes have proven more challenging because these processes involve the formation of a six-membered ring instead of a five-membered ring. During our studies, Douglas reported the first example of alkene hydroacylation involving *N*-allylindole-2-carboxaldehydes (eq 1).[5a] These hydroacylation reactions are enabled





by transient generation of a 2-aminopicoline-based aldimine that stabilizes the acylrhodium hydride intermediate. However, this approach to chelation assistance requires a complex mixture of catalyst precursors and additives, and highly enantioselective hydroacylations involving 2-aminopicoline-based aldimines have not been reported.

We now report catalytic, enantioselective hydroacylations of *N*-allylindole-2-carboxaldehyes and *N*-allylpyrrole-2-carboxaldehydes (eq 2). These hydroacylations occur to form dihydropyridoindolones and dihydroindolizinones in moderate to high yields and represent the first examples of highly enantioselective, transition metal-catalyzed hydroacylation to form six-membered rings in the absence of chelation assistance.

To test whether intramolecular hydroacylations would occur to generate six-membered rings in the absence of chelation assistance, we studied the reaction of 1-(2-methylallyl)-1*H*-

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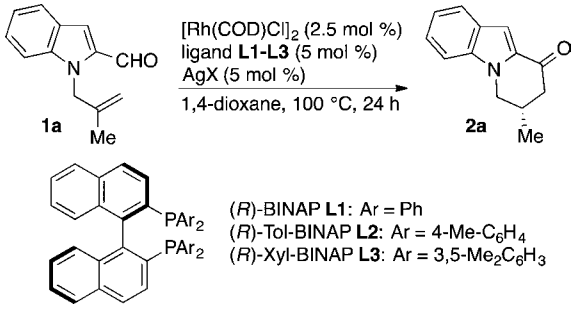
indole-2-carboxaldehyde **1a** catalyzed by complexes prepared *in situ* from $[Rh(COD)Cl]_2$, (*R*)-BINAP **L1**, and a variety of silver salts (Table 1).[8] We found the hydroacylation of **1a** did not occur in the presence of rhodium catalysts with chloride or mesylate counterions (entries 1 and 2) and formed dihydropyridoindolone **2a** in low yield when the catalyst contained a triflate counterion (entry 3).

Table 1. Identification of Catalysts for Hydroacylation of 1-(2-Methylallyl)-1*H*-indole-2-carboxaldehyde 1a



entry	ligand	AgX	conv (%)[a]	yield **2a** (%)[b]	ee (%)[c]
1	**L1**	–	5	0	–
2	**L1**	AgOMs	2	0	–
3	**L1**	AgOTf	18	17 (12)	94
4	**L1**	$AgPF_6$	69	69 (63)	96
5	**L1**	$AgBF_4$	99	86 (83)	95
6	**L1**	$AgSbF_6$	82	82 (79)	96
7	**L2**	$AgBF_4$	99	99 (94)	97
8	**L3**	$AgBF_4$	99	99 (97)	87
9[d]	**L2**	–	98	93 (90)	96

[a]Conversion of **1a** determined by ^{1}H NMR spectroscopy. [b]Yield of **2a** determined by ^{1}H NMR spectroscopy. Isolated yield of **2a** is shown in parentheses. [c]Determined by chiral HPLC analysis. [d]Reaction performed with 5 mol % $[Rh(COD)_2]BF_4$ as a catalyst precursor.

The intramolecular hydroacylation of **1a** occurred in higher yields and formed **2a** with higher enantioselectivities when the rhodium catalyst contained a weakly coordinating counterion.[9] The reaction of **1a** generated **2a** in 63–83% yield with 95–96% enantiomeric excess in the presence of rhodium complexes with hexafluorophosphate, tetrafluoroborate, and hexafluoroantimonate counterions (entries 4–6). The identity of the counterion had minimal effect on the enantioselectivity of the hydroacylations. However, catalysts containing tetrafluoroborate and hexafluorantimonate counterions led to significantly higher yields of **2a**.

To improve the yield and selectivity of our model reaction, we studied the impact of catalysts prepared from additional BINAP derivatives on the reaction of **1a**. The rhodium(I) complexes of (*R*)-Tol-BINAP **L2** and (*R*)-Xyl-BINAP **L3** catalyze the hydroacylation of **1a** to form **2a** in higher yields (94% and 97% yield) than the Rh complex of the parent ligand **L1** (compare entries 7 and 8 with entry 5). However, the hydroacylation of **1a** occurred with the highest enantioselectivity when the reaction was conducted with the Rh complex of (*R*)-Tol-BINAP. The hydroacylation of **1a** occurs with similar enantioselectivity and forms **2a** in 90% yield when the reaction is performed with a catalyst generated from $[Rh(COD)_2]BF_4$ and (*R*)-Tol-BINAP (entry 9), suggesting the role of the Ag(I) salt is limited to anion exchange to generate the active catalyst. In all cases, the formation of six-membered ketone **2a** was favored; the formation of a five-membered ketone product was not observed.[10]

The absolute configuration of **2a** was determined after bromination of **2a** with *N*-bromosuccinimide to generate **3** in nearly quantitative yield (Scheme 1). The absolute configuration of **3** was determined to be (*S*) by X-ray crystallographic analysis.

Scheme 1. Absolute Stereochemistry and Structure of 3

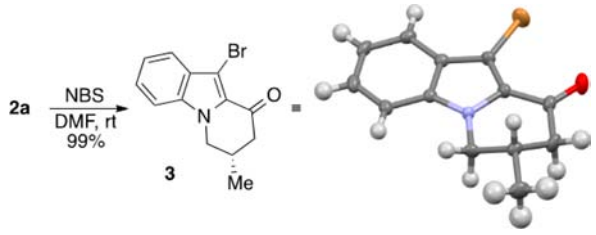
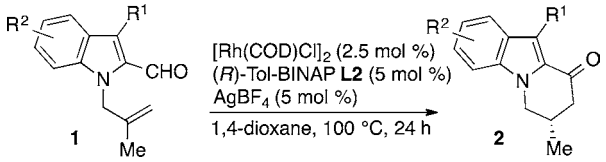


Table 2 summarizes the results of hydroacylations with 1-(2-methylallyl)-indole-2-carboxaldehydes containing substitution at the 3-, 4-, 5-, 6-, and 7-positions on the indole core. In general, hydroacylations of 1-(2-methylallyl)-indole-2-carboxaldehydes containing electron-donating substituents, electron-withdrawing substituents, and halogens at the 4-, 5-, 6-, and 7-positions occur with excellent enantioselectivity (entries 1–8). Hydroacylations of 4-MeO-, 5-MeO-, and 6-MeO-substituted **1b–d** formed **2b–d** in high yields (84–96%) with excellent enantioselectivities (97–99% ee, entries 1–3). The hydroacylation of 4,7-dimethoxy-substituted 1-(2-methylallyl)-indole-2-carboxaldehyde **1e** occurred with high enantioselectivity, but the corresponding dihydropyridoindole **2e** was isolated in 53% yield (entry 4).[11] Hydroacylations of **1f–i** containing halogens or electron-withdrawing groups at the 5- and 6-positions occurred with excellent enantioselectivities (95–98% ee), and **2f–i** were isolated in 65–92% yields (entries 5–8). A 3-substituted 1-(2-methylallyl)-indole-2-carboxaldehyde **1j** was also an excellent substrate for hydroacylation. The reaction of **1j** formed **2j** in 93% yield with 93% ee (entry 9).

Table 2. Rh-Catalyzed Enantioselective Hydroacylation of 1-(2-Methylallyl)-indole-2-carboxaldehydes 1b–j



entry	**1**	R^1	R^2	**2**	yield **2** (%)[a]	ee (%)[b]
1	**1b**	H	4-MeO	**2b**	96	97
2	**1c**	H	5-MeO	**2c**	95	99
3	**1d**	H	6-MeO	**2d**	84	97
4	**1e**	H	4,7-$(MeO)_2$	**2e**	53	95
5	**1f**	H	5-Cl	**2f**	92	98
6	**1g**	H	6-Cl	**2g**	83	96
7	**1h**	H	5-NO_2	**2h**	89	96
8	**1i**	H	6-CF_3	**2i**	65	95
9	**1j**	Et	H	**2j**	93	93

[a]Isolated yield of **2**. [b]Determined by chiral HPLC analysis.

The results of intramolecular hydroacylations of *N*-allyl-indole-2-carboxaldehydes containing a range of 2-substituted

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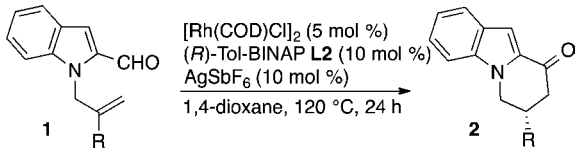
allyl units, are shown in Table 3. Hydroacylations of **1k–q** containing alkyl, benzyl, aryl, and ester substituents at the

Table 3. Enantioselective Hydroacylation of *N*-Allylindole-2-carboxaldehydes 1k–q



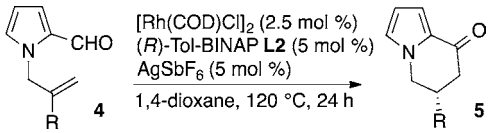
entry	R (**1**)	**2**	conv (%)[a]	yield **2** (%)[b]	ee (%)[c]
1[d]	Et (**1k**)	**2k**	80	53 (75)	97
2[d]	*n*-hexyl (**1l**)	**2l**	73	42 (61)	96
3	CH_2Ph (**1m**)	**2m**	82	45 (55)	97
4	Ph (**1n**)	**2n**	72	37 (64)	97
5	4-Me-C_6H_4 (**1o**)	**2o**	71	31 (63)	96
6	4-Cl-C_6H_4 (**1p**)	**2p**	83	56 (66)	95
7	CO_2Et (**1q**)	**2q**	65	23 (56)	96

[a]Conversion of **1** determined by ^1H NMR spectroscopy. [b]Isolated yield of **2**. NMR yield of **2** is listed in parentheses. [c]Determined by chiral HPLC analysis. [d]$AgBF_4$ was used in place of $AgSbF_6$.

central carbon of the allyl unit occurred with excellent enantioselectivities (95–97% ee), but these reactions formed dihydropyridoindoles **2k–q** in modest yields (55–75% NMR yields, 23–56% isolated yields). The relatively low isolated yields of **2k–q** result from a combination of competitive decarbonylation of **1k–q** and challenging product purifications from reaction mixtures containing unreacted **1k–q** and decarbonylation products. Yields of decarbonylation products ranged from 5% to 15%.

The ability to form dihydropyridoindoles by enantioselective hydroacylations of *N*-allylindole-2-carboxaldehydes led us to investigate analogous hydroacylations of *N*-allylpyrrole-2-carboxaldehydes containing a range of substituted allyl units (Table 4). The hydroacylations of *N*-allylpyrrole-2-carboxaldehydes **4a–c** containing alkyl substitution at the central carbon of the allyl unit formed dihydroindolizinones **5a–c** in modest-to-good yields (51–79%) with 94–97% enantiomeric excess (entries 1–3). The hydroacylation of **4d** (R = CH_2Ph) did not occur to high conversion in the presence of 5 mol %

Table 4. Enantioselective Hydroacylation of *N*-Allylpyrrole-2-carboxaldehydes 4a–h



entry	R (**4**)	**5**	yield **5** (%)[a]	ee (%)[b]
1[c]	Me (**4a**)	**5a**	79	97
2	Et (**4b**)	**5b**	70	96
3	*n*-hexyl (**4c**)	**5c**	51	94
4[d]	CH_2Ph (**4d**)	**5d**	52	92
5	Ph (**4e**)	**5e**	96	97
6	4-Me-C_6H_4 (**4f**)	**5f**	86	97
7	4-Cl-C_6H_4 (**4g**)	**5g**	85	95
8[d]	CO_2Et (**4h**)	**5h**	98	98

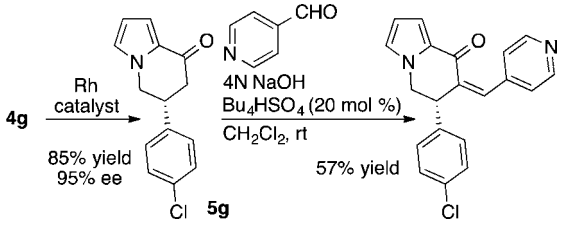
[a]Isolated yield of **5**. [b]Determined by chiral HPLC analysis. [c]Reaction run at 100 °C using $AgBF_4$ in place of $AgSbF_6$. [d]Reaction run in the presence of 10 mol % catalyst.

catalyst. However, the reaction of **4d** formed **5d** in 52% yield with 92% enantiomeric excess when the reaction was run in the presence of 10 mol % rhodium catalyst (entry 4).

In general, the *N*-allylpyrrole-2-carboxaldehydes are less prone to decarbonylation than the related *N*-allylindole-2-carboxaldehydes. These results are particularly evident for pyrroles **4e–g** with aryl substitution at the central carbon of the allyl unit. The hydroacylations of **4e–g** (R = Ph, 4-Me-C_6H_4, and 4-Cl-C_6H_4) occurred with excellent enantioselectivities (95–97% ee), and the heterocyclic ketone products **5e–g** were isolated in 85–96% yields (entries 5–7). These results contrast hydroacylations of *N*-allylindole-2-carboxaldehydes with aryl substitution at the central carbon of the allyl unit (compare entries 4–6 in Table 3 with entries 5–7 in Table 4). Reactions of indoles **1n–p** require 10 mol % catalyst to reach high coversion due to competing decarbonylation, while reactions of the analogous pyrroles **4e–g** require only 5 mol % catalyst to reach full conversion and decarbonlyation side products are not observed.[12] The hydroacylation of pyrrole **4h** containing an electron-withdrawing group at the central carbon of the allyl unit (R = CO_2Et) generated **5h** in 98% yield with 98% ee (entry 8).

The synthetic utility of our enantioselective hydroacylation reactions has been demonstrated through a rapid asymmetric synthesis of the nonsteroidal aromatase inhibitor MR 20492 (Scheme 2).[13] Enantioselective hydroacylation of *N*-allylindole-

Scheme 2. Enantioselective Synthesis of (*S*,*Z*)-MR 20492



2-carboxaldehyde **4g** formed dihydroindolizinone **5g** in 85% yield with 95% ee (Table 4, entry 7). Aldol condensation of **5g** with pyridine-4-carboxaldehyde generated (*S*,*Z*)-MR 20492 in 57% yield.

In summary, we have developed catalytic, enantioselective hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes. These hydroacylation reactions are catalyzed by a readily available Rh complex, occur in the absence of chelation assistance, and form six-membered heterocyclic ketones in moderate-to-excellent yields from a variety of indole and pyrrole substrates. The utility of our method is demonstrated in a straightforward asymmetric synthesis of the nonsteroidal aromatase inhibitor MR 20492. Studies to expand the scope of transition-metal-catalyzed hydroacylation reactions that occur in the absence of chelation assistance and to extend these methods to additional carbocyclic and heterocyclic scaffolds are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization for all new compounds, and crystallographic data for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) The hydroacylation of *N*-allylindole-2-carboxaldehyde, which lacks substitution at the 2-position of the allyl unit, occurs exclusively with anti-Markovnikov selectivity to form the achiral dihydropyrido-indolone product.

(11) 1,4-Dimethoxy-7-methylpyrido[1,2-*a*]indole was isolated as a byproduct in 30% yield. For related cyclizations of *o*-allylbenzaldehydes to form naphthalenes, see: agdale, A. R.; Park, J. H.; Youn, S. W. *J. Org. Chem.* **2011**, *76*, 7204.

(12) Reactions of substrates **1n** and **4e** occur in the presence of 5 mol % catalyst to approximately 50% conversion in 1.5 h suggesting the reactivity of indole and pyrrole substrates are similar in the absence of catalyst deactivation.

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