A Bulky Chiral *N*-Heterocyclic Carbene Nickel Catalyst Enables Enantioselective C–H Functionalizations of Indoles and Pyrroles

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Abstract: An enantioselective nickel(0)-catalyzed C–H functionalization of indoles and pyrroles without the need for the typical Lewis-basic directing groups is disclosed. The reaction provides access to valuable tetrahydropyridoindoles and tetrahydroindolizines in high yields and enantioselectivities under mild reaction conditions. The process is characterized by a clean *endo*-cyclization preference to yield the sought-after six-membered ring products. Key for the success of the activation and selectivity in the cyclization was the development of a novel chiral SIPr carbene ligand analogue with very bulky flanking groups.

Indoles and pyrroles are prevalent structures in a broad variety of natural products and pharmaceuticals.[1] For example, marketed drugs such as tolmetin[2] and ribociclib[3] contain a pyrrole and a pyrrolopyrimidine core, respectively (Figure 1). As prominent substructure, the tricyclic tetrahydropyrido indole scaffold is present in biologically active molecules, like PKC inhibitor Ro 32-0432[4] and CRTH2 antagonist MK-7246,[5] as well as in numerous indole alkaloids exemplified by alstoscholarisine A and vincamine.[6] Moreover, the antiviral agent CMV423 contains a related tetrahydroindolizine core.[7]

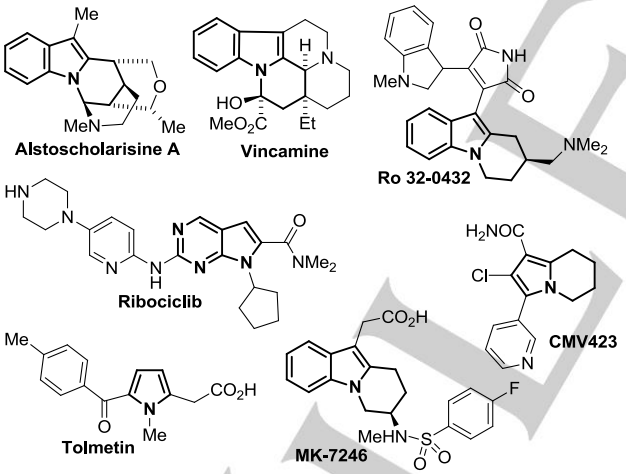
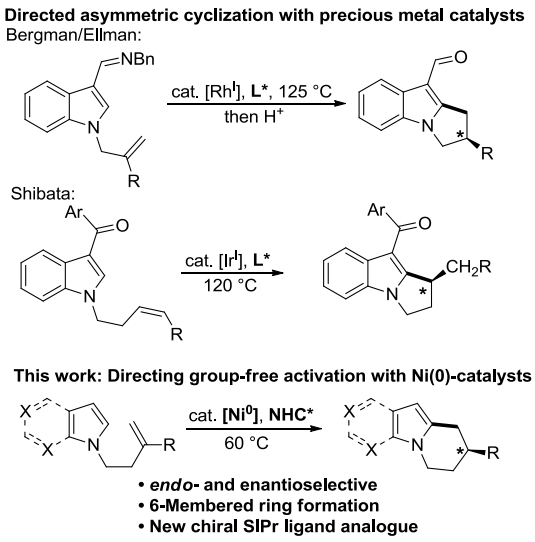


Figure 1. Representative biologically active indole / pyrrole derivatives and examples with tricyclic tetrahydropyridoindole cores.

In this respect, a broad range of construction and modification methods of indoles have been devised.[8] More recently, C–H functionalization has been established as a complementary and powerful tool for the construction of molecular complexity from simple precursors.[9,10] Important advances have been made in the site-selective functionalization of indoles.[11] Enantioselective functionalization methods of indole generally rely on the use of covalently bound directing groups placed at the nitrogen atom or the C3-carbon atom.[12] For instance, Bergman and Ellman[12a,b] reported C3-aldimine-directed enantioselective indole annulations with a Rh(I)-catalyst and Shibata disclosed C3-ketone-directed Ir(I)-catalyzed annulations (Scheme 1).[12c,d] Yoshikai developed a achiral regio-divergent C2-annulation of indoles utilizing a cobalt catalyst and different achiral *N*-heterocyclic carbene (NHC) ligands in conjunction with a covalent aldimine directing group.[13] The iridium(I)-catalyzed enantioselective addition of indole to norbornene is a rare example for an undirected approach.[14] Recently, enantioselective C–H functionalizations with abundant 3d-metal catalysts have gained significant momentum.[12g-h, 15, 16] In this context, asymmetric [Ni^0]NHC-catalyzed processes[17] - aided in several cases by a Lewis-acid co-activation[18] - enabled selective C-H functionalizations of pyridones,[19] pyridines[20] and benzimidazoles.[21] However, the undirected enantioselective functionalization of the important electron-rich heterocycles pyrrole and indole remains an open challenge.

Nakao and Hartwig reported an undirected C2-functionalization of electron-rich heterocycles using an *achiral* nickel-NHC catalyst system for anti-Markovnikov hydroarylations.[22] We recently reported[19,23] a chiral NHC[24] family having large modulation opportunities based on Gawley's carbene.[25] Herein, we introduce new members of this ligand family and apply them as steering ligands in Ni-catalyzed directing group-free enantioselective C–H functionalizations of indoles and pyrroles (Scheme 1).



Scheme 1. Enantioselective C–H annulations of indoles and pyrroles.

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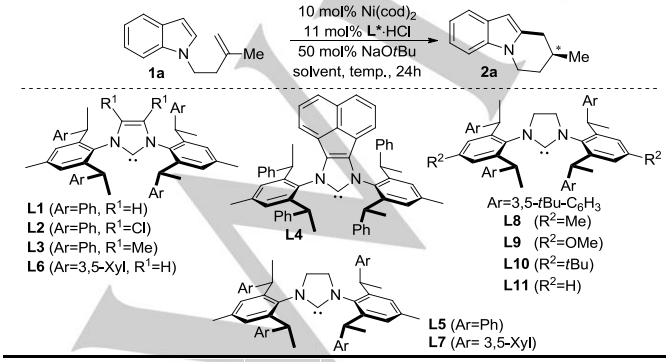
We commenced the development of the enantioselective C–H cyclization with indole substrate **1a** using $Ni(cod)_2$ as nickel source, a screening deck of stable chiral NHC-ligand precursor salts and NaO*t*Bu for the *in situ* generation of the free carbene (Table 1). The parent imidazol-2-ylidene ligand **L1** (Ar=Ph, R^1=H) gave **2a** with 49 % yield and 38:62 enantiomeric ratio, favoring the (*R)*-enantiomer (entry 1). Ligands **L2** (R^1=Cl) and **L3** (R^1=Me) with a substituted imidazol-2-ylidene backbone showed no improvement (entries 2 and 3). Using acenaphthoimidazolylidene-derived **L4** resulted in a sluggish reaction with an almost racemic product **2a** (entry 5). The saturated dihydroimidazol-2-ylidene analog **L5** having otherwise the same substituents of **L1** gave **2a** in similar yield, but intriguingly with a 62:38 selectivity favoring the *opposite* (*S*)-enantiomer (entry 4). We continued the ligand survey with modifications on the aryl side-arms of **L1** and **L5**.[19] 3,5-Xylyl-bearing ligand **L6** gave **2a** in 61 % yield and with 70:30 er in favor of the (*S*)-enantiomer (entry 6). Again, increasing the bulk from **L1** to **L6** *reversed* the enantioselectivity. We wondered if these unusual reversal effects induced by the side-arm bulk and core saturation would be additive and designed **L7**, a dihydroimidazol-2-ylidene version with 3,5-xylyl groups. Indeed, using **L7** improved the (*S*)-preference to 85:15 er (entry 7). This trend could be further reinforced by replacing the 3,5-xylyl units with sterically more demanding 3,5-di-*tert*-butyl phenyl groups (**L8**). Cyclized product **2a** was obtained in 93:7 er (entry 8). Additional benefit of **L8** was its much higher reactivity resulting in complete conversion of **1a**, 93 % yield of **2a** and complete *endo*-selectivity in the cyclization. An X-ray crystal structure analysis of the hydrochloride salt of **L8** provides a good visual of the $A_{1,3}$-strain minimized structure and of the shielding generated by the very bulky 3,5-di-*tert*-butyl phenyl groups (Figure 2).[26] Replacement of the methyl group at the R^2-position of the ligand scaffold by an electron donating methoxy group (**L9**) or a bulky *tert*-butyl group (**L10**) had very little effect on the reaction performance (entries 9-10). In contrast, omission of this substituent (R^2=H, **L11**) significantly reduced the conversion, yield and enantioselectivity of the reaction (entry 11). Carbene **L8** allowed as well for a reaction temperature of 60 °C, which slightly increased the enantioselectivity (entry 12). Switching the solvent to trifluorotoluene improved the enantiomeric ratio to 95:5 (entry 13) and enabled a reduction in catalyst loading to 5 mol% without any loss in reactivity and selectivity (entry 14).

Table 1. Optimization of the enantioselective indole C-H cyclization[a]



Entry	L*	Solvent	T, °C	% conv.[b]	% yield[b]	er[c]
1	**L1**	PhMe	80	59	49	38:62
2	**L2**	PhMe	80	76	0	-
3	**L3**	PhMe	80	80	54	43:57
4	**L4**	PhMe	80	58	47	62:38
5	**L5**	PhMe	80	50	25	52:48
6	**L6**	PhMe	80	84	61	70:30
7	**L7**	PhMe	80	78	57	85:15
8	**L8**	PhMe	80	100	93	93:7
9	**L9**	PhMe	80	100	85	92:8
10	**L10**	PhMe	80	100	95	91:9
11	**L11**	PhMe	80	55	45	80:20
12	**L8**	PhMe	60	100	94	94:6
13	**L8**	$PhCF_3$	60	100	93	95:5
14[d]	**L8**	$PhCF_3$	60	100	91	95:5

[a] Reaction conditions: 0.05 mmol **1a**, 10 mol% $Ni(cod)_2$, 11 mol% **L***·HCl, 50 mol% NaO*t*Bu, 0.25 M, 24 h. [b] Determined by ^{1}H NMR with an internal standard. [c] Determined by HPLC analysis with a chiral stationary phase. [d] With 5 mol% $Ni(cod)_2$, 5.5 mol% **L8**·HCl, 25 mol% NaO*t*Bu, 0.5 M, 24 h.

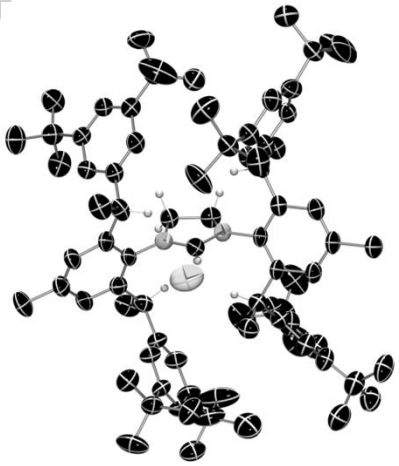
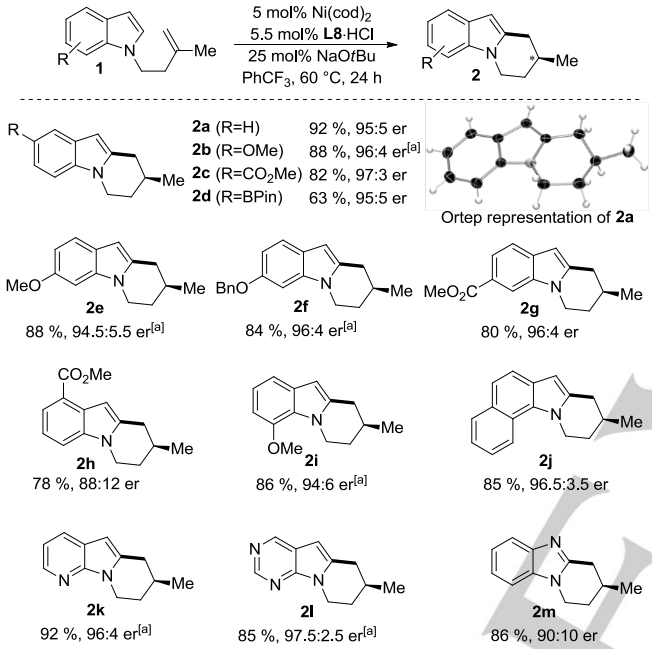


Figure 2. X-ray crystal structure of **L8**·HCl (the majority of the hydrogen atoms are omitted for clarity).

With the optimized reaction conditions, the scope of the enantioselective cyclization was evaluated (Scheme 2). A variety of 5-substituted indoles underwent cyclization smoothly and gave tetrahydropyridoindoles **2** with excellent enantioselectivities. Although both electron-donating (**1b**) and electron-withdrawing (**1c**) groups provide almost identical selectivity, **1b** reacts slower and requires a higher catalyst loading. In terms of functional group tolerance, the B(pin)-group of **1d** remained untouched. Substituents at the 6- and 7-position of the indole core do not alter the reaction performance (**1e**-**1g**, **1i**). An ester moiety in the

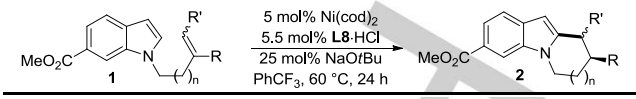
4-position induces a small drop in the enantioselectivity.[27] X-Ray crystal structure analysis of **2a** allowed determination of its absolute configuration.[26] Noteworthy, in addition to indoles, other pharmaceutically relevant azaheterocycles such as pyrrolopyridine **1k** and pyrrolopyrimidine **1l** engaged in the cyclization. No potential detrimental effect of the coordinating nitrogen atom on the reaction performance was observed and the corresponding cyclization products **2k** and **2l** were obtained in excellent yields and enantioselectivities. The more C–H acidic benzimidazole, a substrate considered as more facile for C–H funtionalizations,[21,28] also underwent selective *endo*-cyclization using our catalyst system.

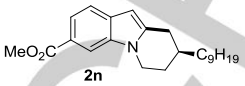
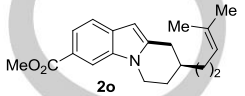
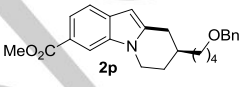
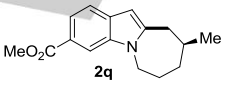
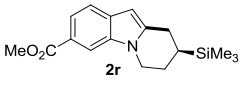
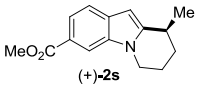
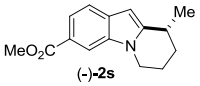


Scheme 2. Enantioselective C–H functionalization of indoles and related aza-heterocycles. Reaction conditions: 5 mol% $Ni(cod)_2$, 5.5 mol% **L8**·HCl, 25 mol% NaO*t*Bu, 0.5 M in $PhCF_3$ at 60 °C for 24 h. [a] With 10 mol% $Ni(cod)_2$, 11 mol% **L8**·HCl, 50 mol% NaO*t*Bu.

Concerning the substitution pattern and length of the alkenyl tether of **1**, longer alkyl chains R, additionally decorated with a second alkene moiety or a benzyl ether, reacted very well and provided products **2n**-**2p** in excellent yield and enantioselectivities (Table 2, entries 1-3). The formation of the seven-membered ring system of **2q** *via* an eight-membered nickelacycle intermediate proceeded smoothly, albeit in moderate enantioselectivity (entry 4).[29] Indole **1r** with trimethylsilyl-bearing alkene cyclized under standard conditions in high yields. The enantioselectivity of product **2r** was attenuated, presumably as a result of the bulky silyl group located directly at the formed stereogenic center (entry 5). Besides 1,1-disubstitued olefins, internal 1,2-substituted olefins such as (*E*)-**1s** smoothly cyclized delivering (+)-**2s** in good yield and enantioselectivity (entry 6). The reaction of *cis*-configured olefins such as (*Z*)-**1s** is less selective, both in terms of enantioselectivity and *exo*/*endo* cyclization ratio.[30]

Table 2. Enantioselective cyclization of indoles with substituted alkenes.[a]

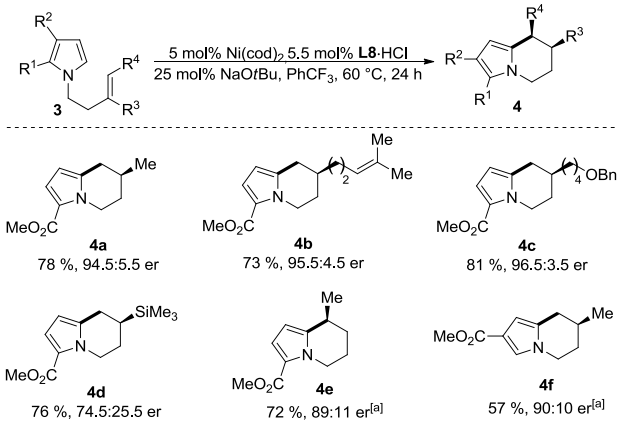


Entry	1	2	% yield	er
1	**1n**	 **2n**	80	97:3
2	**1o**	 **2o**	83	96.5:3.5
3	**1p**	 **2p**	84	97:3
4	**1q**	 **2q**	82	75:25
5	**1r**	 **2r**	86	83.5:16.5
6	(*E*)-**1s**	 (+)-**2s**	84[b]	90.5:9.5
7	(*Z*)-**1s**	 (-)-**2s**	78[c]	33:67

[a] 5 mol% $Ni(cod)_2$, 5.5 mol% **L8**·HCl, 25 mol% NaO*t*Bu, 0.5 M in $PhCF_3$ at 60 °C for 24 h, isolated yield; [b] 10:1 *endo/exo* cyclization ratio [c] 5:1 *endo/exo* cyclization ratio.

Moreover, pyrroles were found to be competent substrates, enabling access to valuable tetrahydroindolizine scaffolds.[31] Noteworthy, reports on asymmetric C–H functionalizations of the C2-position of pyrrole are scarce. They are either limited in scope, or deliver the product in modest enantioselectivity.[14, 32] The inherent high reactivity of the pyrrole scaffold is challenging and frequently leads to undesired side products.[33] Annulations capitalizing on the high nucleophilicity of pyrrole have been realized enantioselectively.[34] Such Friedel-Crafts pathways deliver branched *exo*-cyclization products governed by the higher stability of 2° carbenium-ions. In contrast, we observed a complementary *endo*-cyclization reactivity which is in accordance with the mechanistic proposals for nickel-catalyzed hydroarylations.[35] Moreover, this mechanism is supported by deuterium-transfer experiments. Reaction with $[D]_1$-**1a** resulted in a complete deuteration of the stereogenic carbon atom. No intermolecular cross-over deuteration was observed (see SI for details). For example, electronically toned-down pyrroles **3** reacted faster and yielded exclusively *endo*-cyclization product **4** (Scheme 3). 2-Methyl ester bearing pyrroles **3a**-**3c** underwent

C–H annulation in good yields and with excellent enantioselectivity. As previously noted, substrates with a bulky alkenyl trimethylsilane group gave product **4d** with lower enantioselectivity. Substrate **3e** having a *trans*-configured 1,2-disubstituted olefin cyclized in good yield. Pyrrole **3f**, bearing the methyl ester at the 3-position engaged equally well in the cyclization, leading to a 3:1 mixture of the 5- (**4f**) and 2-annulated (**4f'**) products. The sterically more accessible 5-position was clearly favored and **4f** was isolated in 57% yield.



Scheme 3. Enantioselective C–H functionalization of pyrroles. Reaction conditions: 5 mol% $Ni(cod)_2$, 5.5 mol% **L8**·HCl, 25 mol% NaO*t*Bu, 0.5 M in $PhCF_3$ at 60 °C for 24 h; [a] with 10 mol% $Ni(cod)_2$, 11 mol% **L8**·HCl, 50 mol% NaO*t*Bu.

In conclusion, we have reported highly enantioselective Ni(0)-catalyzed C−H functionalizations of indoles and pyrroles without the need for the typical Lewis-basic directing groups. The reaction provides access to synthetically relevant tetrahydropyridoindoles and tetrahydroindolizines. Key for the success of the activation and selectivity in the cyclization was the development of a new chiral SIPr ligand analogue with very bulky flanking groups. The work showcases the benefits of the broad modularity of this chiral carbene ligand class and further underlines its potential as a general ligand system in different catalytic enantioselective transformations.

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Keywords: Asymmetric Catalysis • Nickel • Chiral NHC ligands • C–H Activation • Heterocycles

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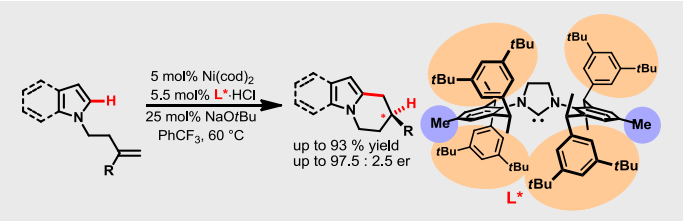

An enantioselective directing-group free Ni(0)-catalyzed C–H functionalization of indoles provides access to tetrahydropyridoindoles and tetrahydroindolizines in high yields and enantioselectivities under mild reaction conditions. The activation and selective cyclization is enabled by a novel chiral SIPr carbene ligand analogue with very bulky flanking groups.

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