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Nickel-Catalyzed Enantioselective Pyridone C−H Functionalizations Enabled by a Bulky *N*-Heterocyclic Carbene Ligand

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Supporting Information

ABSTRACT: Annulated pyridones are an important scaffold found in many biologically active compounds. A Ni(0)-catalyzed C−H functionalization of 2- and 4-pyridones is disclosed, providing access to annulated pyridones via enantioselective intramolecular olefin hydroarylation. Key to the success of the transformation was the development of a sterically hindered and tunable *N*-heterocyclic carbene ligand resembling a chiral version of IPr. This ligand allows for mild reaction temperatures, and leads to the annulated pyridones in excellent yields and enantioselectivities.

The 2-pyridone ring is a prevalent heteroaromatic structure that is found in a broad variety of natural products, bioactive agents and approved drugs.[1] These include ciclopirox, campthotecin, cytisine, leuconicine A and fredericamycin (Figure 1).[2] In addition, isomeric 4-pyridones are an attractive scaffold, displaying different biological activities.[3] Prominent examples are fluoroquinolone antibiotics (e.g., levofloxacin)[4] and the integrase inhibitor bictegravir.[5]

In this respect, many methods for the construction and modification of the pyridone system have been developed.[6] Over the past decade, rapid advances in C−H functionalization technology[7] have been demonstrated to be of utility for the preparation of functionalized pyridones.[8] Moreover, progress in controlling site selectivity of pyridone functionalization has been made. However, synthetically valuable enantioselective methods for pyridone functionalization remain scarce, and pose an excellent challenge for asymmetric catalysis. Along the same lines, nickel(0)-catalyzed enantioselective C−H functionalizations are very rare and underdeveloped.[9] We previously demonstrated *exo*- and *endo*-control of cyclization by choice of the ancillary ligand with a nickel catalyst (Scheme 1).[10] However, any synthetically useful control of enantioselectivity proved elusive, and has remained an excellent challenge for chiral carbene ligands. Herein, we report a modular class of chiral *N*-heterocyclic carbenes (NHCs) aiming to mimic the privileged ligand IPr, and illustrate its potential in a nickel(0)-catalyzed enantioselective C−H functionalization approach to pyridones.

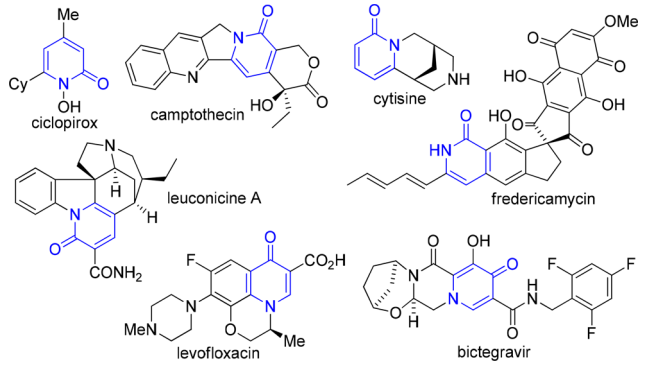
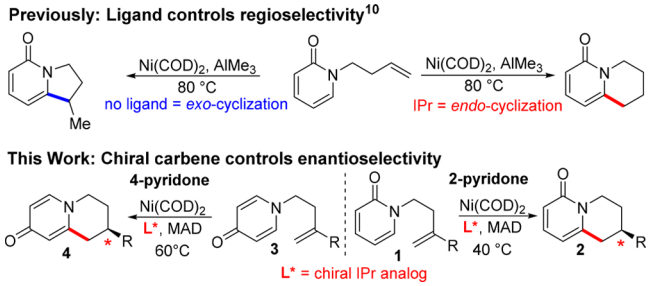


Figure 1. Examples of natural products and pharmaceuticals possessing a 2- or 4-pyridone ring.

Scheme 1. Introducing Enantioselectivity in Pyridone C−H Functionalizations



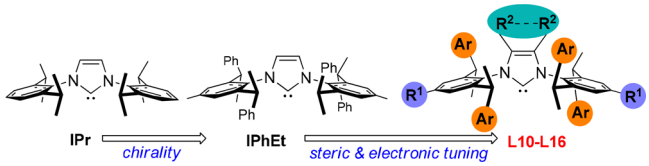


Figure 2. Evolving IPr into a sterically and electronically flexible chiral version.

Chiral NHCs have become more common in asymmetric catalysis,[11] in particular nickel(0)-catalyzed transformations,[12] pairing steric and electronic tunability with an appreciated robustness of monoligated transition-metal species. The development of our enantioselective *endo*-cyclization was initiated with methyl-substituted pyridone **1a** using $Ni(COD)_2$ in combination with trimethyl aluminum as enabling Lewis acid,[13] and a chiral NHC as steering ligand (Table 1). At first, common established chiral NHCs were surveyed. Typical members of the C_2-symmetric α-chiral family such as **L1**[14] and **L2**[15] gave only marginal conversions (Entries 1 and 2).

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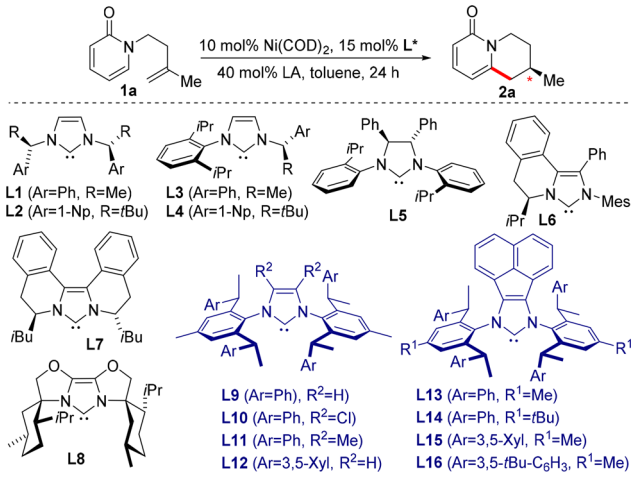
Table 1. Ligand Screening and Reaction Optimization[a]

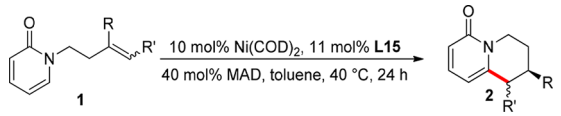


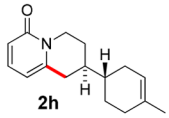
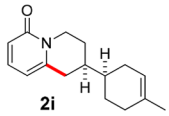
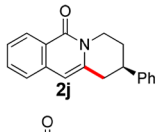
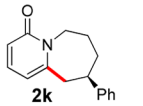
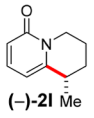
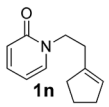
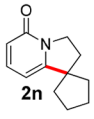
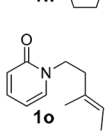
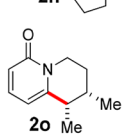
Entry	L*	LA	T (°C)	% yield (% conv.)[b]	er[c]
1	**L1**	$AlMe_3$	80	7 (7)	59.5:40.5
2	**L2**	$AlMe_3$	80	4 (7)	73:27
3	**L3**	$AlMe_3$	80	90 (95)	53:47
4	**L4**	$AlMe_3$	80	79 (79)	59:41
5	**L5**	$AlMe_3$	80	72 (83)	51:49
6	**L6**	$AlMe_3$	80	70 (100)	78.5:21.5
7	**L7**	$AlMe_3$	80	30 (40)	61:39
8	**L8**	$AlMe_3$	80	20 (25)	79:21
9	**L9**	$AlMe_3$	60	95 (100)	82:18
10	**L9**	$AlMe_3$	40	46 (46)	85:15
11	**L9**	$AlMe_2Cl$	40	<5 (20)	
12	**L9**	$B(C_6F_5)_3$	40	75 (100)	81:19
13	**L9**	MAD	40	95 (100)	88:12
14	**L10**	MAD	40	94 (100)	92:8
15	**L11**	MAD	40	71 (100)	84:16
16	**L12**	MAD	40	95 (100)	91:9
17	**L13**	MAD	40	74 (100)	90:10
18	**L14**	MAD	40	51 (76)	81:19
19	**L15**	MAD	40	83 (100)	96:4
20	**L16**	MAD	40	73 (100)	85:15

[a]50 μmol **1a**, 5.0 μmol $Ni(COD)_2$, 7.5 μmol **L***, 20 μmol LA, 0.25 M in toluene at the indicated temperature for 24 h; [b]determined by ^1H NMR with internal standard; [c]determined by HPLC analysis with a chiral stationary phase.

Replacing one flanking chiral group with a bulky 2,6-diisopropyl phenyl unit[12c] gave product **2a** in very high yield but poor enantioselectivity (Entries 3 and 4). Saturated NHCs such as **L5**, drawing their chirality from a C_2-symmetric backbone,[16] gave almost racemic product (Entry 5). Although Hong's isoquinoline-based ligand[17] provided **2a** in 70% yield and 78.5:21.5 er (Entry 6), it failed further optimization. Other popular carbenes such as **L7**[18] and **L8**[19] were not satisfactory (Entries 7–8). Although none of these common carbene ligands proved suitable, our results indicated the importance of at least one bulky aryl nitrogen substituent for high levels of reactivity. Thus, we proposed that an effective chiral version of IPr, the gold-standard carbene, may not only be useful for this transformation but for a large variety of asymmetric reactions (Figure 2). We turned our attention to **L9** (IPhEt), a carbene reported by Gawley.[20] Despite inducing high enantioselectivity in copper-catalyzed hydrosilylations, it has remained largely unnoticed, notably even being excluded in reviews of chiral carbene ligands.[11] **L9** provided the expected high reactivity,

Table 2. Scope for 2-Pyridones 1[a]



Entry	1	2	% yield[b]	er[c]
1	**1a**	**2a** (R=Me, R'=H)	83	96:4
2[d]	**1b**	**2b** (R=Ph, R'=H)	80	99:1
3[e]	**1b**	**2b**	74	94:6
4[f]	**1b**	**2b**	84	99:1
5[d]	**1c**	**2c** (R=PMP, R'=H)	75	99:1
6	**1d**	**2d** (R=4-CF_3-C_6H_4, R'=H)	61	99:1
7	**1e**	**2e** (R=2-Me-C_6H_4, R'=H)	71	96:4
8	**1f**	**2f** (R=2-Naphthyl, R'=H)	79	99:1
9[g]	**1g**	**2g** (R=1-furyl, R'=H)	80	96:4
10	**1h**	 **2h**	90	97.5:2.5
11	**1i**	 **2i**	86	98.5:1.5
12[h]	**1j**	 **2j**	87	99:1
13	**1k**	 **2k**	82	95:5
14[g]			82	82:18
15[e,g]	(*Z*)-**1l**	 **(+)-2l**	32	75:25
16[f,g]			52	83.5:16.5
17[g]	(*E*)-**1l**	 **(−)-2l**	66	87:13
18[g]	(*E*)-**1m**	 **2m**	77	50:50
19[g]	 **1n**	 **2n**	74	-
20[h]	 **1o**	 **2o**	42[i]	89:11

[a]0.10 mmol **1**, 10.0 μmol $Ni(COD)_2$, 11 μmol **L15**, 40 μmol MAD, 0.25 M in toluene at 40 °C for 24 h; [b]isolated yield; [c]er determined by HPLC analysis with a chiral stationary phase; [d]at 23 °C; [e]with **L9**; [f]with **L12**; [g]at 60 °C; [h]at 80 °C; [i]*cis*/*trans* 11:1.

which was pleasingly paired with a selectivity of 82:18 (Entry 9). Importantly, it displayed an enhanced reactivity allowing

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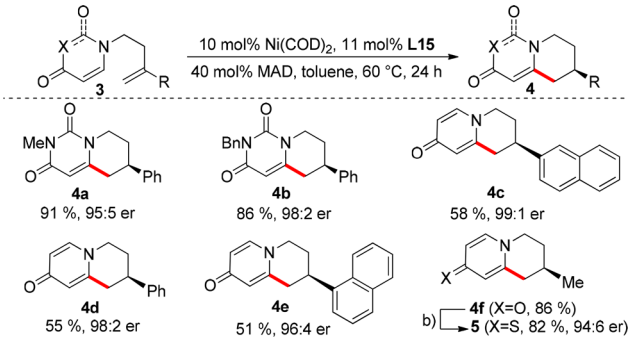
Scheme 2. Scope for 4-Pyridones 4[a]



[a]0.10 mmol **3**, 10.0 μmol Ni(COD)$_2$, 11 μmol **L15**, 40 μmol MAD, 0.25 M in toluene at 60 °C for 24 h, isolated yield, er determined by HPLC analysis with a chiral stationary phase; (b) Lawesson's reagent, toluene, 110 °C for 1 h.

reduction of the reaction temperature. A survey of other Lewis-acids (Entries 11−13) revealed the superiority of MAD,[21] enabling the reaction to proceed at 40 °C with 95% yield and 88:12 er.

With the otherwise optimized reaction parameters, we returned to the task of ligand design. Both enantiomers of the chiral aniline precursors required for **L9** are accessible by enantioselective hydrogenation (see SI for details).[22] This attractive feature allows for a convenient preparation of structural analogs. Intrigued by the large modification potential that this carbene architecture offers, we synthesized analogs **L10**−**L16** to probe the influence of the different substitution locations. We first introduced groups R^2 on the backbone of the imidazolydene ring, hypothesizing they could slightly push the flanking groups toward the metal center (Entries 14 and 15, 17). Both chloride groups (**L10**) and the acenaphthoimidazolylidene[23,24] framework (**L13**) improved the selectivity. The sterics of position R^1 also turned out to be relevant. Replacing the standard methyl group by a bulkier *tert*-butyl unit reduced significantly the yield and selectivity (Entry18). Replacement of the aromatic side arms for larger than phenyl groups required a new route to access the corresponding chiral aniline precursors (see SI). Introduction of 3,5-xylyl groups (**L12** and **L15**) increased the enantioselectivity of **2a** with both backbones (Entries 16 and 19). Attempts to further enhance the selectivity of the ligand **L15** by using even bulkier 3,5-di-*tert*-butyl phenyl groups (**L16**) resulted in a drop in the observed er (Entry 20).

Subsequently, the scope of the transformation was investigated with a range of 2-pyridones **1** (Table 2). In addition to alkyl groups, a variety of aromatic substituents R were tested (Entries 2−9). Electron-donating and withdrawing groups, as well as sterically more demanding examples, such as an *ortho*-tolyl group, have little influence on the reaction performance. In several cases, the reaction proceeds smoothly at room temperature. Condensed arenes and heterocycles perform well (Entries 8 and 9). As exemplified by chiral substrates **1h** and **1j**, the selectivity of the transformation is fully catalyst-controlled (Entries 10 and 11). Moreover, isoquinolones are suitable substrates, giving **2j** in high yield and selectivity (Entry 12). The cyclization works equally well to form 7-membered products (Entry 13). *Cis*- or *trans*-1,2-disubstituted olefins cyclize well, albeit with lower selectivity (Entries 14, 17). In the case of styrene derivative **1m**, racemic product **2m** was formed, possibly involving a configurationally

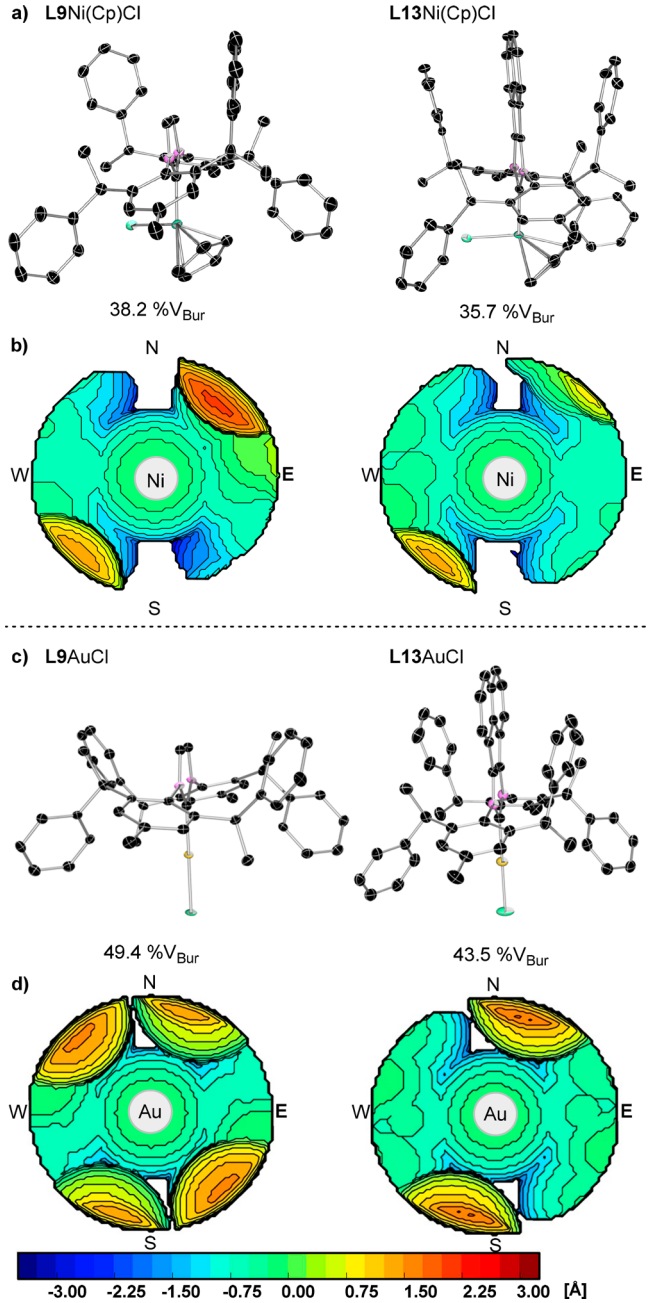


Figure 3. (a) X-ray crystal structures of **L9**Ni(Cp)Cl, **L13**Ni(Cp)Cl and their buried volumes. (b) Corresponding steric maps.[27] (c) Structures of **L9**AuCl and **L13**AuCl and their buried volumes. (d) Corresponding steric maps. Sphere radius 3.5 Å, bond length Metal-C_{NHC} 2.0 Å, mesh spacing = 0.1 Å.

labile benzyl nickel intermediate (Entry 18). Cyclic trisubstituted olefin **1n** underwent *exo*-cyclization giving spirocyclic product **2n** (Entry 19), whereas acyclic **1o** selectively cyclized in *endo*-fashion to give **2o** with a dr of 11:1 (Entry 20). **L15** allowed preserving the double bond geometry whereas the racemic reaction with IPr gave 32% of **2o** as a 2:1 dr mixture. Moreover, for substrates **1b** and (*Z*)-**1l** reactions were additionally performed with ligands **L9** and **L12** (Entries 3, 4 and 15, 16). **L15** always performed best, in particular for the more challenging alkyl-containing substrates.

Moreover, uracil derivatives **3a** and **3b** reacted with similar efficiency, forming cyclized products **4a** and **4b** with excellent

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yields and enantioselectivities (Scheme 2). This prompted us to explore the reactivity of 4-pyridones lacking the additional carbonyl group. Pleasingly, previously failed[10] aryl- as well as alkyl-substituted 4-pyridones **3c**−**3f** cyclized in analogous fashion with up to 99:1 er. Additionally, the carbonyl group of the products can be exchanged with Lawesson's reagent, providing access to thiopyridone **5**, allowing for a determination of the enantioselectivity.

Analogously to IPr, the chiral carbenes are stable and can be isolated (see SI for X-ray crystal structure of **L9**). Trisubstituted Ni-complexes are believed to play a key role in the LLHT (ligand-to-ligand-hydrogen transfer)[25] and hence have a bearing on the enantiodetermining step. To develop an understanding of the selectivity improvement obtained by the backbone modifications, we prepared Ni^{II}-complexes **L9**Ni(Cp)Cl and **L13**Ni(Cp)Cl for which X-ray crystal structures were obtained (Figure 3a).[26] Both complexes show in their steric map a pronounced C_2-symmetric binding pocket with accessible NW and SE quadrants (Figure 3b).[27] Notably, the structure of **L13**Ni(Cp)Cl shows stacking interactions of the flanking aryl arms with the acenaphthene ligand backbone resulting in a reduced percent buried volume (35.7% vs 38.2%). In consequence, the central metal becomes more accessible which may account for the observed increase in performance. Although, X-ray crystal structures of complexes with **L15** could not be obtained, we believe that an extension of the size of the aryl side arm further reinforces the observed quadrant accessibility of **L13**. Moreover, the corresponding X-ray crystal structures of Au^{I}-complexes **L9**AuCl and **L13**AuCl display with 49.4% and 43.5% a significantly higher percent buried volume than that of the corresponding nickel complexes (Figure 3c,d).[26] This highlights the flexibility of the ligand, capable of adjusting to the specific steric environment. Again, the acenaphthene backbone organizes the flanking aryl groups for an improved C_2-symmetric binding pocket.

In conclusion, we have reported highly enantioselective Ni(0)-catalyzed C−H functionalizations of 2- and 4-pyridones. Essential for the success of the transformation is the introduction of a class of sterically demanding chiral NHC ligands with large modulation opportunities based on Gawley's carbene. Their close relationship to the achiral gold-standard IPr ligand holds the promise of enabling further catalytic enantioselective transformation with different transition metals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01181.

Synthetic procedures, characterization data for all new compounds (PDF)
Data for **2j** (CIF)
Data for **L9** (CIF)
Data for **L9**Ni(Cp)Cl (CIF)
Data for **L13**Ni(Cp)Cl (CIF)
Data for **L9**AuCl (CIF)
Data for **L13**AuCl (CIF)

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Notes

The authors declare no competing financial interest.

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