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Modular Chiral *N*-Heterocyclic Carbene Ligands for the Nickel-Catalyzed Enantioselective C–H Functionalization of Heterocycles

Johannes Diesel[§] and Nicolai Cramer*

[§]SCS-DSM Award for best poster presentation in Organic Chemistry

Abstract: *N*-Heterocyclic carbenes (NHCs) are the ligands of choice in a large variety of transformations entailing different transition metals. However, the number and variety of chiral NHCs suitable as stereo-controlling ligands in asymmetric catalysis remains limited. Herein we highlight the introduction of a modular NHC ligand family, consisting of a chiral version of the widely used IPr ligand. These chiral NHC ligands were applied in the nickel-catalyzed enantioselective C–H functionalization of *N*-heterocycles. Nickel-NHC catalysis unlocked the stereoselective C–H annulation of 2- and 4-pyridones, delivering fused bicyclic compounds found in many biologically active compounds. Applying a bulky, yet flexible ligand scaffold enabled the highly enantioselective C–H functionalization of pyridones under mild conditions. The introduction of a bulky chiral SIPr analogue enabled the nickel-catalyzed enantioselective C–H functionalization of indoles, yielding valuable tetrahydropyridoindoles. Additionally, pyrrolopyridines, pyrrolopyrimidines and pyrroles were efficiently functionalized, delivering chiral annulated azoles.

Keywords: Asymmetric catalysis · Carbenes · C–H Functionalization · NHC · Nickel

Johannes Diesel studied chemistry at Leipzig University and at Ohio University as a DAAD ISAP fellow. During the final year of his studies he moved to Basel to join the Roche pRED team as a medicinal chemistry intern. In 2015 he graduated with a MSc in Chemistry, having worked in the Schneider group at Leipzig University. He then moved back to Switzerland for his doctoral studies in the Cramer group in August 2015, where he earned his PhD developing new chiral NHC ligands for asymmetric catalysis. In February 2020, he joined the MacMillan group at Princeton University as an SNF Postdoctoral Fellow.

Chiral *N*-Heterocyclic Carbene Ligands for Asymmetric Transition-Metal Catalysis

Over the last two decades, different scaffolds of chiral monodentate *N*-heterocyclic carbene ligands have been developed (Fig. 1).[1] In 1996, Hermann and co-workers introduced chiral NHC-rhodium complexes, which enabled in proof of concept studies, the enantioselective hydrosilylation of ketones. The applied NHC ligands drew their stereoinformation from chiral *N*-alkyl substituents.[2] Kündig and co-workers later introduced important side arm modifications of this ligand scaffold.[3] In 2001, Grubbs and co-workers introduced chiral NHCs, drawing their chirality from the chiral backbone substitution on the *N*-heterocycle.[4] A variety of backbone and side arm modifications of this ligand scaffold has allowed for applications in conjugation with different transition metals.[5] Additionally, bicyclic or tricyclic chiral NHCs have been successfully applied in asymmetric catalysis.[6] These commonly utilized chiral NHC ligands have different limitations. The free carbenes suffer from low stability and have to be generated *in situ*, or a transition metal complex has to be prepared. Furthermore, the existing ligand scaffold only provide limited modification opportunities, making the efficient synthesis of analogues challenging.

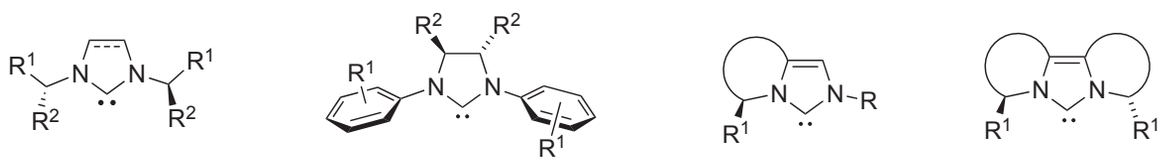


Fig. 1. Common scaffolds of monodentate chiral NHC ligands.

*Correspondence: Prof. Dr. N. Cramer, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSA, BCH 4305, CH-1015 Lausanne, E-mail: nicolai.cramer@epfl.ch

Modular Chiral NHC Ligands Based on the IPhEt Scaffold

One of the most widely applied achiral NHC ligands is IPr, which was first introduced by Nolan in 1999 (Fig. 2).[7] A chiral ligand scaffold retaining the excellent properties of IPr would therefore enable a variety of asymmetric transformations. In 2011, Gawley introduced IPhEt, which merges the IPr scaffold with IPr*[8] under the generation of four stereocenters.[9] At the outset of our work, the ligand had only been applied in an highly enantioselective copper-catalyzed hydrosilylation,[10] and had remained largely unnoticed since.[11] We realized the potential this ligand scaffold has to offer and proposed different sites of modification to obtain a powerful chiral ligand family. A large impact on the ligand properties was expected by backbone modifications (Fig. 2, green), influencing both electronic and steric properties. Additional electronic tuning was envisioned by different *para*-substitution on the aniline cores (Fig. 2, violet). Modification of the aryl side arms at the stereocenters was expected to have large implications on the shape of the binding pocket of a potential NHC-metal complex (Fig. 2, orange).

Main building blocks for the synthesis of the IPr^X ligands are chiral anilines **1**, which can be condensed with different 1,2-dicarbonyl compounds **2** and cyclized with a C1 compound (Scheme 1).[12] Enantioselective rhodium-catalyzed hydrogenation delivered a variety of differently substituted chiral anilines **1** with high stereocontrol (Scheme 1a).[13] Friedel-Crafts type alkenylation proceeded smoothly for electron-rich anilines **4** in combination with phenylacetylene **5** (Scheme 1b).[9] However, the scope of this transformation is limited and we developed a different route to access dialkenyl anilines **3** (Scheme 1c). Highly regioselective nickel-catalyzed hydroalumination of alkynes **6** and subsequent transmetalation delivered α-vinyl boronates **8**,[14] which could be used in a twofold Suzuki cross-coupling with dibromo-aniline **9** to deliver a broad variety of anilines **3**.

Nickel-catalyzed Enantioselective C–H Functionalization of Pyridones[12]

Previously, our group reported on the regioselective C–H annulation of pyridones.[15] In particular, the application of a nickel-NHC catalyst enabled the *endo*-selective cyclization of 2-pyridones **11** (Scheme 2). Annulated pyridones are valuable structural motifs found in a variety of natural products, including cytisine[16] and leuconicine A.[17] Furthermore, 4-pyridones are prevalent scaffolds in bioactive compounds and marketed drugs, such as the integrase inhibitor bictegravir and the antibiotic levofloxacin.[18] We envisioned an enantioselective C–H functionalization of pyridones **11** and **12** by applying chiral NHC ligands.

The initial ligand survey (Table 1) was commenced by applying the previously reported conditions for the *endo*-selective pyridone annulation.[15] Ni(cod)$_2$ served as nickel(0)-source and AlMe$_3$ was used as Lewis acid co-catalyst in toluene at 80 °C. First, we applied NHCs containing chiral *N*-alkyl substituents. **L1** gave a very low conversion and enantioselectivity (Entry 1). Using Kündig's modification of this chiral carbene family (**L2**), the selectivity could be improved, but the conversion remained low (Entry 2).[3b,19] Replacing one of the chiral *N*-alkyl substituents with a bulky 2,6-diisopropyl phenyl group[20] as in **L3** and **L4**, significantly improved the conversion of the reaction and the product was obtained in high yield, but with poor enantioselectivity (Entries 3 and 4). Hong's carbenes (*e.g.* **L5** and **L6**)[6a,21] only gave promising results for the C_1-symmetric versions. **L6** delivered the annulated pyridone **10** in good yield and enantioselectivity (Entry 6), but was not susceptible to further optimization. Using the widely applied NHC **L7**, containing a chiral ligand backbone,[22] gave the product in good yield, but with marginal stereoinduction (Entry 7). From this survey of commonly used chiral NHC ligands, we learned that for high levels of reactivity, at least one *N*-aryl substituent is required in the ligand scaffold. Gawley's carbene IPhEt, which matches the achiral IPr closely, seemed to provide the ideal ligand scaffold. Indeed IPhEt delivered the expected high reactivity, paired with moderate enantioselectivity (Entry 8). Importantly, the reaction temperature could be reduced to 40 °C, without loss in reactivity, by applying the bulky Lewis acid MAD,[23] and **10a** was formed with a selectivity of 88:12 (Entry 9). Next, we focused on the ligand modification to achieve a highly enantioselective transformation. In an effort to push the flanking *N*-substituents closer to the metal center, thereby potentially providing a more pronounced chiral binding pocket, bulky groups were introduced on the ligand backbone (Entries 10–12). Chloride substitution (**L9**) and the acenaphthoimidazolylidene framework (**L12**) delivered **10** with improved enantioselectivity (Entries 10 and 12), while the introduction of methyl groups (**L10**) led to decreased selectivity (Entry 11). **L13** containing 3,5-xylyl groups enabled the formation of **10a** in 83% yield and a very high enantioselectivity of 96:4 (Entry 13). The positive influence of the side arm bulk on the selectivity is general, highlighted by the application of **L11** (Entry 14). Attempts to further increase the enantioselectivity by introducing 3,5-di-*tert*-butyl phenyl groups (**L15**) and *para*-*tert*-butyl groups on the aniline cores (**L13**) led to inferior results, showcasing that all the investigated modification positions have a bearing on the selectivity (Entries 15 and 16).

With the optimal conditions in hand, we evaluated the scope of the transformation (Scheme 3). Replacing one alkyl group of the 1,1-disubstituted alkene with a phenyl substituent gave

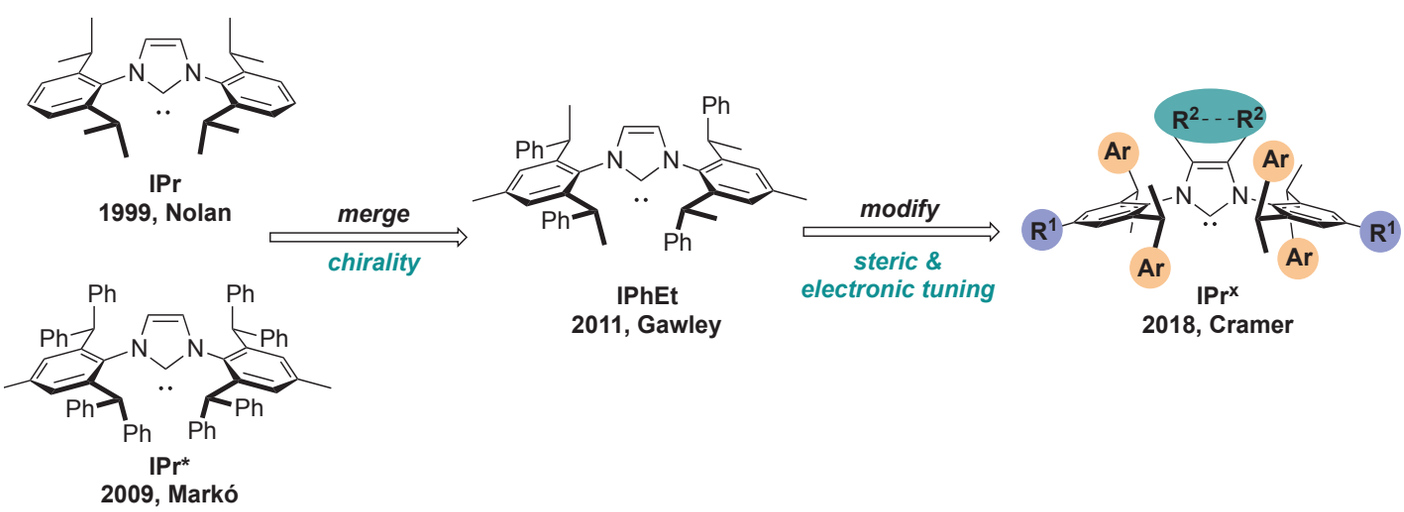
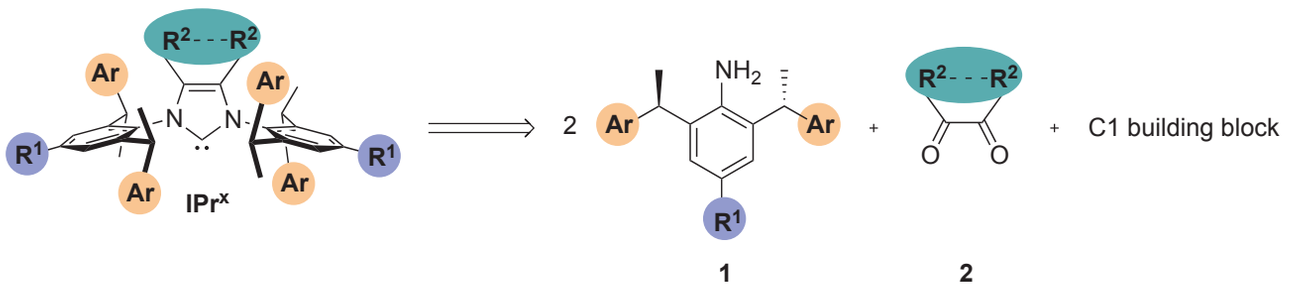


Fig. 2. Evolving IPr into a sterically and electronically flexible chiral version.



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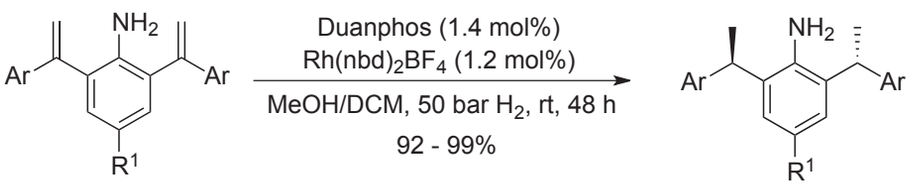

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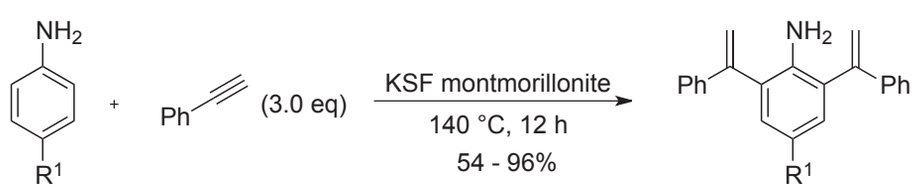

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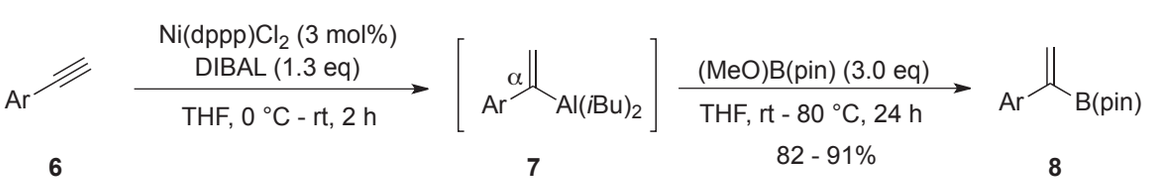
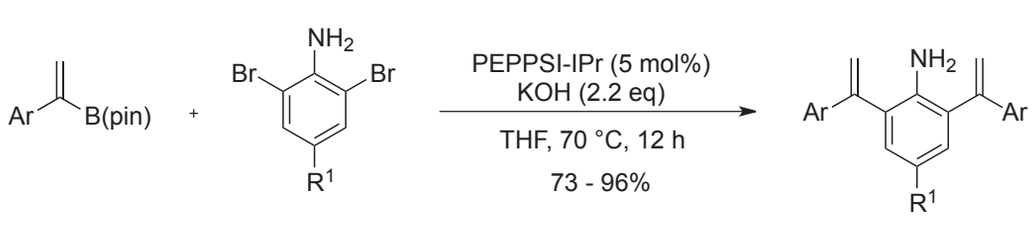
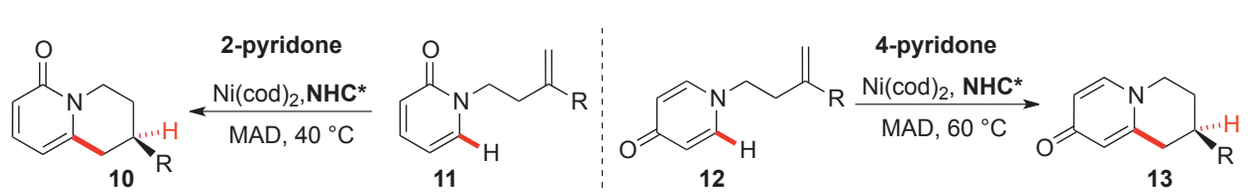
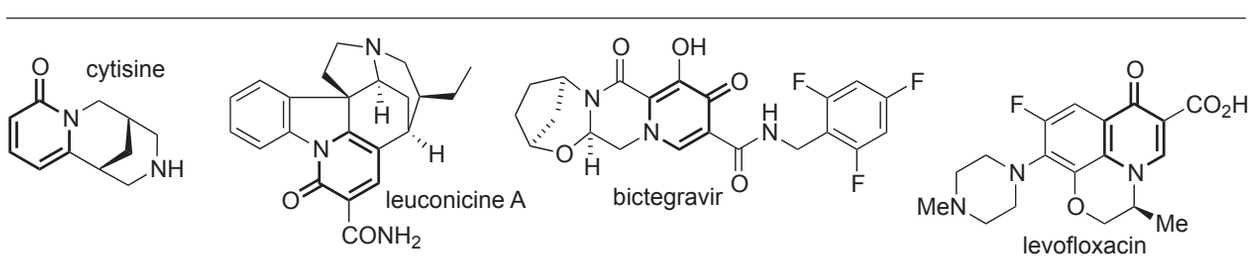




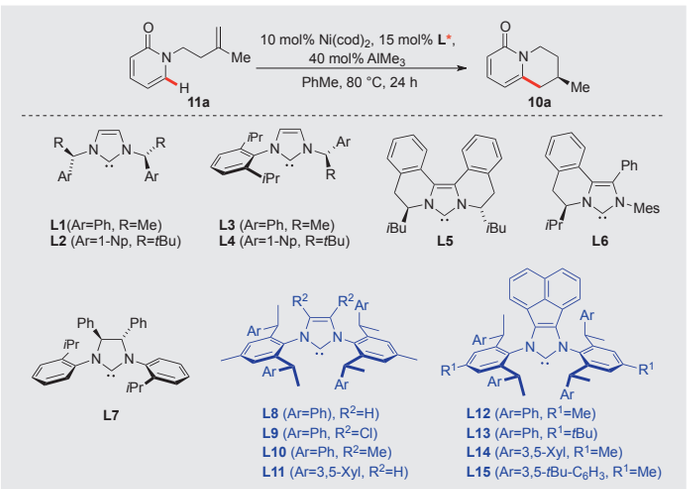
Scheme 1. Access to IPr^x ligand family using chiral aniline building blocks: a) Rh-catalyzed enantioselective hydrogenation of bis(alkenyl) anilines. b) Friedel-crafts-type alkenylation of anilines. c) Suzuki cross-coupling of α-vinyl boronates.





Scheme 2. Annulated pyridones *via* enantioselective nickel-catalyzed C–H functionalization.

Table 1. Ligand screening and development.



Entry	L*	% yield, (% conv.)[a]	er
1	**L1**	7 (7)	59.5:40.5
2	**L2**	4 (7)	73:27
3	**L3**	90 (95)	53:47
4	**L4**	79 (79)	59:41
5	**L5**	30 (40)	61:39
6	**L6**	70 (100)	78.5:21.5
7	**L7**	72 (83)	51:49
8	**L8 (IPhEt)**	95 (100)	69:31
9	**L8 (IPhEt)**	95 (100)	88:12
10[b]	**L9**	94 (100)	92:8
11[b]	**L10**	71 (100)	84:16
12[b]	**L12**	74 (100)	90:10
13[b]	**L14**	83 (100)	96:4
14[b]	**L11**	95 (100)	91:9
15[b]	**L15**	83 (100)	96:4
16[b]	**L14**	51 (76)	81:19

Conditions: 0.05 mmol **11a**, 10 mol% $Ni(cod)_2$, 15 mol% **L***, 40 mol% $AlMe_3$, 0.25 M in PhMe for 24 h at 80 °C. [a]Determined by ^{1}H-NMR with an internal standard. [b]At 40 °C and using 40 mol% MAD.

the annulated product **10a** in almost enantiopure form, and the reaction proceeded smoothly at room temperature. Both electron-donating and electron-withdrawing aryl-substituents were tolerated and had no influence on the er (**11b** and **11c**) and also a furanyl-containing substrate was converted efficiently (**11d**). Furthermore, the NHC-Ni system could catalyze the formation of a seven-membered ring in 95:5 er, *via* an intermediate eight-membered nickellacycle (**10e**). Additionally, isoquinolones were competent reactants at higher temperature, without loss in er (**11f**). Both starting material enantiomers of limonene derived substrates **11g** and **11h** were converted with excellent diastereoselectivities, highlighting that the reaction is fully under catalyst control.

Additionally, 4-pyridones and uracil derivatives **12** were also applied in this transformation (Scheme 4). Pleasingly, 4-pyridones were capable substrates when using our bulky chiral NHC ligands, while application of the IPr ligand led to a sluggish reaction. Aryl- and condensed arene-substituted olefins were converted in excellent enantioselectivities, albeit with lower product yields (**13a** and **13b**). Moreover, alkyl-substituted olefins reacted with good yields and high enantioselectivities (*e.g.* **12c**). The product **13c** was converted to the corresponding thiopyridone using Lawesson's reagent, enabling determination of the enantioselectivity of the highly polar 4-pyridone. Furthermore, highly functionalized uracil derivatives (**13d**) were annulated in high yields and excellent enantioselectivities.

Enantioselective Synthesis of Tetrahydropyridoindoles and Tetrahydroindolizines[24]

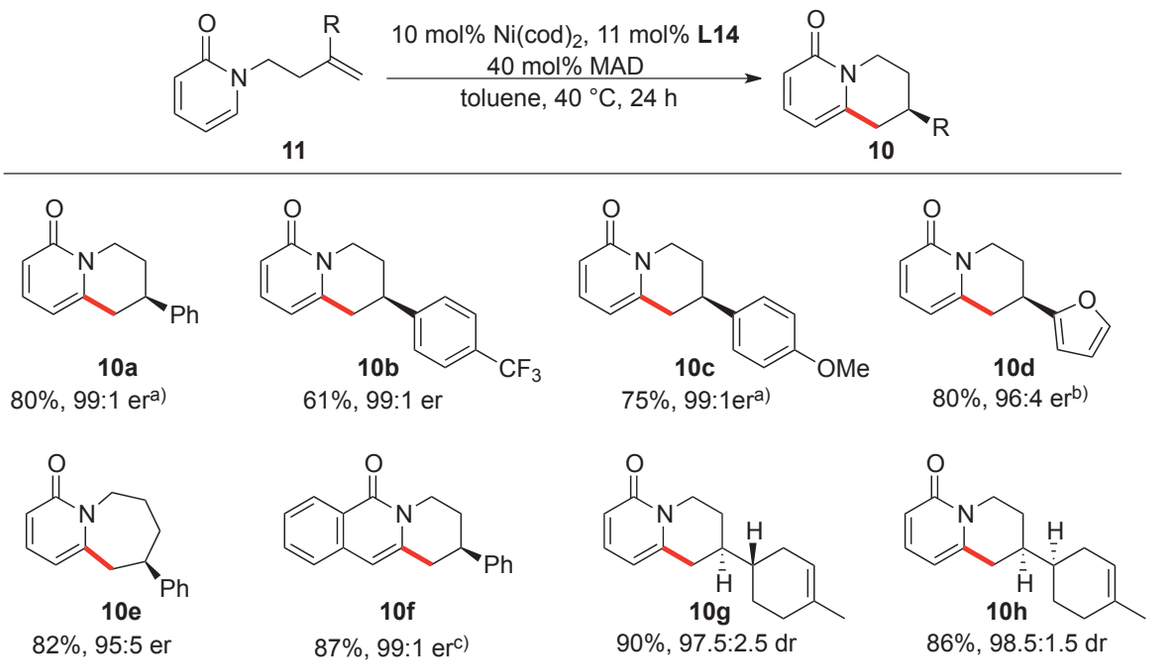
Indoles and pyrroles are prevalent structural motives in biologically active compounds. In particular, the tricyclic tetrahydropyridoindole scaffold can be found in numerous natural products, including alstoscholarisine A (Scheme 5).[25] Furthermore, 1,2-annulated indoles are present in pharmaceuticals, *e.g.* the PKC inhibitor Ro 32-0432.[26] Bioactive compounds such as the CDK inhibitor ribociclib[27] and the antiviral agent CMV423[28] contain pyrrolopyrimidine and the tetrahydroindolizine cores, respectively.

In 2015, Nakao, Hartwig and co-workers developed a linear-selective alkylation of indoles and additional heterocycles relying on nickel-NHC catalysis.[29] We wanted to challenge our chiral NHC family in the nickel-catalyzed enantioselective *endo*-cyclization of different azoles (Scheme 5). This approach is particularly powerful, as previously reported enantioselective indole C–H alkylations rely on the use of Lewis basic directing groups.[30]

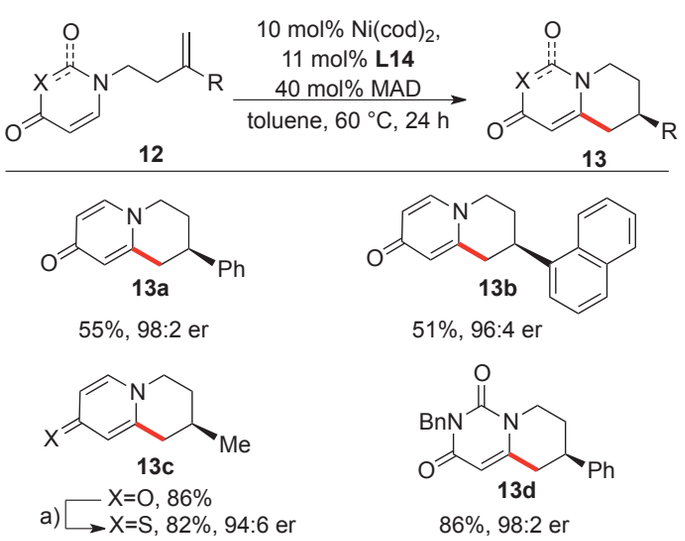
Screening of different backbone-substituted IPr^x ligands identified **L8** and its saturated counterpart **L16** as optimal, delivering product **15a** in moderate yield and the same enantioselectivity, but intriguingly favoring the opposite product enantiomers (Scheme 6). We continued introducing side arm bulk into the ligand scaffold. 3,5-Xylyl-containing **L11** gave the *R* enantiomer with 70:30 er. Both ligand backbone saturation and the introduction of side arm bulk into the parent ligand **L8** resulted in the preferred formation of the opposite enantiomer. In an effort to combine both effects, **L17** was prepared, and indeed the observed ligand effects were additive and product **15a** was obtained with 85:15 er. The trend of increased product enantioselectivity with increasing side arm bulk on the ligand scaffold was further reinforced by using **L18**, delivering the product in high yield and with 93:7 er. With this optimal ligand in hand, we could lower the reaction temperature to 60 °C without loss in reactivity and $PhCF_3$ was identified as optimal solvent delivering the product in very high enantioselectivity.

With the modified ligand and optimized reaction conditions in hand, we started exploring the scope of the transformation (Scheme 7). Indoles substituted at the C5, C6 and C7 position were converted smoothly, delivering the products with high enantioselectivity (**15b**–**15e**). Notably, the valuable B(pin)-group, allowing further product modifications, was well tolerated (**15b**). Alkyl substituents decorated with a benzyl ether group were converted in high yield and with 97:3 er (**15d**). The substrate **14e** containing an *E*-configured internal double bond reacted smoothly delivering the product **14e** in high enantioselectivity. Furthermore, additional Lewis basic nitrogen atoms in the substrate were well tolerated, enabling the conversion of pharmaceutically sought after azaheterocycles. Pyrrolopyridine **14f** and pyrrolopyrimidines **14g** were annulated in excellent enantioselectivities. Additionally, benzimidazoles (**14h**) were capable substrates, delivering the product efficiently, albeit in lower er.

Subsequently, we subjected pyrroles to the enantioselective C–H annulation methodology, delivering valuable tetrahydroindolizine scaffolds (Scheme 8). Reports on the enantioselective C–H functionalization of pyrroles on the C2 position are scarce. Asymmetric protocols utilizing the high nucleophilicity



Scheme 3. Selected scope entries for the enantioselective annulation of 2-pyridones. a) At rt. b) At 60 °C. c) At 80 °C.

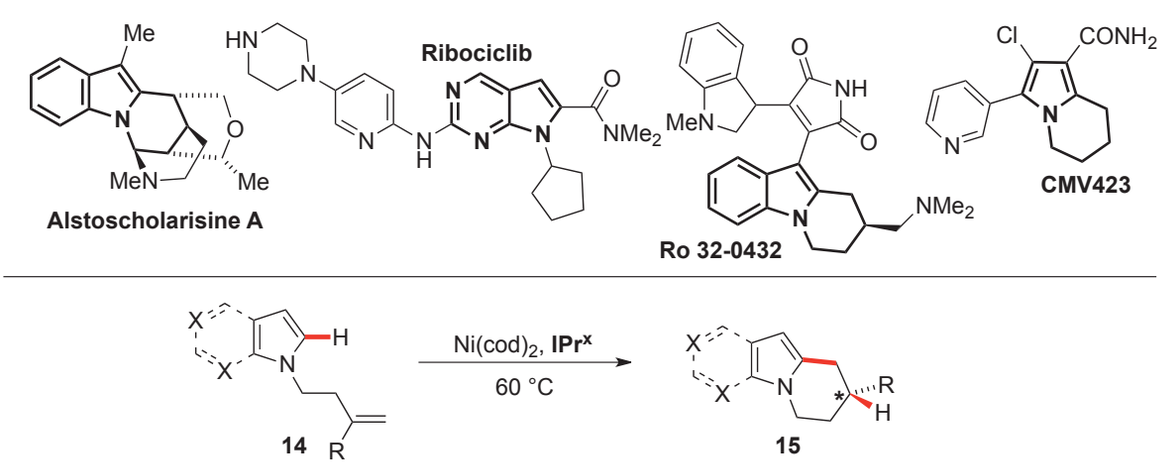


Scheme 4. C–H functionalization of 4-pyridones. a) Lawesson's reagent, toluene, 110 °C for 1 h.

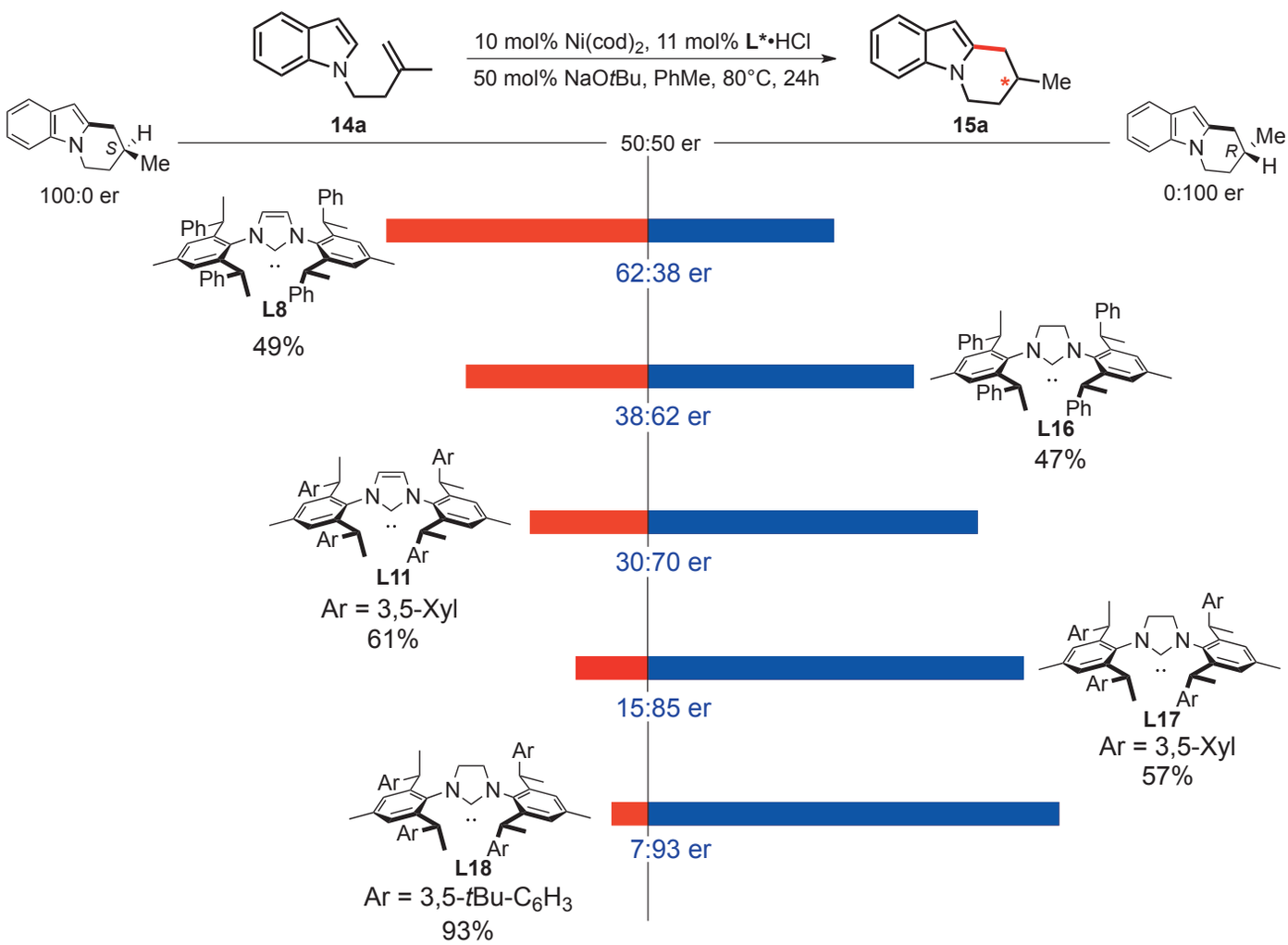
of the pyrrole exist. This type of transformation, however, delivers the complementary *exo*-cyclization product, *via* the more stabilized tertiary carbenium ion, to yield the corresponding branched products.[31] 1,1 disubstituted olefins (**16a**), containing additional alkene functionalization (**16b**) were converted smoothly and delivered the product with high enantioselectivity. Internal alkene **16c** reacted in similar yield and with a decreased enantioselectivity of 89:11 er. Pyrroles containing a methyl ester substituent at the 3-position efficiently underwent annulation and delivered a 3:1 mixture of 5-annulated (**17d**) and 2-annulated (**17d'**) products. The sterically more accessible 5-annulated product (**17d**) was favored and was isolated in 57% yield.

Summary

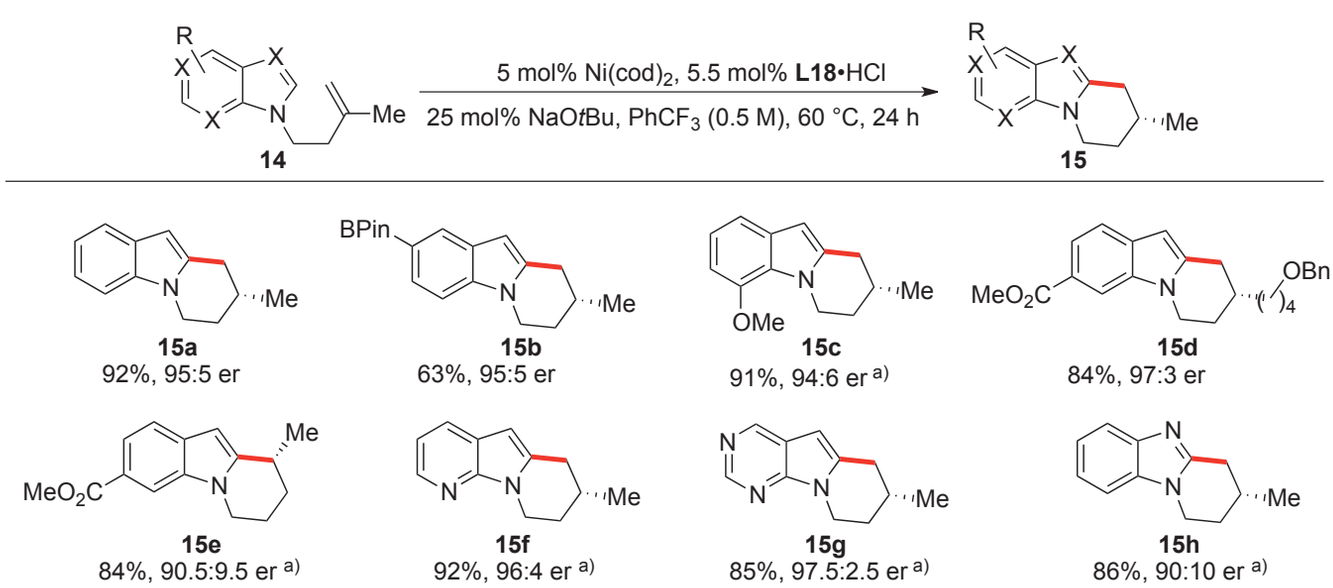
We have introduced a modular NHC ligand family based on Gawley's carbene, serving as chiral version of IPr. Access to readily modifiable chiral aniline building blocks was essential to unlock the full potential of the highly modular ligand scaffold, with large application opportunities. We applied these ligands in the nickel-catalyzed C–H alkylation of pyridones, where the introduction of the acenaphthene derived ligand backbone and bulky side arms proved crucial, to achieve excellent stereocontrol under



Scheme 5. Nickel-catalyzed enantioselective C–H functionalization of Azoles.



Scheme 6. Ligand optimization for enantioselective tetrahydropyridoindole formation.



Scheme 7. Selected scope entries of the enantioselective azole annulation. a) with 10 mol% $Ni(cod)_2$,11 mol% **L18**·HCl, 50 mol% NaOtBu.

mild reaction conditions. Next to 2-pyridones, 4-pyridones and even uracil-derived substrates reacted equally well. Furthermore, we have developed an enantioselective directing group free indole C–H functionalization to obtain valuable tetrahydropyridoindoles by applying a bulky chiral SIPr analogue. Besides indoles, also pyrrolopyridines, pyrrolopyrimidines and pyrroles could be functionalized with high enantioselectivities.

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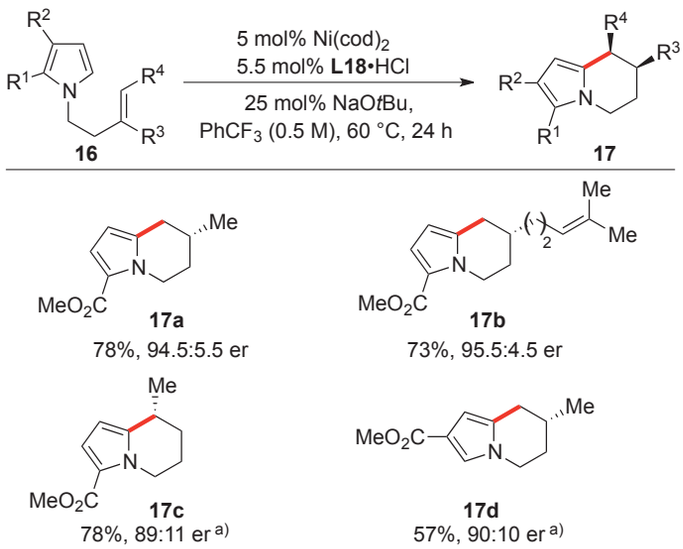

Scheme 8. Selected scope entries of the enantioselective C–H functionalization of pyrroles. a) with 10 mol% $Ni(cod)_2$,11 mol% **L18**·HCl, 50 mol% NaOtBu.

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