Heterocycles

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Synthesis of 3-Fluoro-3-aryl Oxindoles: Direct Enantioselective α Arylation of Amides**

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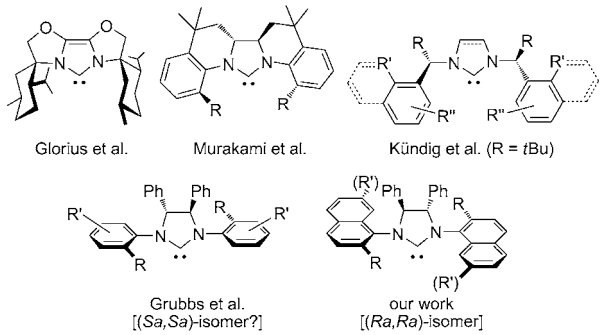
Monodentate N-heterocyclic carbene (NHC) ligands have become ubiquitous in organometallic chemistry and catalysis.[1] Conversely, development of chiral monodentate NHC ligands that induce high selectivity in asymmetric metal catalysis is still at an early stage with relatively few reports detailing enantioselectivities of 90% *ee* and higher.[2–6] The main difficulties in designing efficient ligands of this type reside in placing stereocontrol elements at positions near the metal center without affecting the overall reactivity of the catalysts. Scheme 1 shows some of the most promising ligand designs to date and highlights the fact that the inherent flexibility of the N substituents has to be restricted to afford ligands that efficiently transfer their chiral information. This restriction can be done by fusing these wingtips onto the N heterocycle, a design motif pioneered by Glorius et al.,[2] and more recently developed further by Murakami et al.[3] Decreasing the rotation of the N substituents is also key in the successful C_2-symmetric ligands reported by Kündig et al.,[4] who have been able to show that such ligands can be used very effectively in palladium chemistry.[5] Probably the most versatile ligand system developed so far was first reported by Grubbs et al.,[6,7] and they rely on transferring chirality from a chiral N-heterocyclic backbone onto unsymmetrically substituted aryl side chains and ultimately onto the metal coordination sphere. While the design permits easy access to the precursor imidazolinium salts, such side chains will in principle create three diastereomers which would have to be separated for optimal use in catalysis. Our own efforts,[8] have indeed highlighted the pivotal role the respective orientation of naphthyl wingtips can have on enantioselectivity and, contrary to what other groups have proposed or found, the best ligands with 2-alkyl-substituted naphthyl side chains position their alkyl substituents directly below the corresponding phenyl group of the backbone [(*Ra*,*Ra*)-isomer].



Scheme 1. Examples of chiral, monodentate NHC ligands.

Encouraged by our first results, we became interested in ways of exclusively accessing this particular diastereomer, as it would undoubtedly allow a more straightforward synthesis and use of these ligands. After testing several substitution patterns, we were pleased to find that placing a relatively rigid cyclooctyl group at the 2-position of the naphthyl moieties and ring-closing the corresponding chiral diamine **A** at 120 °C for 2 hours (Scheme 2) generated the virtually pure NHC salt (*Ra*,*Ra*)-**B**. The salt showed one set of signals and a diagnostic single peak for the C2 proton of the imidazolinium ring in the ^{1}H NMR spectrum.

This salt was then used to synthesize the palladium cinnamyl complex (*Ra*,*Ra*)-**C** in high yield, the structure of which was unambiguously confirmed by single-crystal X-ray crystallography.[9,10] Qualitative assessment of the structure shows both the relative bulk and the C_2 symmetry of the ligand. The overall steric demand of the ligand was then quantified by its buried volume (%V_{Bur}), a parameter describing the amount of volume in the first coordination sphere of a metal occupied by a given ligand and its topographic steric map (see the Supporting Information).[11,12] To understand how the C_2 symmetry of the ligand affects the environment around the metal, we evaluated the %V_{Bur} in the four single quadrants of (*Ra*,*Ra*)-**C** and plotted the steric contour map highlighting zones of different steric pressures as shown in Figure 1.[12,13] This analysis was performed on the geometry of the (*Ra*,*Ra*)-**C** obtained from its crystal structure without additional modifications.[9] This analysis shows that the two quadrants where the 2-cyclooctyl groups are located are heavily hindered (bottom left and top right quadrants,

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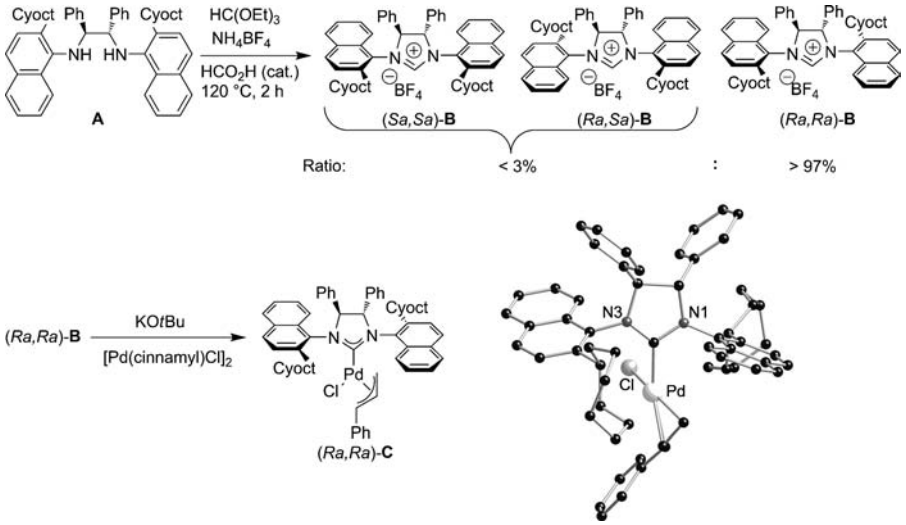


Scheme 2. Synthesis of the chiral NHC complex.

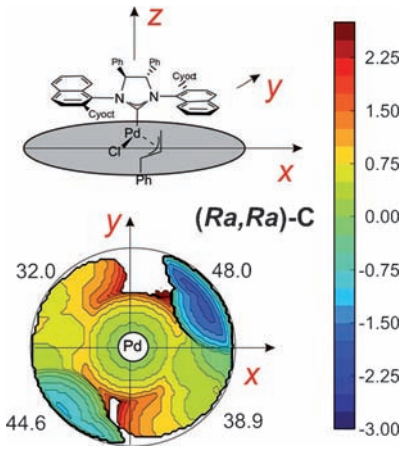
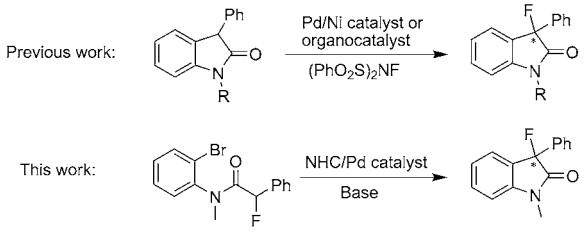


Figure 1. Steric contour maps of the NHC ligand in (*Ra*,*Ra*)-**C**. The complex is oriented as shown in the sketch. The number close to each quadrant is the $\%V_{ur}$ of this quadrant.

$\%V_{Bur} \approx 46\%$), while the other two quadrants are clearly more open (bottom right and top left quadrants, $\%V_{Bur} \approx 35\%$). The map therefore demonstrates that the NHC ligand wraps around the metal center with almost perfect C_2 symmetry, a result that boded well for its application as an effective ancillary ligand in asymmetric transformations.

In earlier work, we had shown that relatives of (*Ra*,*Ra*)-**C** can be used as precatalysts in the α arylation of amides to give

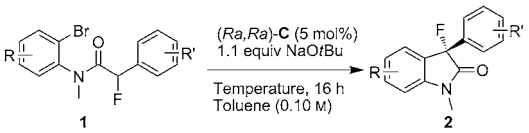


Scheme 3. Catalytic enantioselective synthesis of 3-fluoro-3-aryl oxindoles.

enantioenriched oxindoles with quaternary carbon centers.[8] In this context, an attractive transformation involving such an α-arylation reaction would see the introduction of a fluorine atom onto the oxindole moiety, effectively resulting in the direct formation of enantioenriched 3-fluoro-3-aryl oxindoles. Owing to the often attractive properties of such fluorinated compounds for pharmaceutical applications,[14] incorporation of fluorine into organic molecules through enantioselective catalytic processes has been extensively investigated in the past decade and fluorinated oxindole products can be obtained through the catalytic enantioselective fluorination reaction,[15] employing an electrophilic source of fluorine (Scheme 3).[15d,g,h,l] However, up to now no attempts at developing direct α-arylation reactions to gain access to these or other enantioenriched fluorinated compounds have been documented (Scheme 3).[16,17]

Our catalytic investigation began by screening reaction parameters using model substrate **1a** and 5 mol% of (*Ra*,*Ra*)-**C** as a precatalyst (see the Supporting Information for details). Crucial to obtaining good yields of the product was

Table 1: Substrate scope for the NHC/Pd-catalyzed α arylation.[a]



Entry	Substrate	R[b]	R′	*T* [°C]	Product	Yield [%]	*ee* [%]
1	**1a**	H	H	RT	**2a**	83	97
2	**1b**	5-Me	2-F	RT	**2b**	62	>99
3	**1c**	5-Me	4-Me	RT	**2c**	70	99
4	**1d**	5-MeO	1-Nap	50	**2d**	58	94
5	**1e**	5-MeO	H	RT	**2e**	82	99
6[c]	**1e**	5-MeO	H	RT	**2e**	89	91
7	**1f**	5-MeO	2-F	50	**2f**	82	99
8	**1g**	5-MeO	2-CF_3	50	**2g**	85	98
9	**1h**	5-F	H	RT	**2h**	70	96
10	**1i**	5-F	2-F	RT	**2i**	76	>99
11	**1j**	6-CF_3	H	RT	**2j**	81	94
12	**1k**	6-Me	2-Cl	60	**2k**	86	82
13	**1l**	H	2-Me	RT	**2l**	59	96
14	**1m**	H	2-F	RT	**2m**	65	>99
15[c]	**1m**	H	2-F	RT	**2m**	94	95
16	**1n**	H	3-MeO	RT	**2n**	50	95
17	**1o**	H	3-F	RT	**2o**	80	96 (*S*)
18	**1p**	H	4-Ph	RT	**2p**	61	94

[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv), (*Ra*,*Ra*)-**C** (5.0 mol%), NaO*t*Bu (1.1 equiv), toluene (2.0 mL), 16 h. We assume that all substrates follow the same reaction pathway to give the same relative configuration; [b] Numbering based on the oxindole product. [c] DME as solvent.

not to use excess of the base (NaO*t*Bu), as the substrate would otherwise decompose. Under optimized reaction conditions using toluene as a solvent and running the reaction at ambient temperature, product **2a** was obtained in 83% yield upon isolation and with an excellent enantioselectivity of 97% *ee*. As evidenced from data collected in Table 1, a variety of substrates are tolerated in this reaction. For instance, the introduction of electron-donating and electron-withdrawing groups (methoxy, methyl, phenyl, chloro, fluoro and trifluoromethyl) on the *ortho*-, *meta*-, or *para*-positions of the 3-phenyl groups lead to excellent enantioselectivities and good yields within 16 hours at room temperature or 50 °C. Selected examples with substituents at the 5- and 6-position of the oxindole core lead to equally satisfying results. When DME is used as a solvent (entries 6, 15), reactivity increases while the selectivity is slightly lower. In several cases, virtually enantiopure products were obtained (**2b**, **2f**, **2i**, and **2m**), a rather unique result when employing chiral, monodentate NHC ligands.[18]

The absolute stereochemistry of the products was deduced from an X-ray crystallographic analysis of compound **2o**, the stereogenic carbon center of which had the *S* configuration.[9]

To further support the assigned stereochemistry of the products and to gain first insights into the reaction mechanism we performed a DFT study of the key intermediates, in the case of the prototype substrate **1a**, corresponding to the expected compounds before final reductive elimination and release of product **2a**.[19] The optimized geometries are reported in Figure 2. Structural analysis indicates that in the most stable intermediate (Figure 2a) leading to the experimentally favored *S* enantiomer, the aromatic ring that will form the skeleton of the oxindole product and the Ph substituent on the final chiral C atom of the product are placed below the naphthyl ring, which is in the less buried quadrants highlighted in the steric map of Figure 1. By contrast, in the key intermediate (Figure 2b) leading to the experimentally less favored *R* enantiomer, the Ph substituent on the final chiral C atom of the product is placed below the cyclooctyl ring, which is in a buried quadrant highlighted in the steric contour map of Figure 1. According to calculations, the intermediate of in Figure 2a is favored by 4.4 kcal mol^{-1} in toluene, a value correctly reflecting the high enantioselectivity observed.

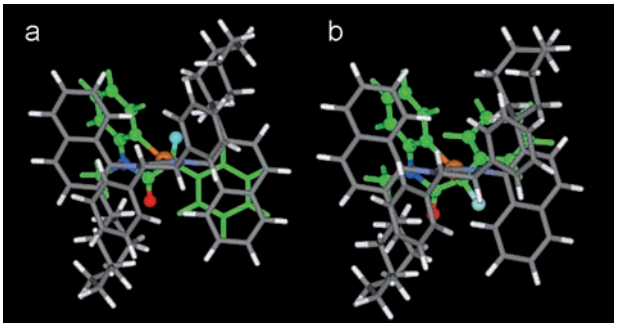


Figure 2. Optimized structure of the key intermediate before reductive elimination. The intermediates leading to the major *S* product (a) and minor *R* product (b) are shown. C atoms of the NHC are colored in grey, and the C and H atoms of the substrate are colored in green.

In conclusion, we have developed a new catalytic method for the enantioselective construction of carbon–fluorine bonds that relies on an asymmetric α-arylation protocol and have demonstrated its efficacy for the direct synthesis of 3-fluoro-3-aryl oxindoles. These target molecules were obtained in good yields and with excellent enantioselectivities when employing a new NHC ligand with a chiral N-heterocycle and naphthyl side chains that is easily accessed as a single diastereomer. Detailed mechanistic studies are in progress to shed light on the whole reaction pathway connecting reactants and products. Ongoing research aims to broaden the scope of this promising new catalytic way of accessing enantioenriched fluorinated compounds and to test ligand (*Ra*,*Ra*)-**B** in other transformations.

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