

Matching the Chirality of Monodentate N-Heterocyclic Carbene Ligands: A Case Study on Well-Defined Palladium Complexes for the Asymmetric α -Arylation of Amides

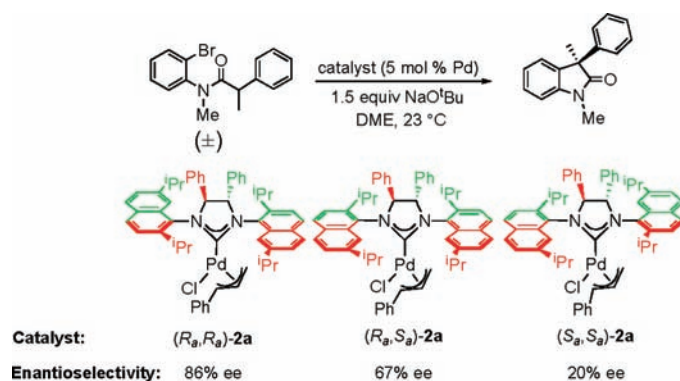
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ABSTRACT



N-Heterocyclic carbene ligands derived from C_2 -symmetric diamines with naphthyl side chains are introduced as chiral monodentate ligands, and their palladium complexes (NHC)Pd(cin)Cl are prepared. These compounds exist as a mixture of diastereomers, and the palladium complexes can be successfully separated and their absolute stereochemistry assigned. When used in the asymmetric intramolecular α -arylation of amides, oxindoles with quaternary carbon centers can be obtained in high yield and selectivity when correctly matching the chirality of the NHC complexes.

N-Heterocyclic carbenes often show increased reactivity and stability when compared to the commonly employed phosphine ligands.¹ Because of their tight metal binding and robustness, monodentate, chiral N-heterocyclic carbene ligands appear to be a very promising ligand class for asymmetric catalysis.² Development in this area has been relatively slow,^{3–5} and versatile chiral NHCs remain elusive.

(1) (a) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim: Germany, 2006. (b) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Topics in Organometallic Chemistry, Vol. 21; Springer: Berlin, 2007.

Two reasons might account for this. First, the overwhelming majority of chiral NHC salts is deprotonated and used in

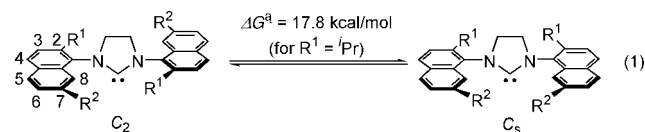
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situ,⁶ a circumstance that precludes a detailed discussion on the reaction/selection pathway of a given transformation and hinders development of optimized ligand structures. Another problem consists in building chirality without losing the reactivity/versatility of the most successful achiral ligand architectures, which incorporate aromatic N-substituents (for instance, IMes/SIMes and IPr/SIPr). Elegant work by Grubbs et al. has shown that NHCs derived from C_2 -symmetric diamines and mono-*ortho*-substituted aryl halide side chains provide successful ligand systems in some ruthenium-catalyzed asymmetric metathesis reactions.⁴ Similar architectures with unsymmetrically 2,6-disubstituted phenyl side chains have been reported more recently showing encouraging results.⁵ In all of these cases, no mention is made regarding the possibly different orientations of the side chains or their ease of rotation with respect to the chiral N-heterocyclic backbone and the resulting impact on selectivity or reactivity in catalysis.⁷

In the course of studying a series of NHCs that incorporate 2-substituted naphthyl side chains,⁸ we found that NHCs with $R^1 = \text{methyl/isopropyl}$ have two atropisomers with C_2 -symmetric (*anti* orientation of side chains) and C_s -symmetric (*syn*) conformations (eq 1). Logically, if the chiral regime of C_2 -symmetric diamines is introduced to the heterocyclic backbone of these NHCs, three diastereomers should be generated. Before embarking on the present study, we reasoned that ligand systems with bulky R^1 groups would be the best candidates because of their rotational stability (eq 1) and excellent catalytic behavior.⁸ Moreover, building upon the successful separation of *anti/syn* palladium complexes in our previous study, we decided to concentrate our preliminary efforts on the palladium-catalyzed asymmetric intramolecular α -arylation of amides to give chiral quaternary carbon centers.⁹



To get the best insight possible into factors that govern the selectivity and reactivity of these new ligands, variations in both the chirality of the imidazolium backbone (R^3) and the steric properties of the side chains ($R^1 = \text{isopropyl or}$

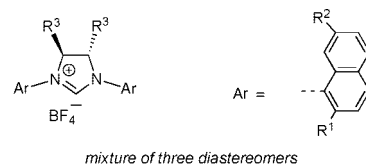
(5) For examples using C_2 -symmetric chiral NHCs with aromatic side chains, see: (a) Martin, D.; Kehrl, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416. (b) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568. (c) Matsumoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578.

(6) In some instances, the conditions used for deprotonation are such that alternative binding modes, for instance η^6 -coordination of the aromatic side chains, appear just as likely as coordination of the presumably deprotonated carbene moiety; see ref 3.

(7) Different rotamers of NHC salts and precatalysts seem to exist; see the Supporting Information of refs 4a and 5b.

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(4*S*,5*S*)-DiPhSiPrNap HBF₄ (**1a**, $R^1 = R^2 = \text{iPr}$, $R^3 = \text{Ph}$) [**54**(R_a, R_a):**36**(R_a, S_a):**10**(S_a, S_a)]
 (4*S*,5*S*)-DiPhSi2PrNap HBF₄ (**1b**, $R^1 = \text{iPr}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$) [**51**(R_a, R_a):**41**(R_a, S_a):**8**(S_a, S_a)]
 (4*S*,5*S*)-DiPhSi2CyNap HBF₄ (**1c**, $R^1 = \text{Cy}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$) [**71**(R_a, R_a):**21**(R_a, S_a):**8**(S_a, S_a)]
 (4*R*,5*R*)-CySiPrNap HBF₄ [**1d**, $R^1 = R^2 = \text{iPr}$, $R^3 = \text{-(R,R)-(CH}_2)_4\text{-}$] (**45**:**40**:**15**)

Figure 1. New chiral N-heterocyclic carbene precursors **1a–d**.

cyclohexyl; $R^2 = \text{isopropyl or hydrogen}$) were introduced, and four different NHC salts were prepared (Figure 1). Careful analysis of the N-heterocyclic proton signals by ¹H NMR showed three different diastereomers for all four ligands (**1a–d**).

Table 1. Asymmetric Intramolecular α -Arylation of Amide **3a** with **1a–d**/Palladium Source

entry	L*	[Pd]	T (°C)	time (h)	% yield ^a (% ee ^{b,c})
1	1a	Pd(dba) ₂	23	12	98 (71)
2	1a	[Pd(cin)Cl] ₂	23	12	98 (69)
3	1a	Pd(OAc) ₂	23	24	96 (66)
4	1b	Pd(dba) ₂	50	24	98 (59)
5	1c	Pd(dba) ₂	50	24	91 (47)
6	1d	Pd(dba) ₂	23	12	92 (–6)

^a Isolated yields. ^b Determined by chiral HPLC. ^c Absolute stereochemistry determined as the (*R*)-configuration; see ref 9d.

Ligand precursors **1a–d** were then tested in the intramolecular α -arylation of **3a** following Hartwig's in situ method (Table 1).^{9a} Results showed that Pd(dba)₂, Pd(OAc)₂, and [Pd(cin)Cl]₂ (cin = cinnamyl) could be used as palladium sources. Although diastereomeric mixtures of ligands **1a–d** were employed, oxindole **4a** was obtained with selectivities of up to 71% ee with ligand **1a** (entry 1), whereas using **1d** resulted in almost racemic product (entry 6). This result already indicates that the chiral information is probably transferred to the substrate from the chiral diamine part of the N-heterocycle.

Diastereomers of **1a–c** were then used for the synthesis of (NHC)Pd(cin)Cl complexes **2a–c**.^{10,11} As expected from our previous studies on similar ligands (eq 1), crude mixtures of the complexes maintained the ratio between the diaster-

(10) Because **1d** performed poorly in the in situ catalysis, it was not employed further.

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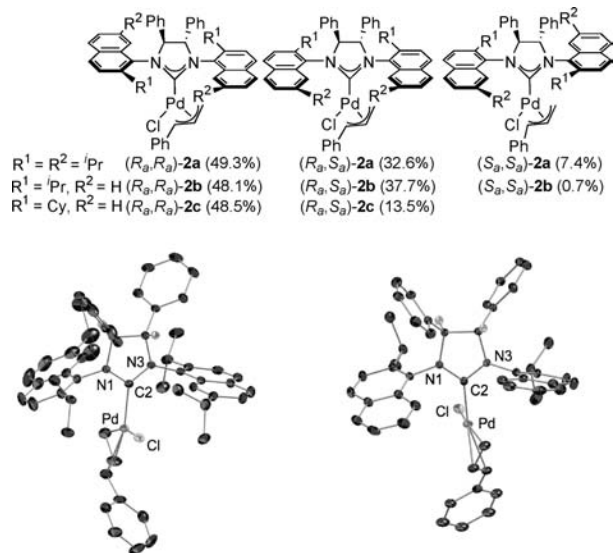


Figure 2. Complexes **2a–c** (top, yields in parentheses) and X-rays of [(R_a,R_a)-(4*S*,5*S*)-DiPhSIPrNap]Pd(cin)Cl (bottom left, (R_a,R_a)-**2a**) and [(R_a,S_a)-(4*S*,5*S*)-DiPhSIPrNap]Pd(cin)Cl (bottom right, (R_a,S_a)-**2b**).

omers of the NHC salts. For all three compounds, we were able to separate these diastereomeric compounds via column chromatography and assign the absolute configurations unequivocally by using a combination of both NMR spectroscopy and X-ray structural determinations (Figure 2). The main *anti* ligand isomer orients its more hindered half of the naphthyl moiety onto the protruding phenyl ring of the backbone, an intriguing result in view of the previously assumed prevalence of (S_a,S_a)-isomers in this ligand class.¹² Numerous broad signals in the ¹H NMR spectra of **2a–c** reflect the important steric crowding and the resulting restricted rotation of both the cinnamyl and NHC side chains in these complexes. Nonetheless, very diagnostic upfield shifts are found for some of the R^1 protons and arise from strong σ - π interactions with the chiral backbone phenyl moieties. Together with the X-ray analyses and the proton signals of the N-heterocyclic backbone, the presence [twice for (R_a,R_a)-**2**, once for (R_a,S_a)-**2**] or absence [for (S_a,S_a)-**2**] of these upfield signals led to the correct assignment of the different diastereomers.

The series of pure precatalysts was then applied to the asymmetric oxindole synthesis starting from different 2-bromoanilides, and the catalytic results are given in Table 2. Yields of isolated products are excellent, and reaction times of less than 24 h were observed. Minor discrepancies in reactivity exist between catalysts (**2a** more active than **2b/2c**),¹³ as well as between the three diastereomers of **2a** (see the Supporting Information). On the other hand, selectivity differences are very pronounced and reflect the crucial importance of the ligand architecture. Precatalysts derived

(12) R_a/S_a denote the axial chirality between the N-heterocycle and the naphthyl side chains.

(13) Compound **2a** performs better than the reference system (SIPr)Pd(cin)Cl; see the Supporting Information.

Table 2. Asymmetric Intramolecular α -Arylation of Amides with **2a–c**

entry	R	Ar	cat.	% yield ^a and (% ee) ^{b,c}		
				R_a,R_a	R_a,S_a	S_a,S_a
7	Me	Ph	2a	98 (86)	98 (67)	98 (20)
8 ^d	Me	Ph	2b	94 (67)	95 (52)	95 (34)
9 ^d	Me	Ph	2c	98 (51)	98 (46)	
10	Bn	Ph	2a	98 (88)	98 (45)	97 (50)
11	Bn	Ph	2b	89 (76)	96 (61)	
12	Me	<i>p</i> -Tol	2a	99 (87)	98 (79)	97 (44)
13	Me	<i>p</i> -Tol	2b	98 (84)	98 (74)	
14	Me	<i>p</i> -Tol	2c	98 (62)	98 (70)	
15	Me	<i>o</i> -Tol	2a	99 (85)	97 (89)	98 (44)
16	Me	<i>m</i> -Tol	2a	99 (80)	96 (65)	98 (24)
17 ^d	Me	<i>m</i> -Tol	2b	98 (71)	98 (49)	
18	Me	1-Nap	2a	93 (85)	95 (80)	95 (34)
19 ^d	Me	1-Nap	2b	92 (77)	95 (68)	
20	Bn	1-Nap	2a	93 (82)	96 (66)	93 (49)

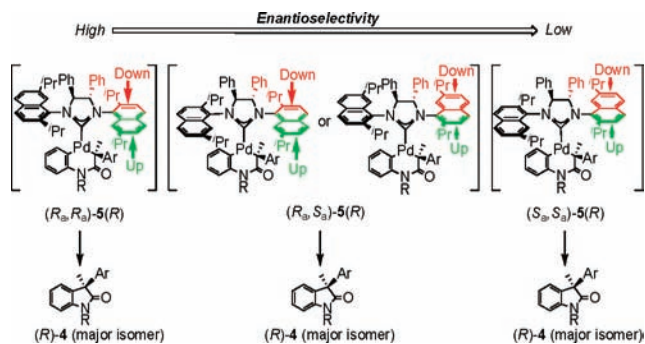
^a Isolated yields. ^b Determined by chiral HPLC. ^c Absolute stereochemistry determined as (*R*)-configuration, see ref 9d. ^d Reaction run at 50 °C.

from the minor diastereomeric form of the ligands (S_a,S_a) failed to give products with more than 50% ee. Both (R_a,S_a)- and (R_a,R_a)-isomers proved superior in terms of selectivity. Enantiomeric excesses when the (R_a,S_a)-complexes were employed ranged from moderate (45% ee) to high (89% ee) and showed a marked substrate-dependence. Of all the precatalysts tested, (R_a,R_a)-**2a** outperformed its congeners and gave high and very evenly distributed chiral induction (80–88% ee) for all substrates. As such, (R_a,R_a)-**2a** compares well with the best systems described recently by Kündig et al.,^{9d} giving generally better yields and slightly higher ee's in two cases (entries 10 and 18).

Overall, the results in Table 2 validate the assumption made above that it is the chiral groups on the N-heterocycle that determine the absolute configuration of the carbon center in products **4a–g** (all *R*-configured). Finally, it should also be noted that adding up the results of entry 7 of Table 2 with (R_a,R_a)-**2a** (86% ee), (R_a,S_a)-**2a** (67% ee), and (S_a,S_a)-**2a** (20% ee) and taking into account the relative abundance of diastereomers in the NHC salt **1a** essentially replicates the in situ performance obtained in entry 2 of Table 1.

A viable model for the differences in selectivity between the three diastereomeric palladium complexes of **2a** is depicted in Scheme 1. The steric pressure exerted by the chiral NHC-phenyl groups onto the naphthyl side chains and subsequently onto the enantiodiscriminating side of the substrate would predominantly give intermediates **5** and, after reductive elimination, products with the observed (*R*)-configuration. Depending on the amount of steric pressure exerted onto the naphthyl side chains, either higher or lower proportions of the depicted intermediate **5** would therefore be generated in the enantiodiscriminating carbon–metal

Scheme 1. Model Explaining the Differences in Selectivity
(Derived from Catalyst **2a**)



bond-forming step preceding intermediate **5**. The higher steric pressure in the (R_a, R_a) -isomer means that the relative orientation of methyl vs aromatic group of the substrate as shown in (R_a, R_a) -**5(R)** is highly favored over (R_a, R_a) -**5(S)**, while the (S_a, S_a) -isomer gives substantial amounts of (S_a, S_a) -**5(S)** and low enantiomeric excess of the (R) -**4** products. The lack of a plane of symmetry in (R_a, S_a) -**5(R)** means that two intermediates leading to the major isomer (R) -**4** may be operative, giving either high (left) or moderate (right) degrees of selectivity. In this case again, the model that we propose correctly reflects the observed experimental results that show an apparently random distribution of high and moderate selectivities when precatalysts (R_a, S_a) -**2** are employed.

In conclusion, we report the synthesis of new NHC ligands with a chiral N-heterocycle and naphthyl side chains. Careful analysis of the imidazolium salts showed the existence of three different isomers in such NHC structures. Pure palladium complexes incorporating these ligands were obtained after successful separation of their diastereomeric mixtures. The resulting compounds were tested in the asymmetric intramolecular α -arylation of amides and lead to the identification of a precatalyst [(R_a, R_a) -**2a**] that formed oxindoles in high yield and high enantiomeric purity. Analysis of the catalytic data demonstrates the dramatic effects on selectivity the orientation of the aromatic side chains can have in catalysis. In view of the experimental results presented here, the assumption that (S_a, S_a) -isomers are responsible for enantioselectivity in this chiral NHC subclass should be questioned. Obviously, direct access to diastereomerically pure ligand precursors **1a–c** and their derivatives would provide an easier entry to their optimized use in catalysis and should also facilitate identification of even more effective and widely applicable ligand architectures. Studies with this aim are ongoing.

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Supporting Information Available: Experimental procedures and CIFs for (R_a, R_a) -**2a** and (R_a, S_a) -**2b**. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL8021808