Monodentate Chiral N-Heterocyclic Carbene–Palladium-Catalyzed Asymmetric Suzuki–Miyaura and Kumada Coupling

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Abstract: N-Heterocyclic carbene ligands derived from C_2-symmetric diamine 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. When used in the asymmetric Suzuki–Miyaura and Kumada coupling, chiral biaryls can be obtained in high yield and moderate selectivity.

Key words: monodentate chiral NHC, palladium, asymmetric catalysis, Suzuki–Miyaura coupling, Kumada coupling

Axially chiral biaryls are common and decisive structure motifs in bioactive compounds[1] and form the basis for some of the most effective chiral ligands, such as the well-known BINAP[2] and BINOL[3] ligands. Modern cross-coupling reactions[4] (i.e., Suzuki–Miyaura coupling and Kumada coupling) have opened a direct and convenient route to such axially chiral biaryl molecules, and these coupling reactions are particularly valuable for obtaining unsymmetric biaryls, which cannot be readily obtained by other catalytic asymmetric reactions. The first successful atroposelective cross-coupling was reported by Hayashi in the late 1980s using aryl halides and aryl Grignard reagents as the coupling partners (Kumada coupling) and chiral ferrocenylphosphine/Ni as the catalyst.[5] Following this seminal work, related phosphine ligands were examined in the Kumada coupling but gave only low to moderate enantioselectivities.[6] Until now, there are various reports of asymmetric Suzuki–Miyaura and Kumada coupling using chiral phosphine ligands.[7] The earliest reports of asymmetric cross-coupling of aryl halides and aryl boron reagents were disclosed by Cammidge[8] and Buchwald[9] using ferrocene- and binaphthyl-derived phosphines, respectively. Since then, a variety of chiral ligands have been examined for the asymmetric Pd-catalyzed Suzuki–Miyaura coupling reaction.[10] Remarkably, in 2008 Lassaletta disclosed a new class of chiral bishydrazone ligands derived from C_2-symmetric hydrazines for the asymmetric Suzuki–Miyaura coupling, providing the biaryls in high selectivities (up to 98% ee).[10e] Recently, Suginome showed that a helically chiral poly(quinoxaline-2,3-diyl)-based phosphine served as highly enantioselective ligand (up to 95% ee) in the Suzuki–Miyaura coupling reaction to form axially chiral biarylphosphinic esters.[10i]

N-Heterocyclic carbenes (NHC) have received enormous attention in the passed two decades and are now considered as ligands of choice for various (asymmetric) catalytic reactions.[11] In the context of cross-coupling reactions, monodentate NHC have been intensively studied by different research groups and they have demonstrated remarkably high activity promoting these transformations.[11c,12] The capacity of NHC has been illustrated not only in cross-coupling reactions but also in different asymmetric transformations.[13] However, little attention has been given to asymmetric cross-coupling reactions using chiral NHC as the ligands. To the best of our knowledge, there are only two reports to date detailing the use of chiral NHC ligands to promote asymmetric cross-coupling reactions. In 2010, Labande disclosed the first example of asymmetric Suzuki–Miyaura coupling with palladium complexes bearing chelating, planar chiral ferrocenyl phosphine–NHC ligands.[14] However, only low enantioselectivities were achieved (less than 40% ee) in this transformation using aryl bromides as the electrophiles. Recently, Zhang and co-workers prepared two palladium complexes of a chelating NHC ligand derived from 1,2-cyclohexanediamine and employed them to catalyze the asymmetric Suzuki–Miyaura couplings of aryl bromides with arylboronic acids in good yields and moderate enantioselectivities (up to 61% ee).[15] Up to now, there are no reports on asymmetric cross-coupling using monodentate NHC as the ligand, and NHC ligands have so far not been used for the asymmetric Kumada cross-coupling (Scheme 1).

Our group has developed a new type of monodentate NHC ligands with a chiral N-heterocycle and naphthyl side chains. These compounds exist as a mixture of diastereomers and their palladium complexes showed different selectivity in asymmetric intramolecular α-arylation reactions.[16] Recently, we were able to access a single NHC diastereomer by introduction of a cyclooctyl group onto the 2-position of the naphthyl side chain, and the palladium cinnamyl complex (Scheme 2, complex **A**) gave excellent results in a new α-arylation protocol that allows the direct synthesis of 3-aryl-3-fluoro-oxindoles.[17]

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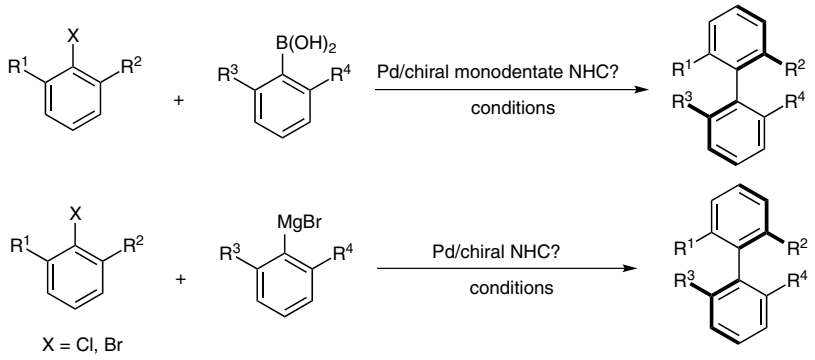
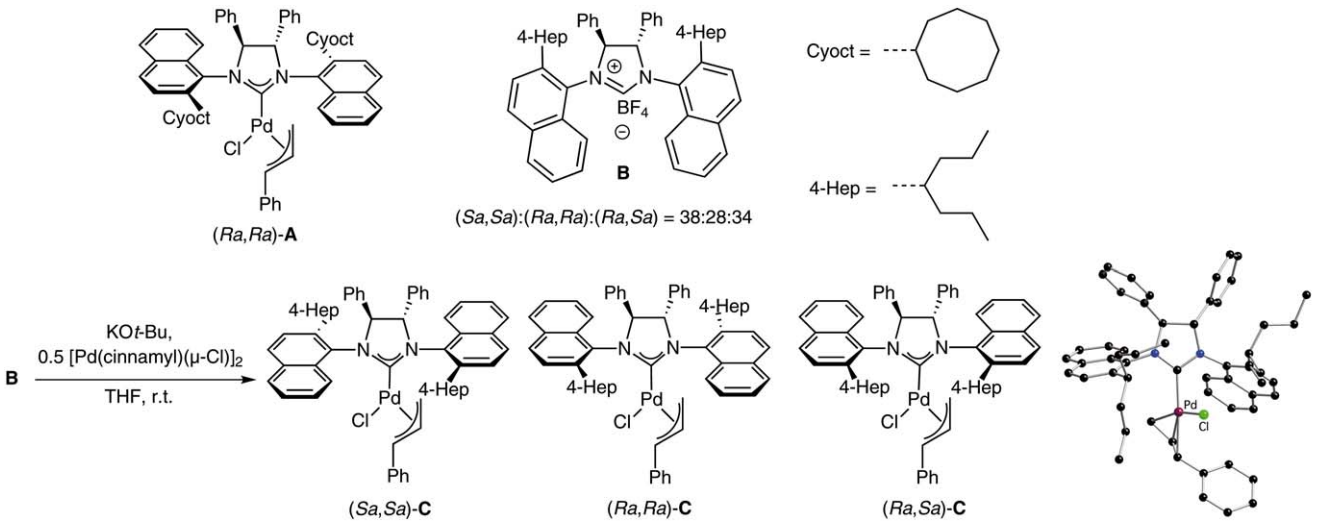


Scheme 1 Asymmetric Suzuki–Miyaura and Kumada coupling

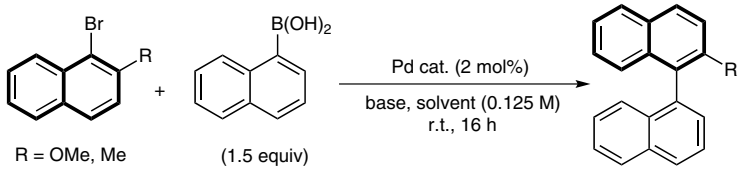


Scheme 2 NHC–Pd complexes tested in this study

When the complex (*Ra*,*Ra*)-**A** was used to catalyze the Suzuki–Miyaura coupling between 1-bromo-2-methoxynaphthalene and 1-naphthylboronic acid, high yields of the product were obtained. However, only low enantioselectivity (25%) was observed (Table 1, entry 1). We therefore decided to modify the structure of the NHC ligand. When the bulky and acyclic 4-heptyl moiety was introduced to the 2-position of the naphthyl group, a new NHC salt (Scheme 2, compound **B**) was generated, and a mixture of three diastereomers were observed in a ratio of 38:28:34 (*Sa*,*Sa*/*Ra*,*Ra*/*Ra*,*Sa*). While the separation of these three diastereomeric salts turned out to be impossible, we successfully separated the corresponding palladium cinnamyl complexes **C** via silica gel chromatography. The structure of one of the isomers [(*Ra*,*Sa*)-**C**] was unambiguously confirmed by single-crystal X-ray crystallography.[18] All of the three complexes were independently tested in the asymmetric Suzuki–Miyaura coupling. To our surprise, the *Ra*,*Ra* isomer [(*Ra*,*Sa*)-**C**], which was the isomer showing the best enantiomeric discrimination in the intramolecular asymmetric α-arylation giving oxindoles,[16a,b,17] again gave low enantioselectivity (Table 1, entry 2). In contrast, isomer (*Ra*,*Sa*)-**C** showed increased reactivity in this transformation while giving essentially racemic product (Table 1, entry 3). To our delight, the (*Sa*,*Sa*)-**C** diastereomer, which orients the 2-alkyl chains of the naphthyl wingtips opposite to the phenyl groups of the N-heterocyclic backbone, promoted this reaction efficiently affording the tri-*ortho*-substituted biaryl in excellent yield (91%) and moderately good enantioselecvitity (60% ee, Table 1, entry 4). When 1-bromo-2-methylnaphthalene instead of 1-bromo-2-methoxynaphthalene was used, a slightly lower ee was observed (Table 1, entry 5). Screening of the solvent revealed that toluene is the best choice and that ethereal solvents and dichloromethane gave lower enantioselectivities (Table 1, entries 6–9). The catalyst showed little reactivity in hexane (Table 1, entry 10). Optimization of the base showed that NaO*t*-Bu gave much lower yields and enantiomeric excesses compared to KO*t*-Bu (Table 1, entry 11), while the use of LiO*t*-Bu and KHMDS led to the recovery of the starting material (Table 1, entries 12 and 13).

With the optimized conditions in hand [2 mol% of the catalyst (*Sa*,*Sa*)-**C**, toluene as solvent and KO*t*-Bu as base], different substrates were tested, and the results are summarized in Table 2. In most of the cases, excellent yields were obtained by using 2 mol% of the (*Sa*,*Sa*)-**C** precatalyst. The coupling of 1-bromo-2-methylnaphthalene and 1-naphthylboronic acid afforded the product in excellent

Table 1 Optimization of Reaction Conditions for the Suzuki–Miyaura Coupling[a]



Entry	Pd catalyst	R	Base	Solvent	Yield (%)[b]	ee (%)[c]
1	**A**	OMe	KO*t*-Bu	toluene	90	25
2	(*Ra*,*Ra*)-**C**	OMe	KO*t*-Bu	toluene	55	22
3	(*Ra*,*Sa*)-**C**	OMe	KO*t*-Bu	toluene	93	8
4	(*Sa*,*Sa*)-**C**	OMe	KO*t*-Bu	toluene	**91**	**60**
5	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	toluene	**94**	**51**
6	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	THF	92	40
7	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	DME	83	50
8	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	dioxane	94	37
9	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	CH_2Cl_2	92	35
10	(*Sa*,*Sa*)-**C**	Me	KO*t*-Bu	hexane	<20	n.d.
11	(*Sa*,*Sa*)-**C**	Me	NaO*t*-Bu	toluene	43	35
12	(*Sa*,*Sa*)-**C**	Me	LiO*t*-Bu	toluene	<15	n.d.
13	(*Sa*,*Sa*)-**C**	Me	KHMDS	toluene	<10	n.d.

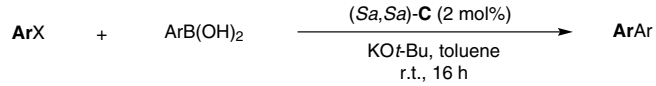
[a] Conditions: aryl bromide (0.125 mmol, 1 equiv), 1-naphthylboronic acid (1.5 equiv), base (2.5 equiv), Pd complex (2 mol%), solvent (1 mL), 25 °C, 16 h.
[b] Isolated yield.
[c] Determined by HPLC.

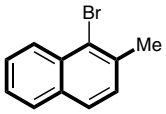
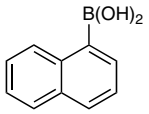
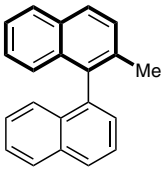
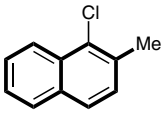
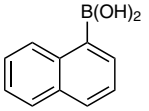
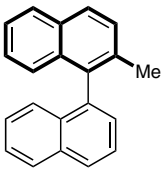
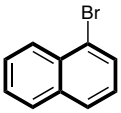
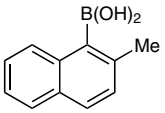
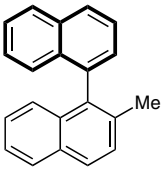
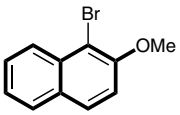
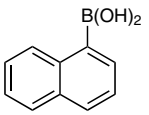
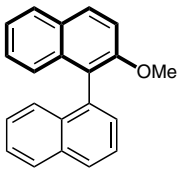
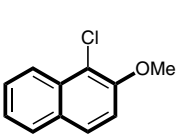
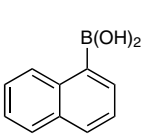
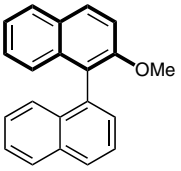
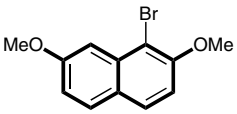
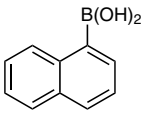
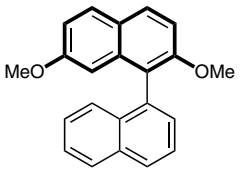
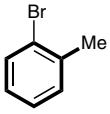
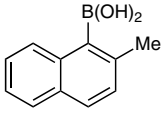
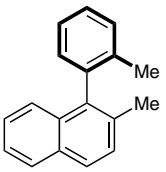
yield and 51% ee (Table 2, entry 1). Increasing the amount of boronic acid, base, and catalyst loading decreased the reactivity and selectivity (Table 2, entry 2). The use of (*Ra*,*Ra*)-**C** or the in situ generated catalyst {mixture of isomers of **B** with [Pd(cinnamyl)(μ-Cl)]$_2$} lowered the enantioselectivity (Table 2, entries 3 and 4) as well. The aryl chloride analogue could serve as the electrophile, although the yields and enantiomeric exesses decreased compared to the bromides (Table 2, entry 1 vs. 5, 7 vs. 8). Switching the electrophile and nucleophile of entry 1 had no effect on the yield and the enantiomeric exess decreased only marginally from 51% to 46% (Table 2, entry 1 vs. 6). Interestingly, the absolute configuration of the product was retained (both *S*).[10e] Introduction of a substituent on the 7-position of the naphthalene electrophile seems to be very deleterious to the selectivity (Table 2, entry 7 vs. 9). One example of *ortho*-substituted phenylbromide was examined, and the product 2-methyl-1-(2-methylphenyl)naphthalene was obtained in good yield (83%) but low enantiomeric excess (28%, Table 2, entry 10).[19]

With the promising results from the asymmetric Suzuki–Miyaura coupling in hand, we turned our attention to another versatile coupling – the Kumada coupling. Our pre-catalyst (*Sa*,*Sa*)-**C** promoted the asymmetric Kumada coupling smoothly giving the chiral biaryls in good yields but relatively low selectivities (Table 3). For instance, the in situ generated 2-methoxynaphthylmagnesium bromide is coupled with 1-bromonaphthalene at room temperature affording the chiral binaphthyl product in 81% yield and 48% ee (Table 3, entry 1). In this case, switching the nucleophile and electrophile with respect to each other reduced the reactivity and selectivity, but again the absolute configuration of the product was maintained, as already seen in the Suzuki–Miyaura coupling mentioned above (Table 3, entry 2). Using aryl chloride retained the selectivity, although the yield of the product decreased dramatically from 81% to 40% (Table 3, entry 3 vs. 1). Replacing 1-bromonaphthalene with 2-methylphenylbromide lowered both the yield and enantiomeric excess (Table 3, entry 4 vs. 1). The yield was improved with slight heating (50 °C), however, with a deleterious effect on the enantioselectivity (31% ee, Table 3, entry 5). Changing the electrophile to the corresponding chloride did not alter the outcome in terms of reactivity and selectivity (Table 3, entry 6). When a sterically more demanding nucleophile was employed (2-methylnaphthylmagnesium bromide), the enantioselectivity decreased (27% ee, Table 3, entry 7 vs. 1).

In conclusion, we report the synthesis of a new NHC ligand with a chiral N-heterocycle and naphthyl side chains substituted by 4-heptyl groups in the 2-position. The imidazolinium salts showed the existence of three different isomers in such NHC structures. Pure palladium complexes incorporating these ligands were obtained after simple chromatography. One of the resulting compounds [(*Sa*,*Sa*)-**C**] was tested in the asymmetric Suzuki–Miyaura and Kumada coupling that formed chiral biaryls in high yields and low to moderate enantioselectivities. This rep-

Table 2 Substrate Scope of the Asymmetric Suzuki–Miyaura Coupling[a]

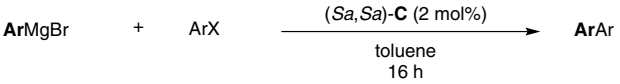


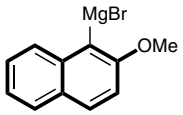
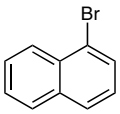
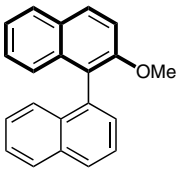
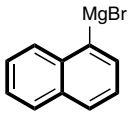
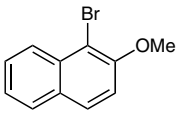
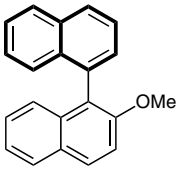
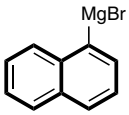
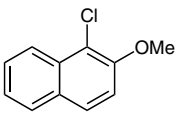
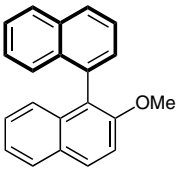
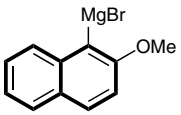
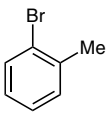
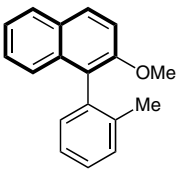
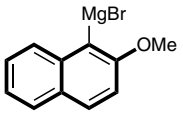
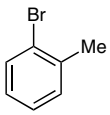
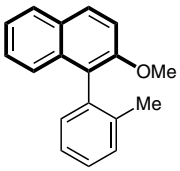
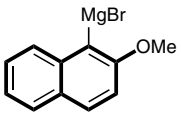
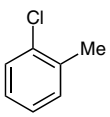
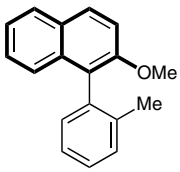
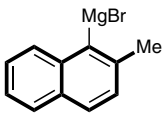
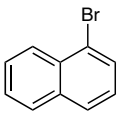
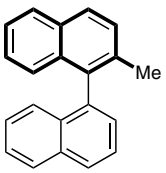
Entry	**Ar**X	$ArB(OH)_2$	**Ar**–Ar	Yield (%)[b]	ee (%)[c]
1				94	51 (*S*)
2				90	43 (*S*)[d]
3				85	30 (*S*)[e]
4				95	27 (*S*)[f]
5				66	33 (*S*)
6				93	46 (*S*)
7				91	60 (*R*)
8				70	50 (*R*)
9				86	12
10				83	28

[a] Conditions: **Ar**X (0.125 mmol, 1 equiv), $ArB(OH)_2$ (1.5 equiv), KO*t*-Bu (2.5 equiv), (*Sa*,*Sa*)-**C** (2 mol%), toluene (1 mL), 25 °C, 16 h.
[b] Isolated yield.
[c] Determined by HPLC. The absolute configuration was assigned by comparison with literature data.
[d] $ArB(OH)_2$ (2.5 equiv), KO*t*-Bu (3.5 equiv), (*Sa*,*Sa*)-**C** (5 mol%).
[e] (*Ra*,*Ra*)-**C** (2 mol%), 50 °C.
[f] **B** (5 mol%), [Pd(cinnamyl) (μ-Cl)]$_2$ (2.5 mol%).

resents the first example of asymmetric coupling giving chiral biaryls by using a monodentate NHC ligand. That precatalysts [(*Ra*,*Ra*)-**A**] and [(*Ra*,*Ra*)-**C**] failed in this reaction warrants further mechanistic studies and might be due to the fact that these NHC structures show a higher steric crowding and/or might not be able to accommodate the substrates via π-stacking as proposed by Lassaletta and co-workers.[10e] Studies aimed at increasing the enantioselectivities via fine-tuning of the NHC structure are under way.

Table 3 Substrate Scope of the Asymmetric Kumada Coupling[a]



Entry	**Ar**MgBr	ArX	Temp. (°C)	**Ar**–Ar	Yield (%)[b]	ee (%)[c]
1			r.t.		81	48 (*R*)
2[d]			50		72	37 (*R*)
3			50		40	41 (*R*)
4			r.t.		51	39
5[d]			50		71	31
6[d]			50		77	31
7			r.t.		78	27 (*S*)

[a] Conditions: **Ar**MgBr (0.25 mmol, 1 equiv), ArX (1.0 or 2.0 equiv), (*Sa*,*Sa*)-**C** (2 mol%), THF (2 ml), 16 h.
[b] Isolated yield.
[c] Determined by HPLC. The absolute configuration was assigned by comparison with literature data.
[d] Conditions: 2.0 equiv of halide were used.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) CCDC 936764 [(*Ra*,*Sa*)-**C**)] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) The Suzuki–Miyaura coupling using the corresponding aryl iodide (2-iodotoluene) gave very similar results (81% yield, 27% ee).

graphical abstract