

New Chiral N-Heterocyclic Carbene Ligands in Palladium-Catalyzed α -Arylations of Amides: Conformational Locking through Allylic Strain as a Device for Stereocontrol

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Dedicated to Professor Reinhard W. Hoffmann

Abstract: New Enders/Herrmann-type chiral N-heterocyclic carbene (NHC) ligands have been developed and applied in asymmetric palladium-catalyzed intramolecular α -arylations of amides. The best ligands feature the bulky *tert*-butyl group and *ortho*-substituted aryl groups at the stereogenic centers. Aryl bromides readily react at room temperature and aryl chlorides at

50 °C. The highly enantiomerically enriched (up to 96 % *ee*) 3-alkyl-3-aryloxindole products were obtained in generally high yields (>95 %) except in

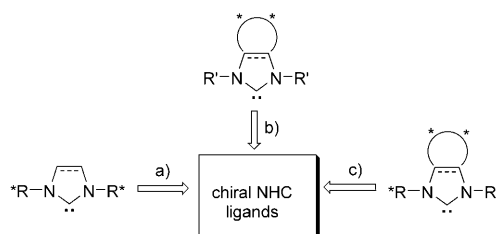
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cases of steric congestion. The critical roles both of the bulky alkyl group and of the *ortho*-aryl substituent at the stereogenic center of the ligand were revealed in the crystal structure of a [Pd(η^3 -allyl)(NHC-L*)(I)] complex. The ligand aryl location and orientation is fixed by conformational locking that minimizes A^{1,3}-strain and enables optimal transfer of chiral information.

Introduction

Isolable and stable N-heterocyclic carbenes (NHCs) were first reported by Arduengo et al. in 1991.^[1] As ligands for transition metals, NHCs are strong σ -donors and weak π -acceptors and they form robust carbon–metal bonds. These characteristics have led to their rapid emergence as a new and important class of ligands for homogeneous catalysis.^[2,3] Chiral NHC ligands are also receiving growing attention^[4] with approaches centered on the strategies depicted in Scheme 1: a) chiral N-substituents (stereogenic centers^[5] chiral biaryls, planar chiral units),^[6] b) chiral N-heterocycles,^[7] or c) a combination of the above strategies.^[8]

A large number of chiral NHC ligands based on these designs have been developed and some of them have been successfully applied in reactions such as ruthenium-catalyzed asymmetric metathesis,^[6c,7,9] rhodium-catalyzed asymmetric



Scheme 1. Strategies for the development of chiral N-heterocyclic carbene ligands.

hydrosilylation,^[6d,10] rhodium-^[11] and copper^[12]-catalyzed conjugated additions, and iridium-catalyzed asymmetric hydrogenation.^[5d,13] Despite the successes in this field, highly enantioselective applications of chiral NHC ligands in catalysis are still rare in relation to those involving chiral N-, O-, and P-ligands. New efficient chiral NHC ligands for asymmetric catalysis are needed along with insight into their modes of asymmetry transfer. This article focuses on this quest.

Pioneered by the groups of Herrmann^[5a] and Enders,^[5b] chiral NHC ligands derived from chiral phenethylamine and its analogues (Figure 1) have become one of the most important types of chiral ligands. Most efforts in their develop-

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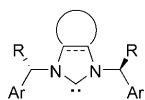


Figure 1. Enders/Herrmann-type chiral NHC ligands.

ment have focused on the modification of the aromatic group and the N-heterocyclic ligand backbone, whereas little attention has been paid to modification of the alkyl R group ($R = \text{Me}$ in almost all cases).^[5a,b,8] We felt that the in-

troduction of sterically more demanding R groups at the ligand stereogenic centers might be beneficial to asymmetric induction and show here that this hypothesis proved correct.

We had previously reported the efficient synthesis of the chiral *ortho*-substituted α -alkylbenzylamines **1a–c** (Figure 2) and shown their applications as chiral auxiliaries,^[14] starting materials for chiral dibenzoazepines,^[15] and as building blocks for chiral bidentate benzoxazine P/N ligands.^[16] We have now turned our attention to the synthesis of chiral NHC ligands starting from these amines. In doing this, a new family of bulky Enders/Herrmann-type chiral NHC ligands containing alkyl groups of different steric demand at their chiral benzylic positions were generated. In addition we have probed the effect of *ortho*-substituents on the aryl groups. As shown below, they play a crucial role in asymmetric induction.

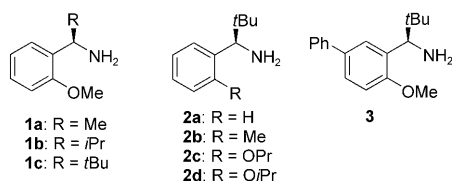


Figure 2. Chiral amines for the synthesis of imidazolium and dihydroimidazolium salts.

The reaction that we chose for testing of the ligands was the palladium-catalyzed asymmetric intramolecular α -arylation of amides. Initial results of this study have been the object of preliminary communications.^[17]

Pioneered by Hartwig and co-workers, intramolecular α -arylation of amides provides efficient and direct access to chiral 3,3-disubstituted oxindoles.^[18] These represent a common structural motif found in many natural products with a variety of significant biological activities, making them interesting and challenging targets for chemical synthesis.^[19]

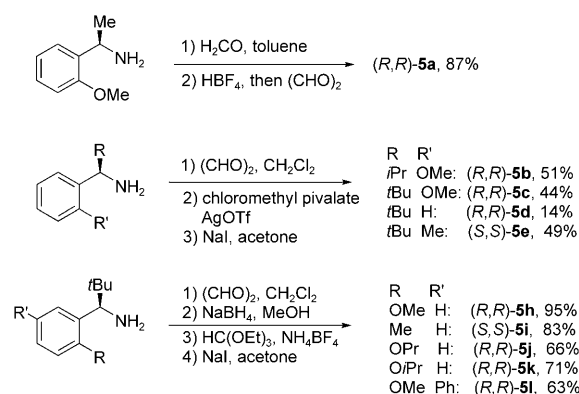
Other asymmetric transition-metal-catalyzed routes to enantiomerically enriched 3,3-disubstituted oxindoles include palladium-catalyzed intramolecular Heck reactions,^[20] allylation of oxindoles,^[21] domino Heck/cyanation reactions,^[22] cyanoamidation reactions,^[23] fluorination of oxindoles,^[24] rhodium-catalyzed addition to isatin,^[25] and zinc-catalyzed hydroxylation of oxindoles.^[26]

Hartwig's group screened a large number of chiral phosphine and NHC ligands. Chiral phosphines generally performed poorly and bulky chiral NHC ligands were best, but

with enantioselectivities not exceeding 76% there remained room for improvement. Efforts directed towards improving these results by other groups did not meet with success,^[18b,c] although after our communications^[17] Glorius and co-workers were very recently also successful in this endeavor.^[19l]

Results and Discussion

Synthesis of ligand precursors: The first series of ligands synthesized were the unsaturated imidazolium salts **5**, from the starting chiral *ortho*-substituted α -alkylbenzylamines **1–3** (Figures 2 and 3). The imidazolium tetrafluoroborate salt (*R,R*)-**5a** was synthesized by a standard one-pot procedure in 87% yield (Scheme 2).^[27] This proved inefficient for



Scheme 2. General procedures for the synthesis of imidazolium and dihydroimidazolium ligand precursors. The R amine precursors are depicted.

(*R,R*)-**5b** and completely failed in the synthesis of (*R,R*)-**5c** with a bulky *t*Bu group at the benzylic position. Compounds (*R,R*)-**5b** and (*R,R*)-**5c** were therefore synthesized by a method involving diimine formation, ring-closure, and anion-exchange (Scheme 2). In the ring-closing step, the method based on chloromethyl pivalate and AgOTf worked well,^[18b] giving the imidazolium triflates in moderate yields. Anion-exchange of TfO^- for I^- allowed us to obtain solid products instead of oily salts, greatly facilitating purification. Overall it is a simple process and no purification of the intermediates was needed. Product yields were moderate (Scheme 2). Similarly, the imidazolium iodides (*R,R*)-**5d** and (*S,S*)-**5e** were obtained in 14 and 49% yields from (*R*)-**2a** and (*S*)-**2b**, respectively.

The dihydroimidazolium salts **5h–l** were synthesized by a four-step procedure that involved diimine formation followed by reduction (NaBH_4) to the diamines, ring-closure, and anion metathesis (Scheme 2). Ring-closure of diamines was carried out with NH_4BF_4 and triethyl orthoformate. Subsequent anion exchange afforded the dihydroimidazolium iodide salts **5h–l** in good to excellent yields (Scheme 2).

The ligand heterocyclic ring was further modified to access the structurally diverse ligand precursors (*R,R*)-**5f**, (*S,S*)-**5g** (with a benzoimidazolium ring), and (*R,R*)-**5m**

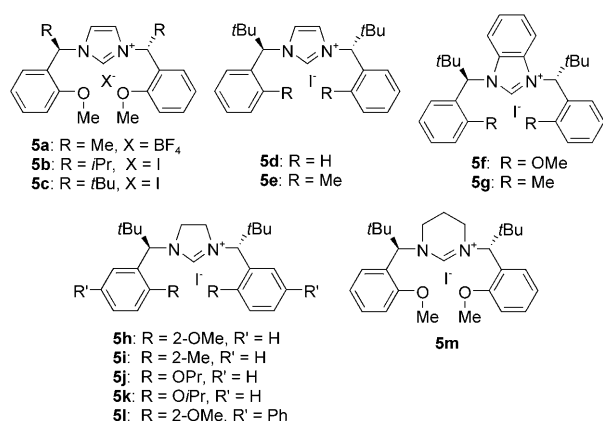
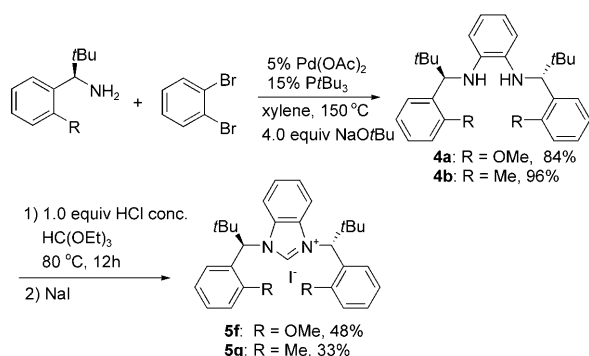


Figure 3. New chiral NHC ligands.

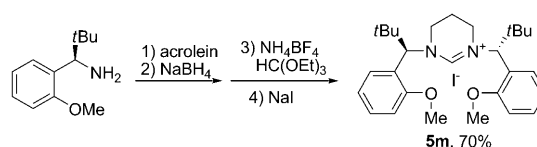
(with a six-membered N-heterocycle). In an application of the Buchwald–Hartwig amination procedure,^[28] reactions between (*R*)-**1c** or (*S*)-**2b** and 1,2-dibromobenzene were carried out with Pd(OAc)₂ (5 mol %), PtBu₃ (15 %), and NaOtBu (4 equiv) in xylene at 150 °C over 16 h to give the chiral amines (*R,R*)-**4a** and (*S,S*)-**4b** in 84 and 96 % yield, respectively (Scheme 3). Chiral HPLC showed that no race-



Scheme 3. Synthesis of the benzoimidazolium iodide salts (*R,R*)-**5f** and (*S,S*)-**5g**.

mization had occurred during this process. The ring-closing method used for the synthesis of dihydroimidazolium salts **5h–l** with NH₄BF₄ and HC(OEt)₃ failed when applied to the syntheses of (*R,R*)-**5f** and (*S,S*)-**5g**. However, treatment of the chiral amines **4** with concentrated HCl in triethyl orthoformate as solvent at 80 °C gave the requisite benzoimidazolium chloride salts in low yields. Through recovery of the starting materials **4** and rerunning the reactions four times, followed by anion-exchange of Cl[−] for I[−] by treatment with NaI, the products (*R,R*)-**5f** and (*S,S*)-**5g** were obtained in 48 and 33 % yield, respectively.

The six-membered N-heterocycle product (*R,R*)-**5m** was synthesized by a four-step procedure (Scheme 4).^[29] Treatment of (*R*)-**1c** with acrolein and subsequent in situ reduction gave the 1,3-diamine; cyclization by treatment with

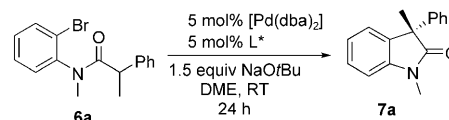


Scheme 4. Synthesis of (*R,R*)-**5m**.

NH₄BF₄ and HC(OEt)₃, followed by anion metathesis with NaI, afforded (*R,R*)-**5m** in 70 % yield.

Oxindole synthesis: The reaction conditions of Hartwig and Lee were initially applied for comparison of results (Table 1, entry 1).^[18a] Ligand (*R,R*)-**5a** with Me groups at the stereogenic benzylic centers afforded the oxindole **7a** in acceptable yield but very low enantiomeric excess (entry 2). The presence of increasing bulk at the stereogenic center (entries 3 and 4) resulted in products of higher enantiomeric purity.

Table 1. Asymmetric intramolecular arylation of amides to form enantioenriched oxindoles **7**.^[a]



Entry	L*	Yield [%] ^[a]	ee [%] ^[b]	Config. ^[c]
1 ^[d]		74	57	n.d.
2 ^[e]	(<i>R,R</i>)- 5a	72	16	<i>S</i>
3 ^[e]	(<i>S,S</i>)- 5b	93	77	<i>S</i>
4 ^[e]	(<i>S,S</i>)- 5c	96	87	<i>S</i>

[a] Isolated yield. [b] Determined by chiral HPLC (Chiralcel OD-H). [c] The absolute configuration was assigned on the basis of the X-ray structure of (−)-(*S*)-**18**. [d] Ref. [18a]. Best result with **6a**. n.d.=not determined. [e] Conditions: **6a** (0.25 mmol, 0.05 M in the indicated solvent), base (1.5 equiv), 24 h.

With these results to hand, optimization of the reaction in the presence of (*S,S*)-**5c** was undertaken (Table 2). Changing from DME to dioxane and THF resulted in only minor decreases in the *ee* of the product, but in a sharp drop in yield in the case of THF (entries 2 and 3). In toluene the reaction was characterized by low conversion and a further erosion of asymmetric induction (entry 4), whereas in benzene the reaction did not take place at all at room temperature, although complete conversion was achieved upon heating to 75 °C, which led to a modest product *ee* of 67 % (entry 5). Starting material was recovered in dichloromethane (entry 6).

Of the bases tested, NaOtBu was the best, as already indicated in the literature.^[18a] With NaH as base only a 14 % *ee* was obtained (entry 7), whereas NaHMDS and LiOtBu did not promote the reaction (entries 8 and 9). The yield was lower when KOtBu was used instead of NaOtBu (entry 10).

Table 2. Variation of solvent, temperature, and base in the Pd/(*S,S*)-**5c**-catalyzed reaction **6a** → (*S*)-**7a**.

Entry	[Pd]	Solvent	Base	<i>T</i> [°C]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	[Pd(dba) ₂]	DME	NaOtBu	23	96	87
2	[Pd(dba) ₂]	dioxane	NaOtBu	23	94	85
3	[Pd(dba) ₂]	THF	NaOtBu	23	10	86
4	[Pd(dba) ₂]	toluene	NaOtBu	23	20	73
5	[Pd(dba) ₂]	benzene	NaOtBu	75	96	67
6	[Pd(dba) ₂]	CH ₂ Cl ₂	NaOtBu	40	0 ^[d]	–
7	[Pd(dba) ₂]	DME	NaH	23	65	14
8	[Pd(dba) ₂]	DME	NaHMDS	23	0 ^[d]	–
9	[Pd(dba) ₂]	DME	LiOtBu	23	0 ^[d]	–
10	[Pd(dba) ₂]	DME	KOtBu	23	76	88
11	Pd(OAc) ₂	DME	NaOtBu	23	98	87
12 ^[e]	Pd(OAc) ₂	DME	NaOtBu	50	90	84

[a] Conditions: **6a** (0.25 mmol, 0.05 M in the indicated solvent), [Pd] (5 mol %), (*S,S*)-**5c** (5 mol %), base (1.5 equiv), 24 h. The absolute configuration was assigned on the basis of the X-ray structure of (–)-(*S*)-**18**. [b] Isolated yield. [c] Determined by chiral HPLC (Chiralcel OD-H). [d] No reaction. [e] 14 h.

The reader is reminded that in this reaction the base has a double role: it generates both the carbene ligand and the enolate in the catalytic cycle. Finally, switching from [Pd(dba)₂] to Pd(OAc)₂ gave an identically high yield of highly enantiomerically enriched product **7a** (entry 11). Increasing the temperature from RT to 50 °C reduced reaction time but also product *ee* (entry 12).

Next, the modified NHC ligands **5d–m** were investigated and the results are shown in Table 3. Pertinent features are:

Table 3. Chiral NHC ligands in the Pd-catalyzed α-arylation of **6a** to give **7a**.^[a]

Entry	Ligand precursor	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	(<i>S,S</i>)- 5c	24	96	87 (<i>S</i>)
2	(<i>R,R</i>)- 5d	24	98	57 (<i>R</i>)
3	(<i>S,S</i>)- 5e	24	99 ^[d]	94 (<i>S</i>)
4 ^[e]	(<i>S,S</i>)- 5e	24	51	96 (<i>S</i>)
5	(<i>R,R</i>)- 5f	48	67	80 (<i>R</i>)
6	(<i>S,S</i>)- 5g	48	65	91 (<i>S</i>)
7	(<i>R,R</i>)- 5h	14	98	88 (<i>R</i>)
8	(<i>S,S</i>)- 5i	48	55	92 (<i>S</i>)
9	(<i>R,R</i>)- 5j	14	98	75 (<i>R</i>)
10	(<i>R,R</i>)- 5k	14	98	71 (<i>R</i>)
11	(<i>R,R</i>)- 5l	14	98	88 (<i>R</i>)
12	(<i>R,R</i>)- 5m	48	60	68 (<i>R</i>)

[a] Same reaction conditions as shown in entry 1 of Table 1 for 14–24 h. [b] Isolated yield. [c] Determined by chiral HPLC (Chiralcel OD-H). [d] 1 mmol scale. [e] At 10 °C for 24 h. [f] 48 h.

- 1) A bulky *t*Bu group at the stereogenic benzylic center is essential, but not sufficient, for high asymmetric induction (compare entries 2–4 in Table 1).
- 2) Equally important is the presence of an *ortho*-aryl substituent (compare entries 1–3 in Table 3). The best performer was the ligand **5e** with an *o*-Me group (entry 3), followed by **5c** with an *o*-OMe group (entry 1). Both give much better inductions than the ligand **5d** (entry 2).
- 3) The dihydroimidazolium-derived N-heterocyclic carbene ligands came close to the imidazoline carbene ligands in

performance and their synthesis is more efficient. The same trend (*o*-Me > *o*-OMe) in asymmetric induction was found in this series: **5i** > **5h** (entries 8 and 7). Larger *o*-substituents as in **5j** (OPr) and **5k** (OiPr) gave lower product *ee* values.

- 4) Modification of the ligand core structure as in **5f**, **5g**, and **5m** led to poorer performance (entries 5, 6, and 12).
- 5) The only ligand bearing an aryl group with two substituents that was tested was **5l** (entry 11). Induction was high but did not reach those achieved with **5i** and **5e**.

Substrate scope: We next probed the scope and limitations of the reaction with the ligand precursor (*S,S*)-**5e** under the conditions established above (Table 3, entry 3). The substrates **6a–6j** were synthesized from the corresponding anilines and acid chlorides and the oxindoles (*S*)-**7a–j** were obtained with good to excellent enantioselectivities and in high yields (Table 4). An exception is the attempted conversion of **6c** (entry 3), which did not afford the oxindole product, showing that the presence of a free N–H bond in the substrate is incompatible with this transformation. The *N*-benzyl-protected substrate **6b** afforded the oxindole (*S*)-**7b** (entry 2) and hydrogenolysis with Li/NH₃ afforded (*S*)-**7c**. Reactions with substrates incorporating *ortho*-aryl substituents were sluggish and led to products in modest (entry 9) to good (entries 6, 7) yields. In these cases the ligand precursor (*S,S*)-**5c** performed better than (*S,S*)-**5e** (entries 7, 9, and 11).

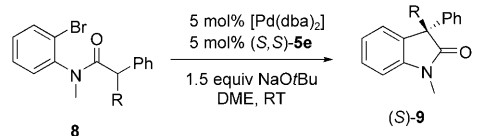
Table 4. Palladium-catalyzed α-arylation of substrates **6a–j**.^[a]

Entry	Product	R	Ar	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1 ^[d]	(<i>S</i>)- 7a	Me	Ph	24	99	94
2	(<i>S</i>)- 7b	Bn	Ph	24	94	84
3	(<i>S</i>)- 7c	H	Ph	24	0 ^[f]	–
4 ^[d]	(<i>S</i>)- 7d	Me	4-tol	24	99	93
5 ^[d]	(<i>S</i>)- 7e	Me	3-tol	24	99	93
6	(<i>S</i>)- 7f	Me	2-tol	24	98	86
7 ^[e]	(<i>S</i>)- 7f	Me	2-tol	36	98	89
8	(<i>S</i>)- 7g	Me	4-MeO-Ph	14	98	93
9 ^[e]	(<i>S</i>)- 7h	Me	2-MeO-Ph	36	42	84
10	(<i>S</i>)- 7i	Me	1-naphth	36	72	79
11 ^[e]	(<i>S</i>)- 7i	Me	1-naphth	24	98	84
12	(<i>S</i>)- 7j	Me	2-naphth	36	96	95

[a] Substrate in DME (0.05 M, 0.2 mmol); absolute configurations were assigned by comparison of the circular dichroism (CD) spectra with that of (*S*)-**7b**. [b] Isolated yield. [c] Determined by chiral HPLC [d] 1 mmol scale. [e] With (*S,S*)-**5c** as ligand precursor. [f] No reaction.

Table 5 lists the results for the reactions of substrates **8** with different alkyl groups at their benzylic positions. Increasing the size of the R groups in **8** led to sluggish reactions and lower enantioselectivities (Table 5). This is particu-

Table 5. Palladium-catalyzed α -arylation of substrate **8**.^[a]



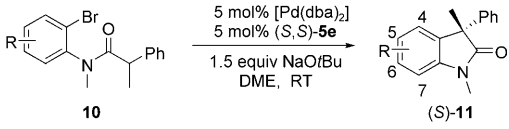
Entry	Product	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	(<i>S</i>)- 9a	48	82	90
2	(<i>S</i>)- 9b	48	80	52
3	(<i>S</i>)- 9c	48	86	89
4	(S)- 9d	0.9	98	55
5 ^[d]		1.5	98	59

[a] Substrate in DME (0.05 M, 0.2 mmol); absolute configurations were assigned by analogy and are tentative. [b] Isolated yield. [c] Determined by chiral HPLC. [d] -20°C .

larly striking with $\text{R} = i\text{Pr}$ (**8b**) and the indanyl substrate **8d**, for which the product *ees* for (*S*)-**9b** and (*S*)-**9d** were in the modest 50–60% *ee* range (entries 2, 4, 5). In contrast with the reactions in entries 1–3, which required up to 2 d to go to completion, the reaction of **8d**, to afford the spirocyclic oxindole **9d**, was complete in <1 h at RT and in 1.5 h at -20°C (entries 4 and 5).

Table 6 lists the results for the reactions of substrates with different substituents in the aniline component. Yields and enantioselectivities were generally very high for substrates with either electron-donating or electron-withdrawing substituents at C(5) or at C(6). Erosion of asymmetric induction was observed for C(7)-substituted substrates; the oxindoles

Table 6. Palladium-catalyzed α -arylation of substrate **10**.^[a]

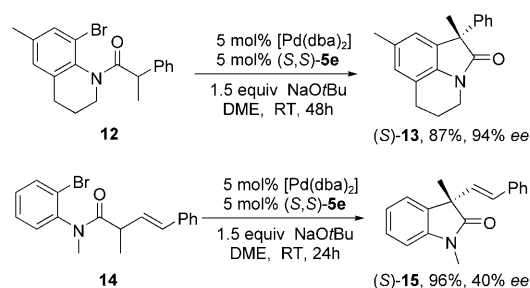


Entry	Product	R	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	(<i>S</i>)- 11a	C5-Me	24	98	95
2	(<i>S</i>)- 11b	C5- <i>i</i> Pr	24	98	92
3	(<i>S</i>)- 11c	C5,7-Me	24	82	26
4	(<i>S</i>)- 11d	C6-CF ₃	48	98	95
5	(<i>S</i>)- 11e	C6-F	48	96	94
6	(<i>S</i>)- 11f	C6-OMe	24	98	95
7 ^d	(<i>S</i>)- 11g	C7-F	24	96	72

[a] Substrate in DME (0.05 M, 0.2 mmol); absolute configurations were assigned by analogy and were tentative. [b] Isolated yield. [c] Determined by chiral HPLC. [d] At 50°C .

(*S*)-**11c** and (*S*)-**11g** were thus obtained with 25 and 72% *ee*, respectively (entries 3 and 7).

Incorporation of C(7) substitution into a six-membered ring structure reestablished very high product *ees*, as shown for substrate **12** (Scheme 5), which yielded the tricyclic oxin-

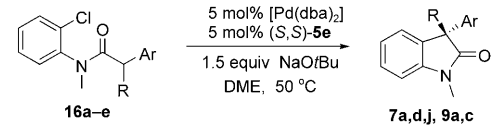


Scheme 5. Asymmetric synthesis of oxindoles (*S*)-**13** and (*S*)-**15**.

dole (*S*)-**13** in 87% yield and with 94% *ee*. Each of the 22 examples above involves an oxindole with an aryl group at the newly formed stereogenic center. An exception is substrate **14**, which yielded the oxindole **15** (Scheme 5), albeit with a very modest *ee* of 40%, attesting to the fact that the search for catalytic systems for this and a wider range of substrates is by no means over.

Finally, attention was turned to the aryl chloride substrates **16** (Table 7). Mechanistic studies showed that the reaction involves rate-limiting oxidative addition of aryl halide.^[18a] In accord with literature precedence, slightly higher reaction temperatures are required for aryl chlorides.^[18a,19] Gratifyingly, at 50°C reactions occurred smoothly and although asymmetric induction is lower than with the bromo analogues, values are still in the range between 84 and 94% *ee*.

Table 7. Palladium-catalyzed α -arylation of chloride-substrates **16**.^[a]

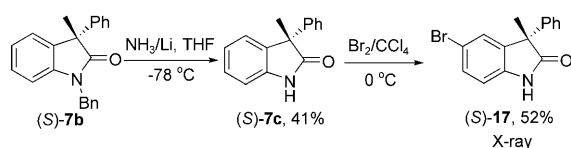


Entry	R	Ar	Product	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	16a	Me	(<i>S</i>)- 7a	24	98	90
2 ^[d]	16a	Me	(<i>S</i>)- 7a	48	21	94
3	16b	Me	(<i>S</i>)- 7d	24	98	91
4	16c	Me	(<i>S</i>)- 7j	24	98	91
5	16d	Et	(<i>S</i>)- 9a	24	98	84
6	16e	Bn	(<i>S</i>)- 9c	24	97	85

[a] Substrate in DME (0.05 M, 0.2 mmol); absolute configurations were assigned by analogy and were tentative. [b] Isolated yield. [c] Determined by chiral HPLC. [d] At room temperature.

Determination of the absolute configuration of (*S*)-7b**:** The absolute configuration of product (*S*)-**7b** was determined through an X-ray crystal structure analysis of compound (*S*)-**17**, which was obtained from (*S*)-**7b** by hydrogenolysis

and bromination (Scheme 6). The X-ray structure of **17** showed it to have the *S* configuration (Figure 4). Assignment of other enantiomerically enriched oxindole products was by analogy (comparison of CD spectra) and is tentative.



Scheme 6. Derivatization of (*S*)-**7b** to (*S*)-**17** for the determination of the absolute stereochemistry through its X-ray structure.

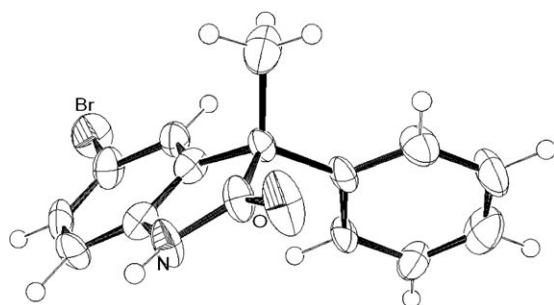
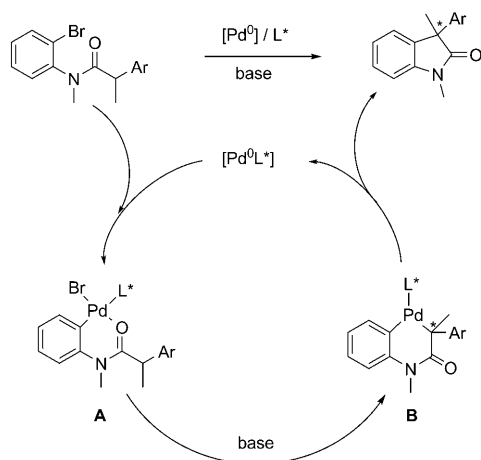


Figure 4. ORTEP structure of (*S*)-**17**.^[17a]

Mechanism: The mechanism proposed by Hartwig is shown in Scheme 7. Although the Pd-C enolate **B** could not be observed, a phosphine complex of the palladacycle **A** was isolated, spectroscopically fully characterized, and shown to yield the oxindole product when treated with base.^[18a] We found that, as expected, a 1:1 mixture of two diastereomers of **A** was formed when **5e** was used in this reaction. Chiral induction from this intermediate could occur during the Pd-O-enolate to Pd-C-enolate rearrangement (**A**→**B**) or during reductive elimination. The process may also be influenced



Scheme 7. Hartwig's proposed catalytic cycle.^[18a]

by different rates of deprotonation of the two diastereomers **A**.^[30]

Asymmetric induction: The ligand screening (Table 3) attests to the importance of the bulky *t*Bu and the *o*-toluyl or *o*-anisyl groups at the stereogenic center. In a search for a rationale for this finding, the complex $[[\text{Pd}(\eta^3\text{-allyl})((S,S)\text{-5e})(\text{I})]]$ (**18**) was synthesized from $[\text{Pd}(\text{allyl})\text{Cl}]_2$, (*S,S*)-**5e**, and NaOtBu in DME.^[31] Its ¹H NMR spectrum indicated the presence of a mixture of *exo* and *endo* allyl complexes. Recrystallization afforded a crystal suitable for X-ray analysis (Figure 5).^[32] In accordance with previous structures of $[\text{Pd}(\text{allyl})(\text{NHC})\text{Cl}]$ complexes,^[33] the structure of **18** is that of a distorted square-planar Pd^{II} complex with one carbon of the η^3 -allyl group *trans* to the iodide and the other *trans* to the NHC ligand. The Pd–C_{allyl} bond *trans* to the NHC ligand is 2.207 Å and that opposite the iodide is 2.145 Å. The Pd–C_{NHC} bond is 2.044 Å. These values are in the typical range for those previously found in closely analogous complexes.^[33]

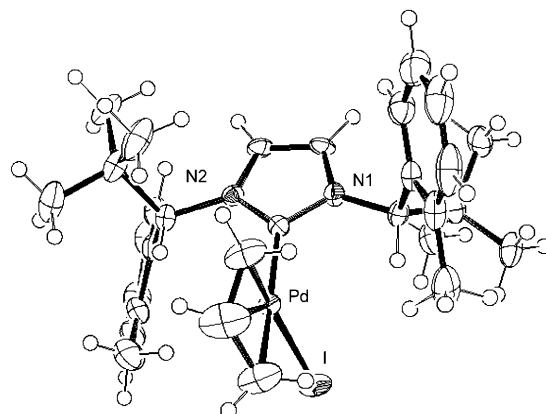


Figure 5. ORTEP structure of $[\text{Pd}(\eta^3\text{-allyl})(S,S\text{-5e})(\text{I})]]$ [(*S,S*)-**18**].

Our interest then focused on the chiral ligand and the role of the different ligand elements in generating the chiral site that led to high asymmetric induction. Figure 6 shows the ligand geometry with respect to the Pd–(*S,S*)-**5e** bond. For clarity, the allyl and iodide moieties have been left out. Also note that the descriptor **5e** is used for both the complexed carbene ligand and the ligand precursor (imidazolium iodide). The large groups at the stereogenic centers enforce coplanarity of the C(ligand)–Pd bond/C–H bond of the stereogenic center. Rotation around the N–C(stereogenic center) bond would lead to allylic strain.^[34] This fixes the aryl groups in space; their orientations are determined by the aryl *o*-substituents. Again, minimization of A^{1,3}-strain is in operation and, as can be seen in Figure 6, the C(Ar)–CH₃ bond is coplanar with the C–H bond of the stereogenic center. Note that rotating the aryl groups by 180° would lead to a situation in which the Me groups would be in conflict with the *t*Bu groups.

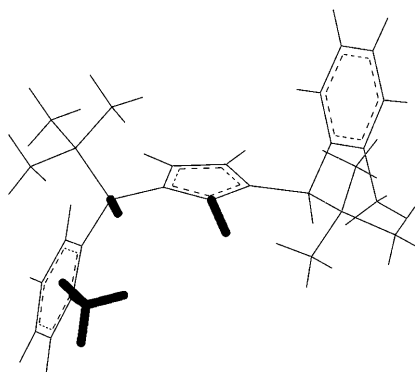


Figure 6. Stereochemical arrangement of key elements in Pd-(*S,S*)-**5e** (from the X-ray structure of complex **18**).

Overall, the ligand, when coordinated to Pd^{II}, adopts a *C*₂ chiral structure. Although it is tempting to use Figure 6 and the knowledge of the absolute stereochemistry of the oxindole products **7** to settle on **B** as a model (Scheme 7) and to hypothesize on the origin of asymmetric induction, we would prefer to collect more data (e.g., an X-ray structure of **A**) rather than to speculate at this stage.^[30]

We note that the X-ray structure of the imidazolium salt (*R,R*)-**5e** is different in that both *t*Bu groups are in one hemisphere and the aryl groups in the other (Figure 7). The H atoms at the stereogenic centers are again coplanar with the imidazolium ring, but in the absence of the large Pd two orientations are possible and the one adopted in the solid-state structure is shown here.

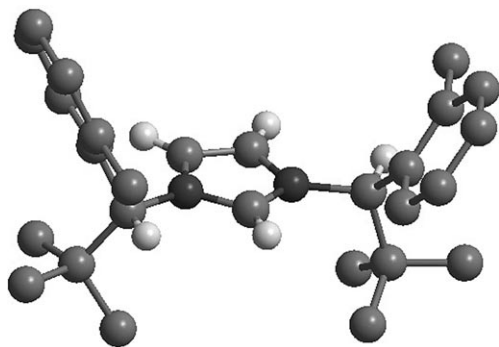


Figure 7. X-ray structure of (*R,R*)-**5e** (iodide omitted).^[17a]

The buried volume (% *V*_{bur}) for ligand **5e** is 37.4%.^[35] The ligand is thus bulkier than common NHC ligands (such as IMes), but its % *V*_{bur} value is far below the value of ~50% recently reported for chiral NHC ligands by Glorius's group, which provided excellent results in the enantioselective arylation of amides.^[19] We conclude that exceptional bulk may help but it is not a necessary requirement. Less bulky ligands can give high asymmetric induction provided that their stereodirecting groups are placed judiciously. Our results with ligands **5e** and **5i** attest to this.

Conclusion

We have developed a new family of Enders/Herrmann-type chiral N-heterocyclic carbene ligands. These were very successfully applied in the asymmetric palladium-catalyzed α -arylation of amides, affording 3,3-disubstituted oxindoles with high enantiomeric excesses. It was confirmed experimentally that the asymmetric induction provided by the metal-ligand system is strongly linked to the presence in the ligand both of a bulky *tert*-butyl group and of an *ortho*-aryl substituent at the stereogenic benzylic centers. The critical role of the *ortho*-aryl substituent has been shown by an X-ray analysis of a crystal structure of a Pd^{II}(allyl)(NHC ligand) iodide complex. The place and orientation of the ligand aryl groups are fixed by the minimization of A^{1,3} strain. Further development of chiral NHC ligands by this principle, their application in organic and organometallic catalysis, and detailed mechanistic studies of chiral induction in oxindole synthesis are in progress in our laboratory.

Experimental Section

General: Solvents were purified by filtration on drying columns with a Solvtek[®] system or by distillation over Na/benzophenone. Reactions and manipulations involving organometallic or moisture-sensitive compounds were carried out under purified nitrogen in glassware dried by heating under high vacuum. M.p.: Büchi 510. GC: Hewlett–Packard 6890 gas chromatograph with FID detection on a Permabond OV-1701–0.25 column (25 m $\times$ 0.32 mm ID). HPLC: Agilent 1100 series chromatograph. NMR: Bruker AMX 500, AMX 400, or AMX 300 FT; internal D-lock. IR spectra: Perkin–Elmer Spectrum One. Neat liquids; Golden Gate accessory. HRMS: +TOF mode, ESI-MS mode, Applied Biosystems/Sciex (Q-STA) spectrometer. [α]_D: Perkin–Elmer 241 polarimeter, quartz cell (*l* = 10 cm), Na high-pressure lamp (λ = 589 nm). CD spectra: Jasco J-715, quartz cell (*l* = 1 cm).

Amines: Synthesis and spectroscopic and analytical details of the chiral precursor amines have been reported as indicated: (*R*)-**1a**,^[36] (*S*)-**1b**,^[37] (*S*)-**1c**,^[37] (*R*)-**2a**,^[17a] (*S*)-**2b**,^[17a] and (*R*)-**3**.^[17b]

Chiral carbene ligand precursors: For details of the synthesis of and data for the chiral carbene precursors see the experimental sections and the supporting information in the references indicated: (*R,R*)-**5a**,^[17a] (*S,S*)-**5b**,^[17a] (*S,S*)-**5c**,^[17a] (*R,R*)-**5d**,^[17a] (*S,S*)-**5e**,^[17a] and (*R,R*)-**5i**.^[17b] For X-ray structure details of (*S*)-**18** and imidazolium salt (*R,R*)-**5e**, see ref. [17a].

a) Synthesis of diamines

General procedure for the synthesis of dihydroimidazolium iodide salts—**a) Synthesis of diamines:** Aq. glyoxal (*n* mmol) was introduced into CH₂Cl₂ (5 mL per mmol glyoxal) and vigorously stirred with freshly dehydrated Na₂SO₄ (2.0 g per mmol glyoxal). After addition of formic acid (7 mol %) and chiral amine (2*n* mmol), the mixture was stirred at RT until completion of the reaction (monitored by TLC). The mixture was then filtered, and volatiles were removed in vacuo to yield the diimine, which was dissolved in MeOH (15 mL per mmol glyoxal) and cooled to 0°C. NaBH₄ (2.5*n* mmol) was added to the solution of diimine in MeOH and the resulting mixture was stirred overnight. After evaporation of MeOH, the residue was filtered through a short SiO₂ pad with ether to give the diamine as a light oil for further use without purification.

b) Synthesis of imidazolium iodides: HC(OEt)₃ (5 mL per mmol diamine) was introduced into the mixture of the above diamine (*n* mmol) and NH₄BF₄ (*n* mmol), and the mixture was stirred under N₂ at 125°C for 8 h. After cooling to RT and evaporation to dryness, the residue was dissolved in acetone and then NaI (5.0*n* mmol) was added. After the system had been stirred at RT for 12 h, acetone was removed, CH₂Cl₂

was added, and the solution was then filtered through cotton. This BF_4^-/I^- exchange was repeated once more. After evaporation of acetone, the residue was purified by flash chromatography to give the dihydroimidazolium iodide salt as a yellow powder.

Compound (R,R)-5h: 95 % yield; m.p. 99–101 °C; $[\alpha]_{\text{D}}^{20} = -40.6$ ($c = 0.5$ in CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3): $\delta = 1.21$ (s, 18H), 3.78–3.85 (m, 2H), 3.91 (s, 6H), 3.97–4.04 (m, 2H), 5.36 (s, 2H), 7.01 (dd, $J = 7.5$, 15.2 Hz, 4H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.53 (d, $J = 7.6$ Hz, 2H), 9.29 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 28.2$, 36.2, 49.4, 55.9, 64.4, 111.5, 120.5, 122.4, 129.6, 130.2, 157.4, 158.9 ppm; IR (ATR diam.): $\tilde{\nu} = 2960$, 2838, 1620, 1600, 1584, 1490, 1461, 1438 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{27}\text{H}_{39}\text{N}_2\text{O}_2$ $[M-\text{I}]^+$: 423.3006; found: 423.3029.

Compound (S,S)-5i: 83 % yield; m.p. 220–222 °C; $[\alpha]_{\text{D}}^{20} = +45.7$ ($c = 0.5$ in CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 1.22$ (s, 18H), 2.63 (s, 6H), 3.79–3.91 (m, 2H), 3.98–4.08 (m, 2H), 5.47 (s, 2H), 7.27–7.35 (m, 6H), 7.49 (m, $J = 7.1$ Hz, 2H), 10.83 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 22.0$, 28.1, 37.3, 48.8, 65.7, 125.9, 128.1, 128.7, 132.0, 132.4, 138.6, 159.2 ppm; IR (ATR diam.): $\tilde{\nu} = 2958$, 2909, 2871, 1623, 1479, 1462 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{27}\text{H}_{39}\text{N}_2$ $[M-\text{I}]^+$: 391.3107; found: 391.3114.

Procedures and spectral and analytical data for ligand precursors (R,R)-5f and for (S,S)-5g, (R,R)-5j, (R,R)-5k, and (R,R)-5m are given in the Supporting Information.

Substrates: The synthesis of and spectroscopic and analytical details for the oxindole precursors 6a–j have been reported.^[17a]

Procedures and spectral and analytical data for the bromo and chloro precursors 8a–d, 10a–g, 12, 14, and 16a–e to the oxindoles are given in the Supporting Information.

Catalytic asymmetric intramolecular α -arylation reactions

The synthesis of and spectroscopic and analytical details for the following oxindoles have been reported: (S)-7a–j,^[17a] rac-9a,^[38] rac-9c and rac-9d.^[38]

Compound (S)-11d: A dried Schlenk tube was charged under N_2 with $[\text{Pd}(\text{dba})_2]$ (5.7 mg, 0.01 mmol), (S,S)-5e (5.2 mg, 0.01 mmol), and NaOtBu (28.8 mg, 0.3 mmol). Dimethoxyethane (DME, 1 mL) was added and the mixture was stirred for 10 min. Compound 10d (77.2 mg, 0.2 mmol) was then added as a solution in DME (3 mL). The reaction mixture was stirred at RT for 48 h and then quenched with aq. NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with water and brine and dried over MgSO_4 . Flash chromatography over SiO_2 afforded (S)-11d (59.8 mg, 98 %). HPLC [Chiralcel OD-H] showed (S)-11d to have been formed with 95 % ee. Oil; $[\alpha]_{\text{D}}^{20} = -66.54$ ($c = 1.0$ in CH_2Cl_2), HPLC [Chiralcel OD-H column, *n*-hexane/*i*PrOH 99:1, 1.0 mL min⁻¹, 254 nm; $t_{\text{R}} = 18.87$ min (major) and 27.57 min (minor)]; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.86$ (s, 3H), 3.34 (s, 3H), 7.18 (s, 1H), 7.29–7.45 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): 23.5, 26.6, 52.2, 105.0, 105.1, 119.8, 119.9, 124.4, 127.6, 130.5, 130.9, 138.7, 139.8, 143.9, 179.1 ppm; IR (neat): $\tilde{\nu} = 3062$, 2933, 1720, 1624, 1458 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{NO}$ $[M+\text{H}]^+$: 306.1100; found: 306.1086.

Compound (S)-11g: A dried Schlenk tube was charged under N_2 with $[\text{Pd}(\text{dba})_2]$ (5.7 mg, 0.01 mmol), (S,S)-5e (5.2 mg, 0.01 mmol), and NaOtBu (28.8 mg, 0.3 mmol). Dimethoxyethane (DME, 1 mL) was added and the mixture was stirred for 10 min. Compound 10g (67.2 mg, 0.2 mmol) was then added as a solution in DME (3 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched with aq. NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with water and brine and dried over MgSO_4 . Flash chromatography over SiO_2 afforded (S)-11g (49.0 mg, 96 %). HPLC [Chiralcel OD-H] showed (S)-11g to have been formed with 72 % ee. Oil; $[\alpha]_{\text{D}}^{20} = -40.9$ ($c = 0.1$ in CH_2Cl_2); HPLC [Chiralcel OD-H column, *n*-hexane/*i*PrOH 99:1, 1.0 mL min⁻¹, 254 nm; $t_{\text{R}} = 8.92$ min (major) and 12.0 min (minor)]; ^1H NMR (300 MHz, CDCl_3): $\delta = 1.84$ (s, 3H), 3.5 (d, $J = 2.1$ Hz, 3H), 6.95–7.15 (m, 3H), 7.28–7.41 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl_3): $\delta = 14.2$, 23.8, 28.9, 29.0, 52.4, 60.4, 115.9, 116.1, 120.0, 120.1, 123.3, 123.35, 125.4, 126.5, 127.4, 128.6, 129.9, 137.7, 140.3, 146.6, 149.0, 179.1 ppm; IR (neat): $\tilde{\nu} = 3057$, 2973, 1717, 1631, 1631, 1480, 1366, 1334,

1279, 1235, 1098, 1054, 951, 776, 731, 696 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{16}\text{H}_{14}\text{FNO}$ $[M+\text{H}]^+$: 256.1131; found: 256.1123.

Compound (S)-13: A dried Schlenk tube was charged under N_2 with $[\text{Pd}(\text{dba})_2]$ (5.7 mg, 0.01 mmol), (S,S)-5e (5.2 mg, 0.01 mmol), and NaOtBu (28.8 mg, 0.3 mmol). DME (1 mL) was added and the mixture was stirred for 10 min. Compound 12 (71.6 mg, 0.2 mmol) was then added as a solution in DME (3 mL). The reaction mixture was stirred at RT for 48 h and was then quenched with aq. NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with water and brine and dried over MgSO_4 . Flash chromatography over SiO_2 afforded (S)-13 (48.3 mg, 87 %). HPLC [Chiralcel OD-H] showed (S)-13 to have been formed with 94 % ee. Oil; $[\alpha]_{\text{D}}^{20} = -109.2$ ($c = 1.0$ in CH_2Cl_2), HPLC [Chiralcel OD-H column, *n*-hexane/*i*PrOH 99:1, 1.0 mL min⁻¹, 254 nm; $t_{\text{R}} = 24.33$ min (major) and 31.36 min (minor)]; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.84$ (s, 3H), 2.05–2.1 (m, 2H), 2.38 (s, 3H), 2.84 (t, $J = 8$ Hz, 2H), 3.78 (q, $J = 4.8$ Hz, 2H), 6.93 (d, $J = 10$ Hz, 2H), 7.27–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): 21.4, 23.7, 24.6, 39.1, 53.5, 120.1, 122.6, 126.7, 127.1, 127.3, 128.5, 131.7, 133.4, 136.6, 141.0, 178.3 ppm; IR (neat): $\tilde{\nu} = 3021$, 2928, 2868, 1703, 1626, 1491, 1432 cm^{-1} ; HRMS (EI): m/z : calcd for $\text{C}_{19}\text{H}_{19}\text{NO}$ $[M+\text{H}]^+$: 278.1539; found: 278.1538.

Procedures and spectral and analytical data for oxindoles (S)-9a–d, (S)-11a–g, (S)-13, (S,E)-15 and for $[\text{Pd}(\eta^3\text{-allyl})(\text{S,S}-5\text{e})\text{-I}]$ [(S,S)-19] are given in the Supporting Information.

Acknowledgements

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