Asymmetric Catalysis

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Bulky Chiral Carbene Ligands and Their Application in the Palladium-Catalyzed Asymmetric Intramolecular α-Arylation of Amides**

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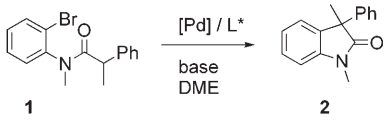
In memory of Yoshihiko Ito

Single enantiomers of chiral amines are starting materials for N-heterocyclic carbenes (NHC),[1] and these NHCs have found very significant applications in asymmetric catalysis.[2] The first chiral NHC ligands that were evaluated in asymmetric catalysis were carbenes derived from enantiopure 1-phenylethylamines.[3] We felt that sterically more demanding carbene ligands derived from *o*-alkyl- and *o*-alkoxy-α-alkylbenzylamines merited attention. As an application we chose the palladium-catalyzed asymmetric intramolecular α-arylation of amides because chiral oxindole products are of synthetic interest and because the literature precedents for this reaction showed that there was room for improvement in asymmetric induction.[4–6] Herein we report the first results of our studies.

Oxindole alkaloids containing a quaternary benzylic center belong to a large family of natural products that exhibit a variety of significant biological activities, making them interesting and challenging targets for chemical synthesis.[7] Asymmetric transition-metal-catalyzed reactions that provide access to enantiomerically enriched 3-alkyl-3-aryl oxindoles are scarce: Overman and co-workers' elegant intramolecular Heck reactions,[8] palladium-catalyzed allylation of 3-arylindoles,[9] and the palladium-catalyzed intramolecular α-arylation of amides,[4–6] which are the focus of the present study.

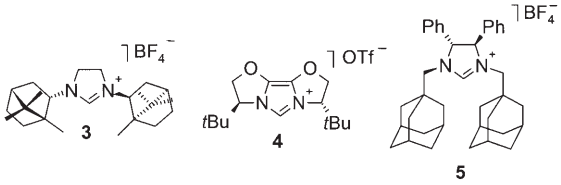
Hartwig and Lee tested nineteen mono- and bidentate chiral phosphorous ligands and three in-situ-generated chiral carbene ligands in this reaction, and showed the carbenes outperformed the phosphines.[4] As an example, the best result for the asymmetric cyclization of amide **1** is shown in Scheme 1 together with the results of subsequent reports on this reaction.[5,6]



1 **2**

Carbene precursor	[Pd]		Base	Conditions	Yield of **2** (*ee*)	Ref
3	$[Pd(dba)_2]$	(5%)	NaO*t*Bu	25 °C, 24h	74% (57%)[a]	[4]
4	$[Pd_2(dba)_3]$	(10%)	NaO*t*Bu	20 °C, 14h	95% (43%)[a]	[5]
5	$Pd(OAc)_2$	(10%)	LiO*t*Bu	100 °C, 12h	62% (61%)[b]	[6]

[a] (+)-enantiomer. [b] (*S*)-enantiomer.



Scheme 1. Literature precedents for the palladium-catalyzed asymmetric intramolecular α-arylation of amides. L* = chiral carbene, dba = *trans*,*trans*-dibenzylideneacetone.

Herein we report new chiral carbene ligands that are derived from readily synthesized highly enantiomerically enriched *ortho*-substituted α-alkylbenzylamines.[10] They have found application as chiral auxiliaries in chromium-mediated transformations of arenes,[11] as starting materials for chiral dibenzoazepines,[12] building blocks for chiral bidentate benzoxazine P/N ligands,[13] chiral phosphoramidite ligands,[14] and they have been used in the synthesis of a chiral Ti^{IV} amine triphenolate complex.[15]

The imidazolium tetrafluoroborate salt **7a** was obtained in good yield by a standard one-pot procedure: condensation of **6a** with formaldehyde and cyclization with glyoxal and tetrafluoroboronic acid (Scheme 2, upper route).[16] This procedure did not give satisfactory results when applied to the more bulky analogues, and hence **7b** and **7c** were synthesized from **6b** and **6c**, respectively, using the method of Glorius and co-workers.[5] This two-step sequence involving diimine formation and ring closure with chloromethylpivalate and silver triflate afforded the imidazolium triflates. The oily products were difficult to purify but this problem was solved

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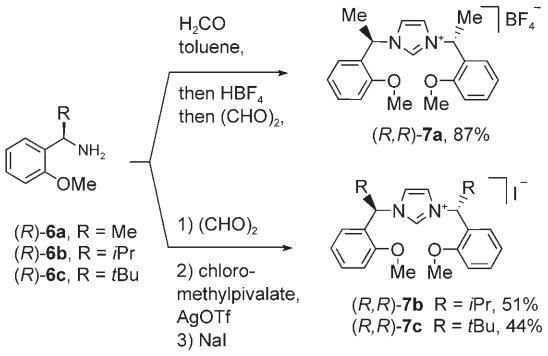
Supporting information for this article (synthesis of **8a** and **8b**, **7a–e** (NMR, IR, MS data, CD spectra, $[\alpha]_D^{20}$), **1b,f,i** (NMR, IR, MS data), the palladium-catalyzed asymmetric intramolecular α-arylation to give **2a-i** (NMR data, HPLC data and traces, CD spectra, $[\alpha]_D^{20}$), the conversion of (−)-**2i** into **10**, and the X-ray structure determinations of (*R*,*R*)-**7e** and (−)-(*S*)-**10**) is available on the WWW under http://www.angewandte.org or from the author.



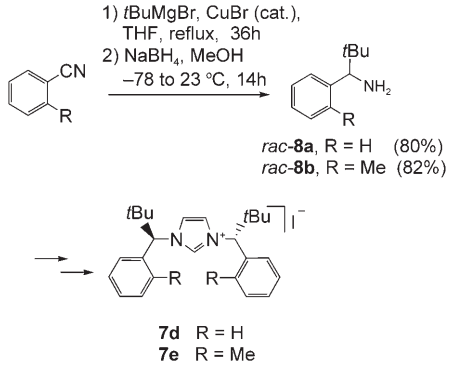
Scheme 2. Synthesis of imidazolium salts (*R,R*)-**7a–c**. Identical procedures were used for (*S,S*)-**7a–c**. OTf = triflate.

by anion metathesis with NaI to give **7b** and **7c**. This also removed residual silver salts (Scheme 2, lower route).

Hartwig and Lee's conditions were applied in our study to compare results with those depicted in Scheme 1; the results are shown in Table 1. The ligand **7a** with methyl groups at the stereogenic benzylic centers afforded the oxindole in acceptable yield but very low enantiomeric excess (*ee* value; Table 1, entry 1).

The result was markedly improved with ligand **7b** (Table 1, entry 2) which shows much higher induction and also a switch in asymmetric induction. A further significant increase in product *ee* value occurred when ligand **7c** was used (Table 1, entry 3). Changing the solvent to dioxane produced very similar results in both yield and asymmetric induction (Table 1, entry 4). In aromatic solvents, the reaction is sluggish but can be driven to completion by heating. The *ee* values in these reactions were however considerably lower (Table 1, entries 5 and 6). CH_2Cl_2 was not a suitable solvent; no oxindole product was formed and decomposition was evident. Going back to DME and switching from $[Pd(dba)_2]$ (dba = *trans,trans*-dibenzylideneacetone) to $Pd(OAc)_2$ produced a near-identical result in the two reactions (Table 1, entries 3 and 7). The reaction time could be shortened to 14 h by heating to 50 °C but with a small erosion of both yield and *ee* (Table 1, entry 8). The question that still remained open at this stage and needed answering was that of the role of the *o*-aryl substituent.

The imidazolium salts **7d** and **7e** (Scheme 3) were to shed light on this question and the requisite amines were synthesized by arylnitrile alkylation with *t*BuMgCl in the presence of CuBr as catalyst, followed by in situ reduction with $NaBH_4$. This procedure afforded the primary amines *rac*-**8a** and *rac*-**8b** in 80 % and 82 % yield, respectively (Scheme 3).



Scheme 3. Synthesis of the amines *rac*-**8a** and *rac*-**8b** followed by resolution and conversion into the imidazolium salts **7d** and **7e** (*R,R*)-enantiomers shown).

An enantiopure sample of (*R*)-**8a** was obtained according to a literature procedure,[17] and enantiomerically pure imidazolium salt (*R,R*)-**7d** was obtained using the same procedure as described for (*R,R*)-**7c**. *Rac*-**8b** was resolved by forming the diastereoisomeric salt with L-malic acid in ethanol. Other acids tested included *N*-acetyl leucine, mandelic acid, tartaric acid, camphor sulfonic acid, and 5-oxoproline, but their performance as resolving agent of **8b** was very poor. The (*S,S*)-salt of malic acid/**8b** crystallized preferentially (97:3 d.r.) and a second recrystallization afforded, after separation, the amine (*S*)-**8b** in 33 % overall yield (max. = 50 %) and > 99 % *ee*. The imidazolium salt (*S,S*)-**7e** was synthesized as detailed for (*R,R*)-**7c**. (*R,R*)-**7e** was prepared analogously from (*R*)-(+)-**8b** and its absolute configuration was determined by X-ray analysis (see Supporting Information).[18] Applying (*R,R*)-**7d** to the asymmetric cyclization afforded product **2** efficiently, albeit in modest enantiomeric purity (Table 1, entry 9). With the importance of the *ortho*-aryl substituent established, the question of ether versus alkyl group was probed.

The result in Table 1, entry 10 shows that the chiral carbene ligand derived from **7e** tops the performance of that based on **7c**. These two chiral carbene ligands

Table 1: Chiral carbene ligands in the palladium-catalyzed intramolecular cyclization of amide **1** to oxindole **2**.[a]

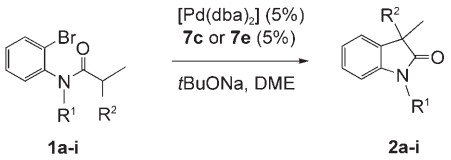
Entry	L*	[Pd]	*T* [°C]	*t* [h]	Solvent	Yield of **2** [%][b]	*ee* [%][c]	Optical rotation	Config[d]
1	(*R,R*)-**7a**	$[Pd(dba)_2]$	23	24	DME	72	16	(−)	*S*
2	(*S,S*)-**7b**	$[Pd(dba)_2]$	23	24	DME	93	77	(−)	*S*
3	(*S,S*)-**7c**	$[Pd(dba)_2]$	23	24	DME	96	87	(−)	*S*
4	(*S,S*)-**7c**	$[Pd(dba)_2]$	23	24	dioxane	94	85	(−)	*S*
5	(*S,S*)-**7c**	$[Pd(dba)_2]$	23	24	toluene	20	73	(−)	*S*
6	(*S,S*)-**7c**	$[Pd(dba)_2]$	75	24	benzene	96	67	(−)	*S*
7	(*S,S*)-**7c**	$Pd(OAc)_2$	23	24	DME	98	87	(−)	*S*
8	(*S,S*)-**7c**	$Pd(OAc)_2$	50	14	DME	90	84	(−)	*S*
9	(*R,R*)-**7d**	$[Pd(dba)_2]$	23	24	DME	98	57	(+)	*R*
10	(*S,S*)-**7e**	$[Pd(dba)_2]$	23	24	DME	99[e]	94	(−)	*S*

[a] Conditions: 0.25 mmol **1**, 0.05 M in the indicated solvent, [Pd] 5 mol %, L* 5 mol %, 1.5 equiv NaO*t*Bu. dba = *trans,trans*-dibenzylideneacetone. [b] Yield of isolated product after flash chromatography. [c] Determined by HPLC chromatography (Chiralcel ODH). [d] Assigned on the basis of the X-ray structure determination of (−)-(*S*)-**10**. [e] 1-mmol scale.

7c and **7e** generated in situ were then applied to different substrates (Scheme 4, Table 2).

The data in Table 2 show the new bulky chiral carbene ligands to yield chiral oxindoles with good to excellent asymmetric inductions. Yields are generally very high. Exceptions are reactions with substrates incorporating the *o*-anisyl substituent (Table 2, entry 8), and electron-poor aryl substituents (*p*-CF_3, CO_2Me, not shown) for which reactions were very sluggish and yields low.

Attempts at obtaining crystals suitable for an X-ray structure determination of a Pd/**7c** or Pd/**7e** complex have not yet met with success and we therefore defer discussion of mechanism and a rationale for the asymmetric induction to a later date.

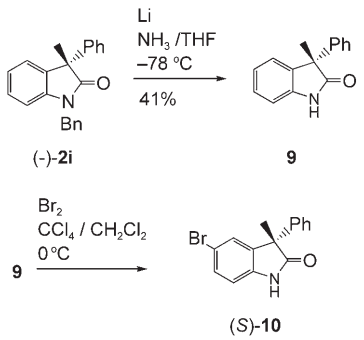


Scheme 4. Scope of the palladium-catalyzed asymmetric intramolecular α-arylation of amides (see Table 2 for details).

Table 2: Asymmetric oxindole synthesis from 2-bromoanilides.[a]

Entry	L*	R^1	R^2	*t* [h]	Product	Yield[b] [%]	*ee* [%][c]
1	(*S*,*S*)-**7c**	Me	Ph	24	(*S*)-(−)-**2a**	98	87
2	(*S*,*S*)-**7e**	Me	Ph	24	(*S*)-(−)-**2a**[d]	99	94
3	(*S*,*S*)-**7e**	Me	*p*-Tol	24	(*S*)-(−)-**2b**[d]	99	93
4	(*S*,*S*)-**7e**	Me	*m*-Tol	24	(*S*)-(−)-**2c**[d]	99	93
5	(*S*,*S*)-**7c**	Me	*o*-Tol	36	(*S*)-(+)-**2d**	98	89
6	(*S*,*S*)-**7e**	Me	*o*-Tol	24	(*S*)-(+)-**2d**	98	86
7	(*S*,*S*)-**7e**	Me	*p*-PhOMe	14	(*S*)-(−)-**2e**	98	93
8	(*S*,*S*)-**7c**	Me	*o*-PhOMe	36	(*S*)-(+)-**2f**	42	84
9	(*S*,*S*)-**7c**	Me	1-Napht	24	(*S*)-(−)-**2g**	98	84
10	(*S*,*S*)-**7e**	Me	1-Napht	36	(*S*)-(−)-**2g**	72	79
11	(*S*,*S*)-**7e**	Me	2-Napht	36	(*S*)-(−)-**2h**	96	95
12	(*S*,*S*)-**7c**	Bn[e]	Ph	24	(*S*)-(−)-**2i**	75	79
13	(*S*,*S*)-**7e**	Bn[e]	Ph	24	(*S*)-(−)-**2i**	94	84

[a] Unless otherwise noted: 0.2–0.25 mmol substrate, DME, [Pd(dba)$_2$] 5 mol%, 1.5 equiv of NaO*t*Bu, 23 °C [b] Yield of isolated product after flash chromatography. [c] Determined by HPLC chromatography (see Supporting Information). [d] 1 mmol of substrate. [e] Bn = benzyl.



Scheme 5. Conversion of oxindole (−)-**2i** into the 5-bromo derivative **10**. Bn = benzyl.

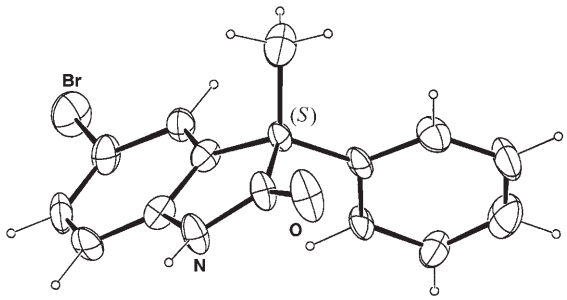


Figure 1. X-ray structure of (−)-(*S*)-**10**. Thermal ellipsoids are set at 50% probability.

Oxindole (−)-**2i**, formed using the catalyst derived from [Pd(dba)$_2$] and (*S*,*S*)-**7c** (Table 2, entry 12) was transformed into the bromo-derivative of **10** by the route shown in Scheme 5 as adapted from the literature.[8] The X-ray structure determination (Figure 1) showed **10** to have the (*S*)-configuration.[18] The absolute configuration of the oxindoles reported in Table 2 was assigned by comparison of the circular-dichroism (CD) spectra of **2a–h** with that of **2i**.

In summary, we report new bulky chiral carbene ligands from readily prepared *ortho*-substituted α-alkylbenzylamines. Applied to the palladium-catalyzed asymmetric intramolecular α-arylation of amides, oxindoles containing a quaternary benzylic stereogenic center are formed in high yield and excellent enantiomeric purity.

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[18] CCDC-629335 ((−)-(*S*)-**10**) and CCDC-629336 ((*R*,*R*)-**7e**) contain 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.

