

Highly Chemo- and Enantioselective Synthesis of 3-Allyl-3-aryl Oxindoles via the Direct Palladium-Catalyzed α -Arylation of Amides

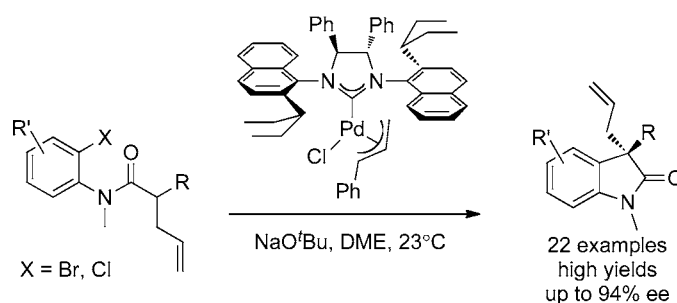
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ABSTRACT



A new NHC-Pd-catalyzed asymmetric α -arylation of amides is reported that gives direct access to synthetically valuable, allylated oxindoles with quaternary carbon centers. The reaction is made possible by the introduction of a new chiral NHC ligand. The palladium complexes derived therefrom combine excellent reactivity with high chemo- and enantioselectivity for the title transformation.

Oxindoles bearing a quaternary carbon stereocenter at the 3-position represent a prominent structural motif in a range of alkaloid natural products¹ and pharmaceutical compounds,² and the development of synthetic methods for these compounds, including the ones with new substitution patterns, is therefore of high importance in organic chemistry. Consequently, several transition-metal-catalyzed enantioselective approaches were established over the past decade: Overman's elegant intramolecular Heck reactions,^{1b,c,3} Trost's Pd- or Mo-mediated allylic alkylations,⁴ Pd-catalyzed intra-

and intermolecular arylations pioneered by Hartwig⁵ and Buchwald,⁶ Takemoto's Pd-catalyzed cyanoamidation protocol,⁷ and most recently, Stoltz's Cu-catalyzed alkylations.^{8,9}

As part of our ongoing research on employing chiral monodentate *N*-heterocyclic carbene (NHC) ligands for

(1) For reviews, see: (a) Bindra, J. S. In *Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, p 83. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488. (d) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (e) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (f) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (g) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003.

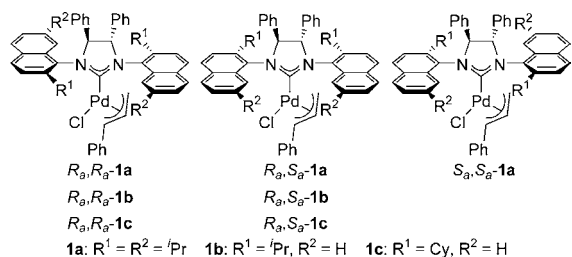
(2) (a) Berg, S.; Bhat, R.; Edwards, P.; Hellberg, S. *PCT Int. Appl.* **2003** (WO 2003055877 AI 20030710 CAN 139:101026). (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. (c) Jiang, T.; Kuhnen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105. (d) Hewawasam, P.; Gribkoff, V. K.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487. (e) Jensen, B. S. *CNS Drug Rev.* **2002**, *8*, 353.

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(4) (a) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548.

metal-catalyzed asymmetric catalysis, we recently reported the synthesis of diastereomerically pure palladium complexes incorporating new chiral NHC ligands and their successful application in the Pd-catalyzed intramolecular α -arylation of amides to obtain enantiomerically enriched 3-aryl-3-methyl oxindoles.^{5c} While elegant as a methodology to obtain chiral quaternary carbon centers, the intramolecular α -arylation at present has the drawback of providing oxindoles that are difficult to functionalize further. We therefore wondered whether 3-allyl-3-aryl oxindoles, previously accessible only via a two-step procedure involving a Pd-catalyzed intramolecular α -arylation followed by an asymmetric Pd-catalyzed allylic alkylation,^{4a,9} could be obtained directly. Herein we report the successful achievement of this strategy by using a newly designed NHC ligand.

Scheme 1. Previously Reported Palladium Complexes **1a–c**



Our investigation commenced by examining the ability of previously reported NHC·Pd complexes **1a–c** (Scheme 1)^{5f} to promote the intramolecular α -arylation of the model substrate **2a**. At the outset, it was not clear whether such α -arylations would be preferred over a reaction scenario involving Heck cyclizations giving rise to 7-*exo-trig* (or 8-*endo-trig*) products. The results reported in Table 1 indeed indicate that product **4a** was formed in noticeable amounts (15–20%) with all diastereomers of catalysts **1a–c**. Trends

(5) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (b) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704. (c) Arao, T.; Sato, K.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1576. (d) Arao, T.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 1743. (e) Kundig, E. P.; Seidel, T. M.; Jia, Y.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484. (f) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10*, 5569. (g) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344.

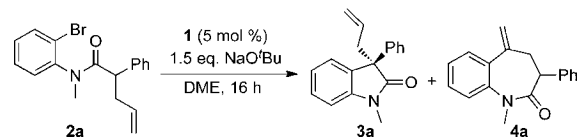
(6) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.

(7) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.

(8) Ma, S.; Han, X.; Krishnan, S.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8037.

(9) For other metal-catalyzed reactions leading to similar oxindoles, see: (a) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. (b) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (c) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.–Eur. J.* **2007**, *13*, 961. (d) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chem. Commun.* **2008**, 4040. (e) Jia, Y.-X.; Katayev, D.; Kundig, E. P. *Chem. Commun.* **2010**, 46, 130. For asymmetric organocatalytic approaches leading to similar products with quaternary carbon centers starting from preformed 3-aryloxindoles and derivatives, see: (f) Hills, I. D.; Fu, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (g) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559. (h) Jiang, K.; Peng, J.; Cui, H.; Chen, Y. *Chem. Commun.* **2009**, 3955.

Table 1. Initial Screening of Pd-Complexes **1a–c**



entry	NHC·Pd	<i>t</i> [°C]	convn [%] ^a	3a:4a ^b	ee [%] ^{c,d}
1	<i>R_αR_α-1a</i>	23	>99	5:1	–24 (<i>S</i>)
2	<i>R_αS_α-1a</i>	23	>99	4:1	56 (<i>R</i>)
3	<i>S_αS_α-1a</i>	23	>99	5:1	34 (<i>R</i>)
4	<i>R_αR_α-1b</i>	50	>99	4:1	39 (<i>R</i>)
5	<i>R_αS_α-1b</i>	50	>99	4:1	58 (<i>R</i>)
6	<i>R_αR_α-1c</i>	50	>99	6:1	46 (<i>R</i>)
7	<i>R_αS_α-1c</i>	50	>99	4:1	66 (<i>R</i>)

^a Determined by GC–MS. ^b Determined by analysis of ¹H NMR spectra of product mixtures prior to purification. ^c Determined by HPLC for **3a**. ^d Configuration of **3a** assigned according to ref 10.

in enantioselectivity though were immediately apparent. Diastereomers of catalyst **1a**, which performed best in our previous investigation, gave erratic results with inconsistent absolute configurations of product **3a**. Omitting the *R*²-isopropyl group on the wingtips of the NHC (precatalysts **1b**) gave more usable results (entries 4 and 5). Furthermore, precatalyst **1c** that incorporates a slightly bulkier *R*¹-cyclohexyl group resulted in better enantioselection (entries 6 and 7). Although both the chemoselectivity as well as the enantioselectivity (66% ee) were still not practical, the simple fact that representative chiral mono- and bidentate phosphorus ligands showed inferior results (see Supporting Information) suggested that complexes **1a–c** contained the more promising overall catalyst motif.

The tendencies in selectivity observed in Table 1 were subsequently implemented in the design of a modified chiral NHC structure that lacks the *R*² wingtip group and incorporates a bulkier, unstrained 3-pentyl moiety on the 2-position of the naphthyl side chains. The precursor imidazolium salt was obtained relatively easily (see Supporting Information), and subsequent deprotonation, reaction with [Pd(cinnamyl)Cl]₂, and chromatographic workup gave precatalyst **1d** in 82% yield as three separable diastereomers [*R_αR_α-1d* (37%), *R_αS_α-1d* (32%) and *S_αS_α-1d* (13%)] (Scheme 2).

The results with standard substrate **2a** (Table 2, entries 1–3) were very encouraging and all three diastereomeric precatalysts **1d** proved superior to their congeners **1a–c** both in terms of their higher reactivity (room temperature)¹¹ and their enhanced selectivity. As an unexpected and extremely welcome side effect, incorporation of the new ligand greatly

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(11) Bulkier NHC side chains have been shown to enhance reactivity in classical Pd-coupling reactions; see, for example: (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15159. (b) Song, C.; Ma, Y.; Chai, Q.; Ma, C.; Jiang, W.; Andrus, M. B. *Tetrahedron* **2005**, *61*, 7438. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (d) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2383.

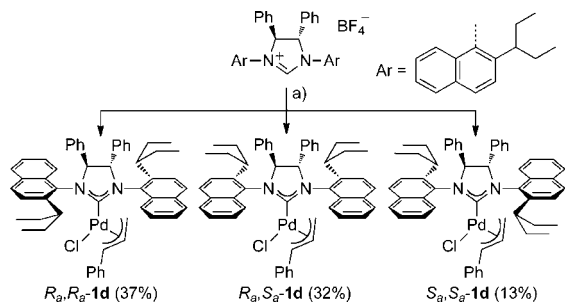
Table 2. Identification of the Optimal Catalyst

entry	NHC-Pd	substrate (Ar, PG)	3:4 ^a	yield [%] ^b	ee [%] ^c
1	<i>R_a,R_a</i> - 1d	2a (Ph, Me)	<i>d</i>	96	81 (<i>R</i>)
2	<i>R_a,S_a</i> - 1d	2a (Ph, Me)	16:1	90	81 (<i>R</i>)
3	<i>S_a,S_a</i> - 1d	2a (Ph, Me)	<i>d</i>	93	52 (<i>R</i>)
4	<i>R_a,R_a</i> - 1d	2b (1-Napht, Me)	<i>d</i>	98	87 (<i>R</i>)
5	<i>R_a,S_a</i> - 1d	2b (1-Napht, Me)	17:1	88	39 (<i>R</i>)
6	<i>S_a,S_a</i> - 1d	2b (1-Napht, Me)	19:1	91	53 (<i>R</i>)
7	<i>R_a,R_a</i> - 1d	2c (2-Napht, Me)	<i>d</i>	98	82 (<i>R</i>)
8	<i>R_a,S_a</i> - 1d	2c (2-Napht, Me)	18:1	90	85 (<i>R</i>)
9	<i>S_a,S_a</i> - 1d	2c (2-Napht, Me)	<i>d</i>	97	56 (<i>R</i>)
10	<i>R_a,R_a</i> - 1d	2d (Ph, Bn)	10:1	86	81 (<i>R</i>)
11	<i>R_a,S_a</i> - 1d	2d (Ph, Bn)	8:1	83	63 (<i>R</i>)

^a Determined by ¹H NMR analysis of product mixtures prior to purification. ^b Isolated yields. ^c Determined by HPLC. ^d Compound **4** is not observed.

enhanced the chemoselectivity of the transformation with generation of only trace amounts (if any) of Heck byproduct **4a**. As a consequence, treatment of **2a** in the presence of 5 mol % *R_a,R_a*-**1d** gave rise to oxindole **3a** in 96% isolated yield and 81% ee. Because both catalysts *R_a,R_a*-**1d** and *R_a,S_a*-**1d** showed identical enantiomeric excesses with substrate **2a**, before embarking in a thorough substrate scope study, we examined catalysts **1d** with three other substrates, varying both the aromatic group at the α-carbon and the protecting group at nitrogen (Table 2, entries 4–11). The results indicated that *R_a,R_a*-**1d** was overall giving the best chemoselectivities and evenly high enantiomeric excesses with all four substrates (with the exception of entries 7 and 8; see discussion below).

With the optimized catalyst in hand, we sought to examine the scope of the reaction. Thus, an important number of different amides were synthesized and subjected to the standard reaction conditions (5 mol % *R_a,R_a*-**1d**, 1.5 equiv of NaOtBu, DME, 23 °C, 16 h). Results in Table 3 show

Scheme 2. Synthesis of **1d**^a

^a 0.5 equiv [Pd(cin)Cl]₂, KOtBu, THF, 82%.

Table 3. Scope of Asymmetric Oxindole Synthesis with *R_a,R_a*-**1d**

Entry	Substrate	Product	R	Yield (ee) [%] ^[a]	
				<i>R_a,R_a</i> - 1d	<i>R_a,S_a</i> - 1d
1			<i>o</i> -Me	97 (85)	
2			<i>o</i> -F	94 (91)	
3			<i>o</i> -OMe	92 (83)	
4			1-Naph	98 (87)	
5			<i>p</i> -Me	94 (82)	
6			<i>p</i> -F	94 (83)	
7			<i>p</i> -CF ₃	97 (86)	
8			<i>p</i> -Ph	95 (87)	
9			<i>m</i> -Me	93 (77)	91 (83)
10			<i>m</i> -F	98 (79)	97 (85)
11			<i>m</i> -OMe	91 (80)	90 (85)
12			2-Naph	98 (82)	90 (85)
13				95 (60)	90 (84)
14				90 (86)	
15				94 (86)	
16			<i>o</i> -F	91 (94)	
17			<i>p</i> -Ph	90 (88)	
18				40 (8)	95 (4)
19				92 (70)	
20 ^[b]				88 (69)	
21 ^[b]				55 (38)	

^a Isolated yields; enantioselectivities determined by HPLC; absolute configuration of products **3** as depicted. ^b 50 °C.

that broad structural variations in the amide system can be accommodated. In nearly all cases, excellent yields, virtually complete chemoselectivities and good-to-excellent enantioselectivities were obtained. For example, electron-rich and electron-poor *ortho*- or *para*-substituted aromatic groups are tolerated, and the sterically demanding products were obtained with selectivities of up to 91% ee (entries 1–8). In line with the preliminary data in Table 2, enantioselectivities

with *meta*-substituted aromatic moieties are slightly higher when precatalyst R_a,S_a -**1d** is used (entries 9–12). Indeed, these differences are further amplified with sterically more demanding, doubly *meta*-substituted amide **2o** (entry 13) and point to subtle steric differences between the two catalysts during the enantioselection step. Entry 14 highlights the superior reactivity of the present system as catalyst R_a,R_a -**1d** allows the reaction with less reactive aryl chlorides to proceed at room temperature with high yield and ee.^{5a,g} Equally satisfying results were obtained when incorporating motifs commonly found in bioactive oxindole-based compounds.^{2a,b} Substrate **2q** containing a heteroaromatic *N*-Me-3-indolyl moiety (entry 15)¹² or compounds featuring a 5-methoxy substitution (entries 16 and 17) also undergo smooth cyclization to give the corresponding oxindoles. Limitations became only apparent when the sterically highly congested substrate **2t** was tested. Here, a complete loss of enantioselectivity was accompanied by lower than normal reactivity (entry 18). Nevertheless, the simple fact that catalyst R_a,S_a -**1d** could promote such a difficult C–C coupling at room temperature is noteworthy.

The unique steric environment created by catalyst R_a,R_a -**1d** apparently recognizes the allyl moiety even in substrates containing a second alkyl substituent (**2u**, entry 19). The reaction with this challenging compound not only proceeded smoothly at ambient temperature with excellent chemoselectivity (>20:1) but produced oxindole **3u** with acceptable levels of enantioselectivity of the same absolute configuration

(12) Interestingly, competitive arylation of the indolyl moiety is not observed in our case; for references, see: (a) Beccalli, E. M.; Brogginì, G.; Martinelli, M.; Paladino, G.; Rossi, E. *Synthesis* **2006**, 2404. (b) Joucla, L.; Popowycz, F.; Lozach, O.; Meijer, L.; Joseph, B. *Helv. Chim. Acta* **2007**, *90*, 753.

as seen for aryl-substituted substrates.^{13,14} Further evidence that recognition of the allyl moiety by the catalyst is crucial is provided in the last two entries (20, 21), where the results show that perturbing the sterics of the allyl group leads to a gradual loss of selectivity in the system.

In conclusion, we have devised a new synthetic strategy to access functionalizable 3-allyl oxindoles bearing a chiral quaternary carbon stereocenter via a direct palladium-catalyzed α -arylation protocol. Impressive reactivities and high chemo- and enantioselectivities were achieved through the use of a new chiral *N*-heterocyclic carbene ligand structure. Diastereomerically pure palladium complex R_a,R_a -**1d** proved to be the most general catalyst and gave oxindoles with selectivities of up to 94% ee. For making oxindoles bearing *meta*-substituted aromatic groups at the 3-position, catalyst R_a,S_a -**1d** was found to be slightly more efficient.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) This is the first successful asymmetric α -arylation to access 3,3'-dialkyl oxindoles. For an example that gives moderate yields (60%) and almost racemic product (11% ee), see: Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363.

(14) Compound **3u** is a key intermediate for the synthesis of (–)-physostigmine; see ref 4b and Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.