Asymmetric Catalysis

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Asymmetric Palladium-Catalyzed Intramolecular α-Arylation of Aldehydes**

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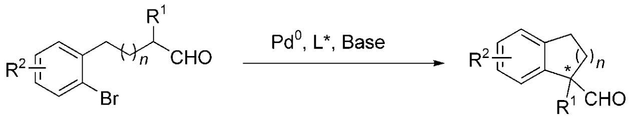
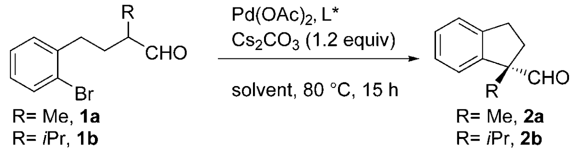
The prevalence of chiral quaternary stereocenters in many natural products has attracted a growing interest in the development of methods for their construction with absolute stereocontrol.[1,2] In recent years, the α-arylation of carbonyl compounds has received a great deal of attention.[3] Despite substantial advances, the asymmetric metal-catalyzed α-arylation of carbonyl compounds remains a formidable challenge, and few examples have been described.[4–7] To the best of our knowledge, no examples of asymmetric metal-catalyzed α-arylation of aldehydes have yet been reported.[8] Herein, we present the first asymmetric metal-catalyzed α-arylation of aldehydes forming all-carbon-substituted asymmetric centers in high yields and enantioselectivities (Scheme 1).



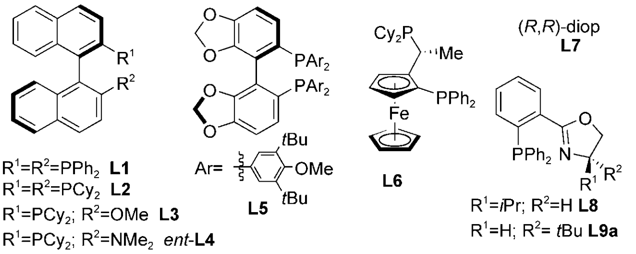
Scheme 1. General scheme for the asymmetric intramolecular α-arylation of aldehydes.

The racemic α-arylation of aldehydes remains challenging due to competing aldol condensation under the reaction conditions.[9] In 2007 our group described a general method for the α-arylation of aldehydes with both ArBr and ArCl.[9d] It was found that the catalytic system based upon $Pd(OAc)_2$/binap provided the best results when aryl bromides were used. Given that binap has been successfully used as a ligand in related α-arylation methodologies[4–7] we decided to examine the utility of this ligand for the asymmetric α-arylation of **1a** (Table 1). After some initial screening of palladium sources, bases and solvents,[10] we obtained the desired compound **2a** in 54% yield and 49% *ee* using DME as a solvent and Cs_2CO_3 as a base (Table 1, entry 1).

Table 1: Screening of reaction conditions.[a]



Entry	Aldehyde	L	Pd (mol %)	Pd:L	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a**	**L1**	2	1:2	DME	54	49 (*S*)
2	**1a**	**L2**	2	1:2	DME	25	37 (*S*)
3	**1a**	**L3**	2	1:2	DME	5	6 (*S*)
4	**1a**	**L4**	2	1:2	DME	5	10 (*R*)
5	**1a**	**L5**	2	1:2	DME	18	30 (*S*)
6	**1a**	**L6**	2	1:2	DME	9	2 (*S*)
7	**1a**	**L7**	2	1:2	DME	44	1 (*S*)
8	**1a**	**L8**	2	1:2	DME	25	68 (*S*)
9	**1a**	**L8**	3	1:2	DME	40	68 (*S*)
10	**1a**	**L8**	3	1:2	DMF	53	73 (*S*)
11	**1a**	**L8**	3	1:2	toluene	50	66 (*S*)
12	**1a**	**L8**	3	1:2	*t*BuOH	73	76 (*S*)
13	**1a**	**L8**	3	1:3	*t*BuOH	90	76 (*S*)
14	**1a**	**L9a**	3	1:3	*t*BuOH	92	81 (*R*)
15	**1b**	**L9a**	3	1:3	*t*BuOH	85	86 (*R*)



[a] Aldehyde (0.10 mmol) in solvent (1 mL). [b] GC yields using dodecane as an internal standard. [c] The *ee* values were determined by chiral GC analysis. The absolute configuration of the products was determined by derivatization of **2a** into known literature compound. See Supporting Information for more details.

Encouraged by the initial results, we next examined the use of different chiral ligands in this transformation. Our experiments with other axially-chiral ligands such as CyBinap (**L2**), CyMop (**L3**), KenPhos (**L4**) and dtmb-segphos (**L5**), however, did not provide results with improved enantioselectivity (Table 1, entries 2–5). The use of of Josiphos (**L6**) or diop (**L7**) gave rise to **2a** in 9 and 44% GC yield, respectively (Table 1, entries 6 and 7), with very low enantioselectivity. Notably, the use of phosphanyloxazoline-based ligands such as *i*Pr-phox (**L8**)[11] provided the desired α-aryl aldehyde **2a** in 68% *ee*, albeit in only 25% yield. Further optimization

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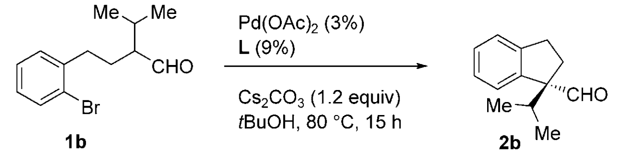
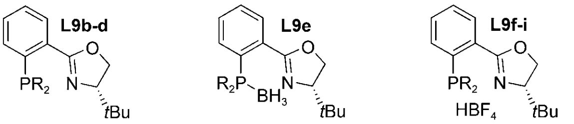
showed that higher enantioselectivities could be achieved by carrying out the process in polar solvents (Table 1, entries 9–12), with *t*BuOH providing the best results. It is well known that the substituent of the oxazoline moiety plays an important role in the enantioselectivity.[12] Indeed, the use of a more sterically encumbered *t*Bu-phox (**L9a**) increased the optical purity of the product to 81 % *ee* (Table 1, entry 14). Particularly significant is the effect of the α-substituent to the aldehyde (see below), thus, **1b** afforded the desired compound **2b** in 85 % yield and 86 % *ee* (Table 1, entry 15).

We next focused on the influence of both steric and electronic effects of the phosphine moiety of the phox ligands (Table 2). Although we observed no clear trend in electronic effects of the phosphine in the enantioselectivity and the yield of the reaction (Table 2, entry 7 vs 8), the size of the substituents has a substantial impact. Along these lines, the use of bulkier phosphine substituents resulted in lower enantioselectivity (Table 2, entry 2 vs 6). As depicted in Table 2, the best results were obtained when the reagents were stirred at 80 °C for 24 h using Cs_2CO_3 as the base and ligand **L9i** in *t*BuOH (0.1 M) affording the desired indane derivative **2b** in 94 % *ee* and 93 % yield, respectively (Table 1, entry 9).

Table 2: Screening of different phox ligands.[a]



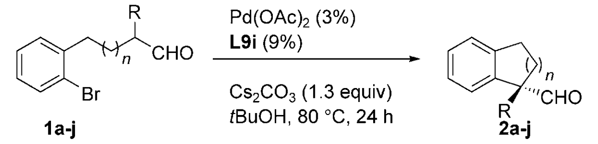
Entry	R	L	Yield [%][b]	*ee* [%][c]
1	cyclopentyl	**L9b**	66	85 (*R*)
2	2-MeC_6H_4	**L9c**	32	55 (*R*)
3	3,5-$(CF_3)C_6H_4$	**L9d**	47	78 (*R*)
4	2-furyl	**L9e**[d]	69	83 (*R*)
5	cyclohexyl	**L9f**	69[e]	80 (*R*)
6	4-MeC_6H_4	**L9g**	88[e]	90 (*R*)
7	4-$(CF_3)C_6H_4$	**L9h**	77[e]	90 (*R*)
8	4-$(MeO)C_6H_4$	**L9i**	79[e]	94 (*R*)
9	4-$(MeO)C_6H_4$	**L9i**	93[e,f]	94 (*R*)



[a] Aldehyde (0.1 mmol) in *t*BuOH (1 mL), Cs_2CO_3 (0.12 mmol), $Pd(OAc)_2$ (3 mol %), **L** (9 mol %), 80 °C, 15 h. [b] GC yields using dodecane as internal standard. [c] The *ee* values were determined by chiral GC analysis. [d] DABCO (13.5 mol %) was used [13]. [e] Cs_2CO_3 (1.3 equiv) was used. [f] The reaction was carried out for 24 h at 80 °C.

With the optimized reaction conditions in hand, we further investigated the influence of the α-substituent to the aldehyde on the reaction outcome (Table 3). Substrates containing both α-alkyl and α-aryl substituents yielded the product aldehydes in high enantioselectivity. Generally, substrates with α-aryl substituents gave rise to products with higher optical purity than these with α-alkyl analogues (Table 3, entries 1–5 vs entries 6–8). In regard to the nature of the alkyl substituent, enantioselectivity increased with the size of the α-substituent to the carbonyl group (Table 3, entries 1–5). Under our reaction conditions, *o*-tolyl derivative **1h** proved to be a difficult case, in which even higher catalyst loadings produced the desired product **2h** in only 36 % yield, but with 98 % *ee* (Table 3, entry 8).[14] The efficiency of the method dropped significantly for substrates forming a six-membered ring; tetrahydronaphthalene derivatives were prepared in moderate to good yields with moderate enantioselectivities (Table 3, entries 9–10). The absolute configuration of two of the products was established by X-ray crystallography of **2g** (Figure 1)[15] and by comparison with a reported compound derived from **2a**.[16,17]

Table 3: Scope of the asymmetric Pd-catalyzed intramolecular α-arylation.[a]



Entry	R	*n*	Yield [%][b]	*ee* [%][c]
1	Me (**1a**)	1	64	87 (*S*)
2	*i*Pr (**1b**)	1	86	94 (*R*)
3	Et (**1c**)	1	58	88 (*S*)
4	*t*Bu (**1d**)	1	88	96 (*R*)
5	Cy (**1e**)	1	87	96 (*R*)
6	Ph (**1f**)	1	81	98 (*R*)
7	2-$(MeO)C_6H_4$ (**1g**)	1	73	98 (*S*)
8	2-MeC_6H_4 (**1h**)	1	27 (36)[d,e]	98 (*R*)
9	*i*Pr (**1i**)	2	69	53 (*R*)
10	Ph (**1j**)	2	53	63 (*R*)

[a] Aldehyde (0.5 mmol) in *t*BuOH (5 mL), Cs_2CO_3 (0.65 mmol), $Pd(OAc)_2$ (3 mol %), **L** (9 mol %), 80 °C, 24 h. [b] Yields of isolated products are an average of at least two independent runs. [c] The *ee* values were determined by chiral GC or HPLC. [d] Values in parentheses correspond to the yield of isolated product obtained using 5 mol % of $Pd(OAc)_2$ and 15 mol % of **L9i**. [e] Incomplete conversion of substrate was observed.

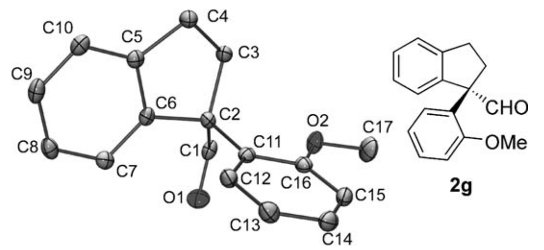
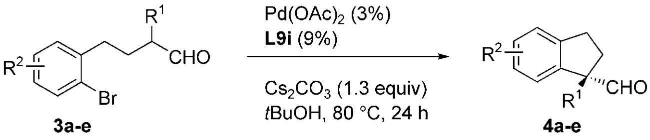


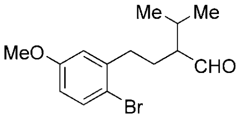
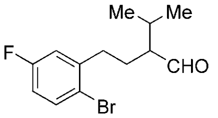
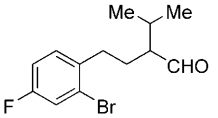
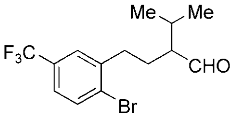
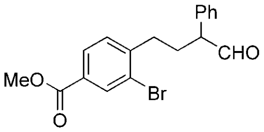
Figure 1. Molecular structure of **2g** with ellipsoids set at 50 % probability. Hydrogen atoms are omitted for clarity.

The fact that products with both aryl as well as alkyl α-substituents were of the same absolute configuration suggests that the enantioselectivity-limiting step in the catalytic system is common for both classes of substrates.

The influence of the substitution pattern in the aromatic ring on the outcome of the reaction is shown in Table 4. The

Table 4: Scope of the asymmetric Pd-catalyzed intramolecular α-arylation.[a]

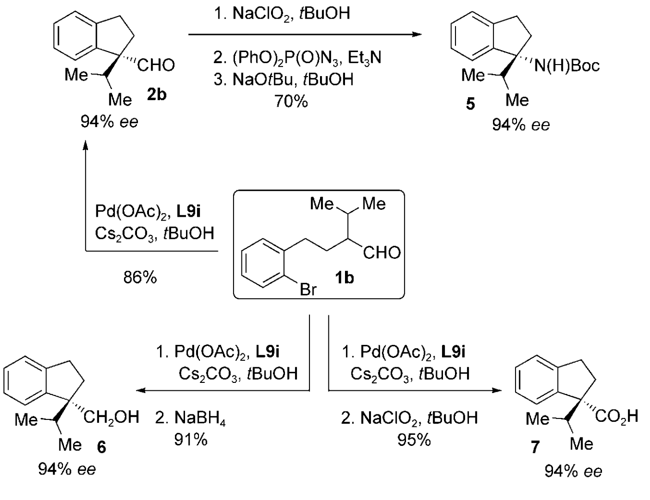


Entry	Aldehyde	Yield [%][b]	*ee* [%][c]
1	 **3a**	57 (72)[d]	93 (*R*)
2	 **3b**	82	95 (*R*)
3	 **3c**	78	93 (*R*)
4	 **3d**	(87)[d]	94 (*R*)
5	 **3e**	46 (58)[d]	97 (*R*)

[a] Reaction conditions as in Table 3. [b] Yields of isolated product are an average of at least two independent runs. [c] The *ee* values were determined by chiral GC or HPLC. [d] Values in parentheses correspond to the yield of isolated products obtained using 5 mol% of Pd(OAc)$_2$ and 15 mol% of **L9i**.

enantiomeric purity of the reaction product is not affected by the electronic density of the aryl moiety (Table 4, entry 1 vs 4).

Some representative applications of this methodology are illustrated in Scheme 2. For example, compound **5** was obtained from **2b** by means of Lindgren oxidation,[18,19] Curtius rearrangement,[20] and reaction of the resulting isocyanate with NaO*t*Bu in 70% overall yield with no loss of the optical activity. This result is particulary interesting given the wide variety of pharmacologically active compounds with a chiral tertiary amine scaffold.[21] Alternatively, a one-pot oxidation or reduction of the corresponding aldehyde afforded the alcohol **6** or the carboxylic acid **7** in excellent overall yield.



Scheme 2. Synthesis of different derivatives from **1b**.

In summary, we have developed the first asymmetric metal-catalyzed α-arylation of aldehydes. The high yields and enantioselectivities achieved make this process particularly attractive for further synthetic applications. Further investigations into this reaction and the development of an intermolecular protocol are currently underway in our laboratories.

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Keywords: α-arylation · aldehydes · asymmetric catalysis · P ligands · palladium

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[10] Other palladium sources tested: $[Pd_2(dba)_3]$, $[Pd(dba)_2]$, $[\{(allyl)PdCl\}_2]$, and $[\{(Me\text{-}allyl)PdCl\}_2]$; other bases tested: Na_2CO_3, K_2CO_3, K_3PO_4, NaO*t*Bu, KO*t*Bu, and LiHMDS; other solvents tested: 1,4-dioxane, toluene, THF, DME, $n\mathrm{Bu}_2O$, DMF, and MeCN.

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[14] When harsher reaction conditions were used (stronger inorganic bases such as NaO*t*Bu or higher temperature) only decomposition of the starting material was obtained.

[15] CCDC 699068 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.

[16] See Suporting Information for details.

[17] The absolute configuration of compounds **2i** and **2j** was assigned by analogy to the other compounds in Table 3 and Table 4.

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