Asymmetric Catalysis

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Enantioselective Palladium-Catalyzed Direct Arylations at Ambient Temperature: Access to Indanes with Quaternary Stereocenters**

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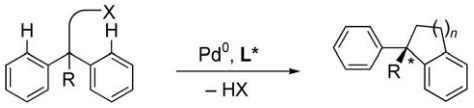
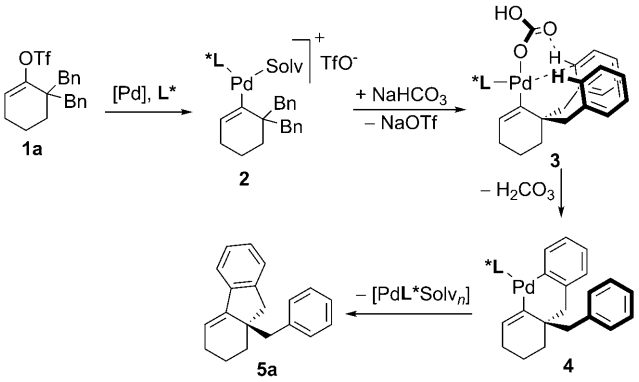
The selective catalytic activation and functionalization of carbon–hydrogen (C–H) bonds by transition-metal complexes has broad synthetic potential because of its economic and ecological benefits.[1] The recent impressive progress of this vibrant and fast advancing research area opens unimaginable opportunities of more efficient strategic disconnections and streamlined syntheses.[2] Despite its enormous dormant potential, efficient enantioselective catalytic reactions are still a largely unsolved challenge in C–H activations.[3] A main issue remaining is the identification of a suitable set of external ligands which efficiently control the stereoselectivity of the insertion event, without obstructing the general activity of the whole catalyst system. To our knowledge—except for a pioneering study from Yu and coworkers describing chiral *N*-Boc amino acids as ligands for directed C(sp^2)–H activations[4]—there are no examples of enantioselective aromatic C(sp^2)–H functionalizations using palladium catalysts.[5] For example, it would be of significant synthetic value to selectively address one of the enantiotopic aromatic substituents of a symmetrical substrate by a metalation and subsequent functionalization [Eq. (1)]. Such a



(1)

process should also be well-suited to the construction of congested quaternary stereogenic centers[6] as the transformation occurs remotely from the tetrasubstituted carbon atom.

Herein, we report our initial results exploiting a palladium(0)-catalyst ligated by a designed taddol-based phosphoramidite to access indanes with quaternary stereogenic centers in excellent enantioselectivities. The fundamental mechanistic picture of the palladium-catalyzed direct arylation reactions recently became clearer as a result of intense investigations.[7] Several mechanistic models have been discussed, and the one proposed by Maseras, Echavarren and coworkers, and by Fagnou and co-workers, in which a carbonate/carboxylate acts in an intramolecular fashion as an ancillary base initiating a concerted deprotonation/metalation of the aryl group, is supported by most experimental and theoretical evidence.[8] As illustrated by the anticipated intermediate **3** (Scheme 1), this would leave one coordination site on the palladium atom for the required external steering ligand. We therefore turned our attention to bulky monodentate phosphines that would favor monoligated palladium species or enable facile dissociation to ensure high reactivity of the catalyst. The good overall reactivity of alkenyl triflates in direct arylation reactions has been reported by Willis and coworkers[9] and their ease of accessibility from ketones make them an attractive substrate class. Furthermore, the assumed cationic palladium(II) intermediate **2**, formed upon oxidative addition, should undergo rapid association with a carboxylate or carbonate anion of the bulk base to form—according to the current model—the crucial complex **3** for the metalation process. Reductive elimination of the arising six-membered palladacycle **4** ultimately releases the cyclized product **5a**.



Scheme 1. Mechanistic model for the enantioselective C–H functionalization of one of the prochiral C(sp^2)–H bonds of **1a**. Tf = trifluoromethanesulfonyl, Bn = benzyl, Solv = solvent.

A brief initial survey of some phosphines confirmed that monodentate ligands indeed showed the highest activity towards the desired arylation reaction. As exemplified for the cyclohexyl-mop ligand **L1** (Table 1, entry 1), most of the screened ligands provided nearly no differentiation of the two aryl groups. Pleasingly, phosphoramidites such as Monophos

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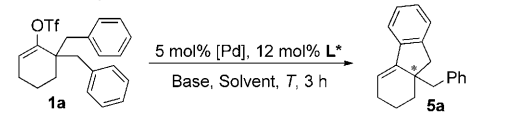
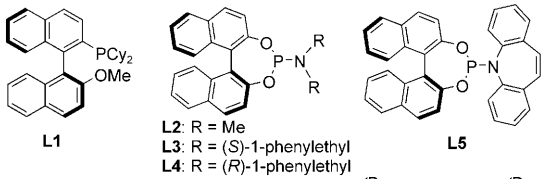
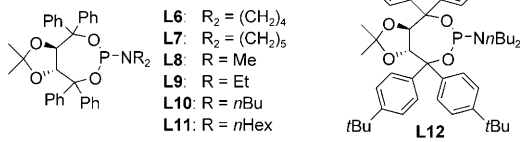
Table 1: Selected optimization studies.[a]







Entry	Solvent	Base	*T* [°C]	[Pd]	L*	Yield [%][b]	*ee* [%][c]
1	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L1**	86	3
2	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L2**	63	51
3	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L3**	89	56
4	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L4**	85	52
5	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L5**	88	60
6[d]	toluene	K_2CO_3	100	$Pd_2(dba)_3$	**L5**	91	66
7	DMAc	K_2CO_3	23	$Pd(OAc)_2$	**L6**	85	63
8	DMAc	K_2CO_3	23	$Pd(OAc)_2$	**L7**	87	59
9	toluene	K_3PO_4	100	$[Pd_2(dba)_3]$	**L8**	77	69
10	DMAc	K_2CO_3	23	$Pd(OAc)_2$	**L8**	98	78
11[d]	CH_3CN	K_2CO_3	23	$Pd(OAc)_2$	**L8**	72	29
12[d]	DMSO	K_2CO_3	23	$Pd(OAc)_2$	**L8**	86	49
13[d]	EtOAc	K_2CO_3	23	$Pd(OAc)_2$	**L8**	80	19
14	DMAc	Na_2CO_3	23	$Pd(OAc)_2$	**L9**	95	81
15	DMAc	Na_2CO_3	23	$Pd(OAc)_2$	**L10**	92	86
16	DMAc	Na_2CO_3	23	$Pd(OAc)_2$	**L11**	90	81
17	DMAc	Na_2CO_3	23	$Pd(OAc)_2$	**L12**	93	93
18	DMAc	$NaHCO_3$	23	$Pd(OAc)_2$	**L12**	**93**	**93**

[a] Reaction conditions: **1a** (0.1 mmol), base (3 equiv), 0.10 M in the indicated solvent, 3 h. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [d] 12 h. dba = (*E*,*E*)-dibenzylideneacetone, DMSO = dimethylsulfoxide.

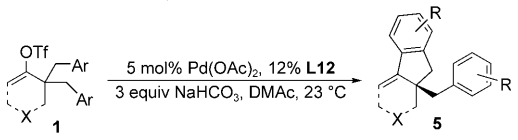
(**L2**), the Feringa ligands **L3** and **L4**, and the phosphoramidite-olefin ligand **L5**[10] gave rise to promising enantioselectivities (Table 1, entries 1–6). However, the amine portion of the phosphoramidite seems to have little influence on the selectivity of this reaction. We therefore chose the taddol-based phosphoramidite **L8** as the lead structure as it provided comparable results (Table 1, entry 9), and its highly modular nature would allow facile modifications with regard to the acetal backbone, the aryl groups, and the substituents of the nitrogen atom.[11] Ligand **L8** was used in our initial examination of the reaction conditions, and we found a pronounced dependence of the enantioselectivity upon the palladium source, the base, and the solvent (Table 1, entries 10–13). Apart from the first set of reaction conditions ($[Pd_2(dba)_3]$/K_3PO_4/toluene/100 °C) the reaction proceeds in a higher selectivity using palladium acetate and a carbonate base in a polar solvent. Under these conditions, the arylation is completed in three hours at ambient temperature. A carbonate base is essential and, remarkably, the milder $NaHCO_3$ can replace K_2CO_3 or Na_2CO_3 to give identical results, whereas Cs_2CO_3 significantly slows down the reaction.

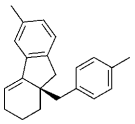
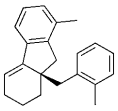
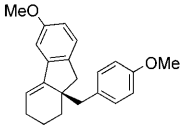
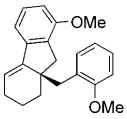
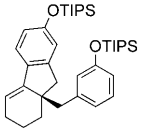
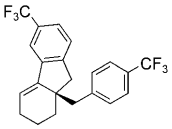
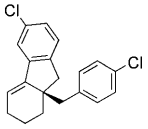
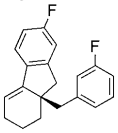
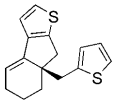
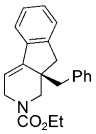
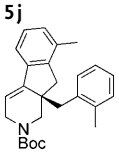
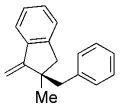
As solvents, dimethylacetamide (DMAc) provides the highest *ee* value (Table 1, entry 10), whereas acetonitrile, ethyl acetate, and DMSO were detrimental for the selectivity (Table 1, entries 11–13). With the optimized parameters in hand, we turned our attention to the development of a more selective phosphoramidite. Changing the acetal bridge of the taddol had little impact or even a slightly negative influence on the enantioselectivity. Replacement of the phenyl substituents by bulkier aryl groups (2-naphthyl, 1-naphthyl and *m*-xylyl) resulted in poorly reactive catalyst systems (data not shown). Modifications of the amine portion with cyclic (pyrrolidine or piperidine; Table 1, entries 7 and 8), and α- or β-branched secondary amines substituents gave ligands of poorer performance than the parent ligand **L8**. However, a substitution of the dimethylamido group with its diethyl congener increased the *ee* value from 78% to 81% (Table 1, entry 14). Furthermore, *n*-butyl chains gave an even better selectivity of 86% *ee* (Table 1, entry 15). Longer dialkylamido chains (e.g., the *n*-hexyl homologue **L11**; Table 1, entry 16) provided no further enhancement, instead the selectivity fell to that obtained with the diethylamino variant **L9**. The *n*-butyl substitution pattern of the nitrogen atom seems to be optimal, and when combined with the *para*-*tert*-butylphenyl taddol congener a ligand (**L12**) with an optimal reactivity/selectivity profile resulted, promoting the arylation reaction in 93% yield and with an *ee* value of 93% (Table 1, entries 17 and 18).

Next, we explored the scope of the palladium-catalyzed arylation. In general, under the aforementioned optimized reaction conditions different aromatic substitution patterns are well tolerated in the reaction (Table 2). *Ortho*- and *para*-substitution has little impact upon the reaction rate and the enantioselectivity (Table 2, entries 1 and 2). Electron-rich substrates bearing an either an *ortho*- or *para*-methoxy group as well as one having a *meta*-triisopropylsiloxy group, furnish the indanes in comparable selectivities and yields (Table 2, entries 3–5). Substrates with electron-poor aromatic substituents are more reactive and, notably, **1i** which has a *meta*-fluorine substituent reacts almost in a completely regioselective manner to provide the depicted isomer **5i** in greater than 20:1 regioselectivity (Table 2, entry 8).[12] Chlorinated aromatics remain untouched during the reaction and could be functionalized subsequently (Table 2, entry 7). Heteroaromatics, exemplified by the thiophene substrate **1j**, react in an analogous manner; furthermore, the absolute configuration of the cyclized product **5j** was determined to be *R* by using the X-ray crystallographic analysis.[13] Substrates deriving from 4-piperidones maintain the selectivity and provide access to fused tetrahydropyridines **5k** and **5l** (Table 2, entries 10 and 11). A vinyl palladium species not embedded within a cyclic, conformationally restricted environment, such as the one generated from the acyclic derivative **1m**, reacts less selectively and furnishes the product **5m** in 45% *ee*, thereby requiring additional ligand improvements.

In summary, we demonstrated a very mild intramolecular direct arylation of vinyl triflates which proceeds with excel-

Table 2: Scope of the enantioselective arylation reaction.[a]



Entry	Product[b]	Yield [%][c]	*ee* [%][d]	Entry	Product[b]	Yield [%][c]	*ee* [%][d]
1				2			
	5b	96	93		**5c**	99	97
3				4			
	5d	94	91		**5e**	98	86
5				6			
	5f[e]	70	98		**5g**	97	87
7				8			
	5h	96	93		**5i**	82	94
9				10			
	5j	98	93 (99)[f]		**5k**	98	85
11				12			
	5l	98	87		**5m**	80	45

[a] Reaction conditions: **1** (0.1 mmol), 0.1 m, 3–12 h. [b] Configuration assigned by analogy to **5j**. [c] Yields of isolated products. [d] The *ee* values were determined by HPLC analysis using a chiral stationary phase. [e] A 10:1 mixture of products in favor of the depicted regioisomer. [f] After recrystallization. TIPS = triisopropylsilyl, Boc = *tert*-butoxycarbonyl.

lent enantioselectivities at room temperature. Key to obtaining these selectivities was the development of tailored taddol-based phosphoramidite ligands in combination with highly polar solvents. Studies extending this process to other substrate classes and gaining better understanding of the selectivity and reactivity determining factors of the catalysts are ongoing and will be reported in due course.

Experimental Section

Typical procedure: 6,6-dibenzylcyclohex-1-enyl triflate (**1a**; 41.0 mg, 0.10 mmol), $Pd(OAc)_2$ (1.12 mg, 5.00 μmol), ligand **L12** (10.2 mg, 12.0 μmol), and sodium bicarbonate (25.2 mg, 0.30 mmol) were weighed into a glass vial equipped with a magnetic stir bar, sealed with a rubber septum, and flushed with nitrogen. After the addition of 1.0 mL of dry dimethylacetamide, the reaction mixture was stirred at 23 °C until complete conversion (3 h) was determined by TLC analysis. The reaction mixture was extracted with pentanes, and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was purified on silica gel (pentanes, R_f = 0.30) giving 24.3 mg (93 %, 93 % *ee*) of **5a** as a colorless viscous oil.

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[12] In general, electron-poor substrates react faster, which is in agreement with the described mechanism of reference [8].

[13] See the Supporting Information. CCDC 745459 (**5j**) 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..

