C–H Activation

DOI: 10.1002/anie.201108511

Chiral Monodentate Phosphines and Bulky Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp^3)–H Functionalization**

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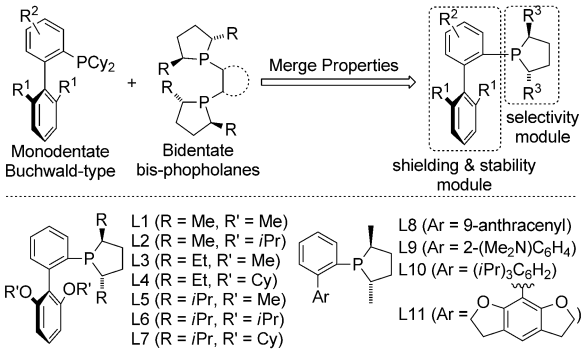
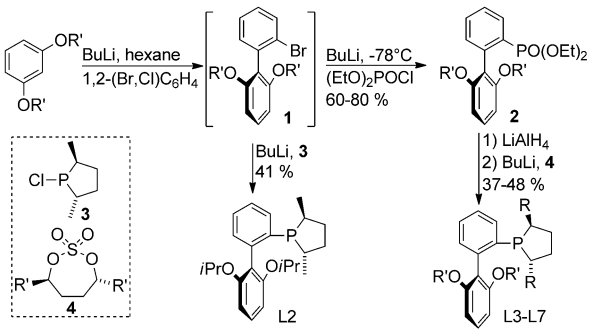
Advances in transition-metal catalysis are closely linked to the development of tailored phosphine ligands enabling previously impossible transformations.[1] In this respect, the development of the Buchwald-type ligands was a game-changer in cross-coupling reactions.[2] Being monodentate,[3] bulky, and electron-rich ligands, they resulted in very reactive and yet very stable palladium complexes enabling a multitude of previously unfeasible transformations. In comparison to the plethora of chiral bidentate phosphine ligands, there is only a rather limited portfolio of efficient chiral monodentate phosphines available.[4] By and large the most popular ones are phosphoramidites derived from the Binol or Taddol backbone.[5] Ligands mimicking the favorable electronic properties of tricyclohexylphosphine or tri-*tert*-butylphosphine are rarer. Besides MOP and KenPhos,[6] other phosphines which are chiral at phosphorous have been used with limited success as they are often difficult to synthesize and/or not configurationally stable at elevated temperatures.[7] An increasing number of metal-catalyzed transformations function only with monodentate phosphines as ligands, thus novel, modular, and efficient, electron-rich chiral monodentate phosphines are highly valued for further developments in asymmetric catalysis. The C_2-symmetric and electron-rich phospholane module has been used with great success in several diphosphine ligands, such as Duphos, BPE-phos, and related scaffolds.[8] Despite its general utility in bidentate phosphines, it has been surprisingly used only scarcely as a chirality source unit in monodentate phosphines.[9]

Herein, we report a class of new chiral biaryl monophospholanes and demonstrate their utility in combination with a bulky carboxylic acid in highly challenging enantioselective C(sp^3)–H functionalizations of unactivated methyl and methylene bonds. We reasoned that a combination of the outstanding properties of both parent scaffolds, the Buchwald-type backbone[2] and the electron-rich phospholane moiety with its inherent chirality, would lead to a new ligand class with significant potential (Scheme 1). Furthermore, its highly modular nature would allow a rapid synthetic access and fine-tuning to the specific reaction or substrate needs.



Scheme 1. Design and structure of the utilized monodentate electron-rich ligands. Cy = cyclohexyl.

The envisioned ligands were prepared in a straightforward manner from readily available building blocks (Scheme 2). Metalation of different *m*-dialkoxybenzenes and reaction with benzyne generated in situ gave **1**. The subsequently obtained lithiated biaryl species were treated either directly with the chloro phospholane **3** to give L2 or with chloro diethylphosphonate to give **2**. Subsequent reduc-



Scheme 2. Synthesis of the phosphine ligands L2–L7.

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[**] This work is supported by the EPFL, the ETH Zurich (ETH-16 08-3), and by the European Research Council under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC Grant agreement no 257891. We thank Dr. R. Scopelliti for X-ray crystallographic analysis of **9a** and Dr. R. Kadyrov (Evonik Industries AG) for generous donations of 2,5-dimethyl-1-TMS-phospholane.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201108511.

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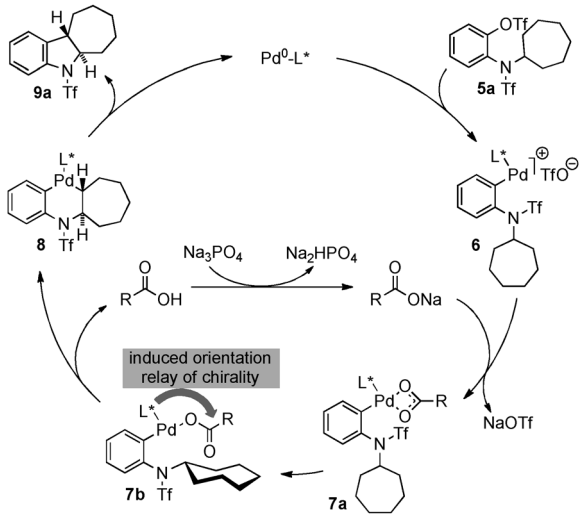
tion to the phosphane and double S_N2 displacement using the classical cyclic sulfate route[8] provides access to congener's L3–L7 having bulkier phospholane units.

The direct enantioselective functionalization of C(sp^3)–H bonds with a palladium(0) system is a prime challenge to evaluate the potential of the prepared ligands (Scheme 3).[10–14] Mechanistic studies as well as theoretical

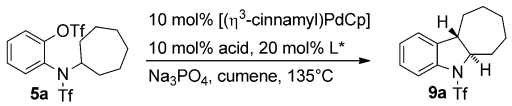


Scheme 3. Proposed catalytic cycle and hypothesis for the cooperative ligand effects in the synthesis of indolines **9**. Tf = triflate.

investigations on the operative concerted-deprotonation-metalation (CMD) pathway, suggest that only a single coordination site of on the palladium atom is available.[15,16] Hence, only a monodentate ligand would lead to a competent catalyst. Moreover, according to the mechanism (Scheme 3), a carboxylate base is required as a second ligand on the metal center, playing a critical role in the proton abstraction step leading to formation of the palladium–carbon bond. It has been shown by Fagnou et al. that pivalate is optimally suited for this task for the achiral reaction.[17] We reasoned that the chiral space crafted by the single phosphine ligand around the metal center of **7** would be too weak and too far away to provide high levels of asymmetric induction. We based the design of our experiments on the hypothesis that the chiral space created by the phosphine ligand could be relayed to the spatial orientation of the specific carboxylate co-ligand. It is much closer to reactive center and directly involved in the enantioselectivity determining step by addressing the enantiotopic proton atoms. This approach would open intriguing opportunities to combine a chiral phosphine with an achiral bulky carboxylic acid or cooperatively use a chiral carboxylic acid to maximize selectivity. A further requirement of the reaction is a bulky ligand to prevent aggregation of additional phosphine units around the metal and at the same time ensuring a high stability of the complex even with thermally forcing reaction conditions. Using aryl triflates **5** has the benefit of giving a cationic aryl palladium species **6**, which in turn reacts rapidly with catalytic amounts of the respective carboxylate to give the crucial intermediate **7**.[13b] Once the metalation has proceeded as discussed above, palladacycle **8**, can then reductively eliminate to give indoline **9** and regenerate the Pd^0 catalyst.

With aryl triflate **5a** as initial screening substrate, we evaluated the different parameters of the reaction (Table 1). The best and most reactive source of palladium(0) proved to be [η^3-cinnamyl)PdCp] (Cp = C_5H_5).[18] In contrast to the findings of previous studies using aryl bromide substrates,[14,19] the aryl triflates display a different trend with respect to the inorganic bulk base, with sodium phosphate being the most efficient.[20] The carboxylic acid additive employed is critically important to the catalyst performance and to the enantioselectivity. An amount of 10 mol% is optimal. Lower amounts reduced the catalytic efficiency and enantioselectivity, whereas higher amounts slightly decreased the conversion. A screening of several simple carboxylic acids of different steric demand with L2 revealed their influence on the enantioselectivity (Table 1, entries 1–9). 9*H*-Xanthene-9-carboxylic acid (A1) showed a robust performance and constantly superior selectivity and was used in the further evaluation of the phosphine ligands. The size of the ether substituent of the shielding aromatic ring (R′ = *i*Pr or Cy is better than R′ = Me) of the ligand has an effect on the selectivity without disturbing the reactivity of the catalyst. The large isopropyl substituent on the phospholane has a strong effect on the selectivity, but at the same time decreases the reactivity (Table 1, entries 12–14). Ligands having other backbone structures, such as L8–L11, were less

Table 1: Optimization of the reaction conditions for the enantioselective C(sp^3)–H activation.[a]



Entry	Carboxylic acid	L*	% Yield[b]	e.r.[c]
1	Acetic acid	L2	35	38.5:61.5
2	Benzoic acid	L2	67	41:59
3	Pivalic acid	L2	86	37:63
4	Phenylacetic acid	L2	88	40:60
5	Diphenylacetic acid	L2	83	41.5:58.5
6	Triphenylacetic acid	L2	73	51:49
7	2,2-Diphenylpropanoic acid	L2	91	42.5:57.5
8	Anthracene-9-carboxylic acid	L2	84	35.5:64.5
9	9*H*-xanthene-9-carboxylic acid (A1)	L2	75	36:64
10	A1	*ent*-L1	81	73.5:26.5
11	A1	L4	79	62:38
12	A1	L5	72	91:9
13[d]	A1	L6	66	97.5:2.5
14	A1	L7	40	>97.5:2.5
15	A1	L8	71	78.5:21.5
16	A1	*ent*-L9	25	43:57
17	A1	*ent*-L10	76	31:69
18	A1	L11	70	25:75

[a] Reaction conditions: 50 μmol **5a**, 5 μmol of the carboxylic acid, 5 μmol [(η^3-cinnamyl)PdCp], 10 μmol L*, 1.2 equiv Na_3PO_4, 0.6 M in cumene at 135 °C for 12 h. [b] Yield of isolated product **9a**. [c] Determined by GC with a chiral stationary phase; e.r. = (2*R*,3*S*)/(2*S*,3*R*). [d] In *p*-xylene as solvent.

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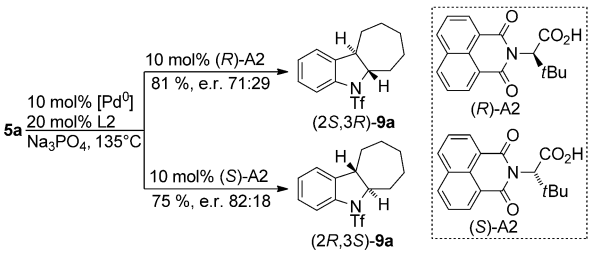
suitable (entries 15–18). The combination of L6 and A1 is the best match, providing **9a** in 66% yield with e.r. 97.5:2.5 (Table 1, entry 13). L7 displays a slightly higher selectivity albeit at expense of the reactivity (entry 14).

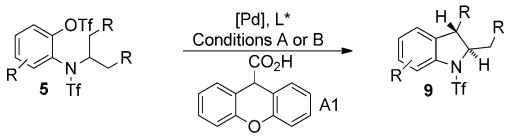
The effect of the carboxylic acid on the selectivity supported our hypothesis of relaying the chirality of the ligand. This prompted us to evaluate the direct influence of chiral carboxylic acids. Indeed, a significant cooperative effect was observed for the pair of enantiomers of acid A2 and L2 (Scheme 4). For instance, the matching (*S*)-isomer of A2 provides 82:18 e.r. in favor of (*2R*,*3S*)-**9a** whereas the mismatched (*R*)-A2 overrides the selectivity of the phosphine and reverses the sense of induction and gives 71:29 e.r. for (*2S*,*3R*)-**9a**. Using an enantiopure carboxylic acid as the sole source of chirality also led to a noteworthy asymmetric induction.[21]



Scheme 4. Cooperative ligand effects: domination of the chiral acid.

Table 2 outlines the scope of the reaction under the optimized conditions. In general, the process provides high enantiomeric ratios for a range of substrates. Apart from different substituents on the aryl ring, pyridine as a coordinating heterocycle is tolerated providing azaindoline **9i**

Table 2: Enantioselective synthesis of indolines **9** from triflates **5**.



Entry	Aryl triflate **5**	Indoline **9**	% Yield[c]	e.r.[d]	Entry	Aryl triflate **5**	Indoline **9**	% Yield[c]	e.r.[d]
1[a]	**5a**	**9a**	66	97.5:2.5	9[b]	**5i**	**9i**	55	94:6
2[a]	**5b**	**9b**	54	97:3	10[b]	**5j**	**9j**	64	96:4
3[a]	**5c**	**9c**	46	96:4	11[b]	**5k**	**9k**	85	86.5:13.5
4[a]	**5d**	**9d**	75	97:3	12[a]	**5l**	**9l**	76	97.5:2.5
5[a]	**5e**	**9e**	64	97:3	13[a]	**5m**	**9m**	71	97.5:2.5
6[a]	**5f**	**9f**	58	96:4	14[a]	**5n**	**9n**	75	98:2
7[a]	**5g**	**9g**	74	96:4	15[a]	**5o**	**9o**	60	97.5:2.5
8[b]	**5h**	**9h**	57	96:4	16[a,e]	**5p**	**9p**	70	81:19

[a] Conditions A: 0.1 mmol **5**, 10 μmol of A1, 10 μmol [(η^3-cinnamyl)PdCp], 20 μmol L7, 1.2 equiv Na_3PO_4, 0.6 M in cumene at 135 °C for 12 h. [b] Conditions B: 0.1 mmol **5**, 5 μmol of A1, 5 μmol [(η^3-cinnamyl)PdCp], 12 μmol L6, 1.2 equiv Na_3PO_4, 0.6 M in *p*-xylene at 135 °C for 12 h. [c] Yield of isolated product **9**. [d] Determined by HPLC or GC using a chiral stationary phase. [e] with L4 instead of L6.

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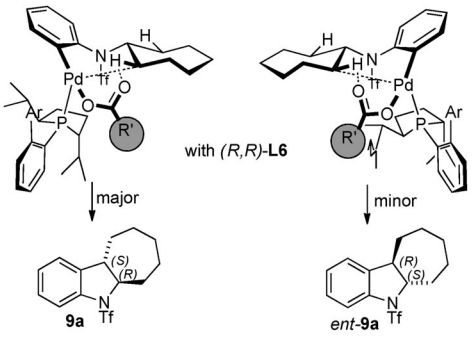
(Table 2, entry 9). For 6-membered-ring substrates with a substituent in the 4-position, both, *trans*-isomer **5e** and *cis*-isomer **5f** provide comparable selectivities (Table 2, entries 5 and 6). Isopropyl amine substrates with enantiotopic CH_3 groups perform well and give access to a variety of 2-methyl-indolines **9g**–**9n** (Table 2, entries 7–14). The reactivity could be further extended to non-cyclic methylene groups providing compounds **9o** in high selectivity (Table 2, entry 15). Even in this case, the *trans*-isomer of the indoline is exclusively observed, underlying the critical importance of a proper spatial arrangement of the hydrogen atom in the reactive conformation **7b** for the reactivity. To investigate this idea, we tested smaller rings which impose *cis*-fused products. For instance, benzocyclopentyl substrate **5p** readily cyclizes and gives rise to **9p** in good yields albeit with diminished enantioselectivity (Table 2, entry 16).

The relative and absolute configuration of the cyclized products was unambiguously established by X-ray crystallographic analysis of product **9a**.[22] (2*R*,3*S*)-Configured indoline **9a** is obtained when the reaction is performed with (*R*,*R*)-SagePhos [(*R*,*R*)-L6]. The absolute configuration might be rationalized by the stereochemical pathway illustrated in Scheme 5. The sterically demanding residue of the carboxylic



Scheme 5. Proposed stereochemical pathway for the formation of **9a**.

acid is oriented to minimize interaction with the bulky substituent of the phospholane, thus proton abstraction leading to the formation of (2*R*,3*S*)-**9a** is favored.

In conclusion, we developed modular monodentate phosphines and demonstrated their utility in palladium-catalyzed C(sp^3)–H activations. The ligands are sterically demanding, electron-rich, yet air-stable. The reaction proceeds well with aryl triflates and provides access to the important indoline scaffold in a highly enantioselective fashion. Moreover, we have shown for the first time that the carboxylic acid required for the metalation participates in the enantiodetermining event in a highly cooperative manner. Exploiting this effect, we aim to enhance the catalyst performance as well as the generality of this functionalization reaction in future studies. Furthermore, we seek to evaluate the profile of this ligand family in other transformations.

Experimental Section

Representative procedure for the enantioselective cyclization (Table 2, entry 7): [η^3-cinnamyl)PdCp] (2.88 mg, 10.0 μmol), A1 (2.24 mg, 10.0 μmol), substrate **5g** (49.1 mg, 0.10 mmol), and sodium phosphate (19.7 mg, 0.12 mmol) were weighed into a vial equipped with a magnetic stir bar. The vial was sealed with a rubber septum and flushed with nitrogen. L6 (8.79 mg, 20.0 μmol) was added as a solution in 0.2 mL *p*-xylene. The mixture was degassed and subsequently heated to 135 °C. After 12 h, the reaction mixture was cooled to 23 °C and directly purified on silica gel (EtOAc/pentane 1:15, $R_f = 0.45$) yielding 25.2 mg (74 %) of **9g** with an e.r. value of 96:4.

Received: December 2, 2011
Published online: February 3, 2012

Keywords: asymmetric catalysis · C—H activation · cooperative effects · palladium · phosphines

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[15] a) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880 – 6886; b) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848 – 10849; c) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 10692 – 10705.

[16] The reaction conditions employed by Kagan et al. (Ref. [14b]) seem at first glance to contradict the CMD-mechanism. However, the palladium source utilized, $Pd^{II}(OAc)_2$, is reduced to the active Pd^0 species by the phosphine ligand (see: V. V. Grushin, *J. Am. Chem. Soc.* **1999**, *121*, 5831 – 5832), thus leading to a mono oxidation of the bidentate Duphos employed to give as the actual active catalyst, presumably a monodentate BozPhos ligated species. Deliberate exposure to air oxidizes the remaining excess Duphos added.

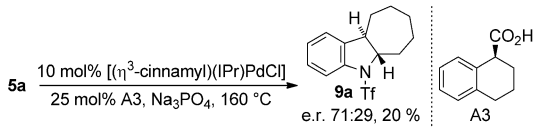
[17] a) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496 – 16497; b) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570 – 14571.

[18] D. M. Norton, E. A. Mitchell, N. R. Botros, P. G. Jessop, M. C. Baird, *J. Org. Chem.* **2009**, *74*, 6674 – 6680.

[19] a) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759 – 1762.

[20] Aryl bromides and other amine substituents provide comparable enantioselectivities albeit in significantly diminished yields.

[21] In a preliminary experiment, we found that chiral carboxylic acid A3 as sole source of chirality and a stabilizing achiral carbene ligand (IPr) provides indoline **9a** with 71:29 e.r.



[22] See Supporting Information. CCDC 852462 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via href = "http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi" > www.ccdc.cam.ac.uk/data_request/cif.

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