Chiral Bifunctional Phosphine-Carboxylate Ligands for Palladium(0)-Catalyzed Enantioselective C–H Arylation

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Abstract: Previous enantioselective Pd⁰-catalyzed C–H activation reactions proceeding via the concerted metalation-deprotonation mechanism employed either a chiral ancillary ligand, a chiral base, or a bimolecular mixture thereof. This study describes the development of new chiral bifunctional ligands based on a binaphthyl scaffold which incorporates both a phosphine and a carboxylic acid moiety. The optimal ligand provided high yields and enantioselectivities for a desymmetrizing C(sp²)–H arylation leading to 5,6-dihydrophenanthridines, whereas the corresponding monofunctional ligands showed low enantioselectivities. The bifunctional system proved applicable to a range of substituted dihydrophenanthridines, and allowed the parallel kinetic resolution of racemic substrates.

In recent years, catalytic enantioselective C–H activation has emerged as a simple and powerful method to construct different types of stereogenic elements (central, planar or axial) and to generate high-value-added enantioenriched molecules.[1] In the context of palladium(0)-catalyzed C–H activation/C–C coupling reactions proceeding via the catalytic cycle depicted in Scheme 1a, the enantiodetermining step is usually the C–H activation, which occurs by a concerted metalation-deprotonation [CMD, or amphiphilic metal ligand activation (AMLA)] mechanism.[2] According to the latter, the substrate, an ancillary ligand (L), and the base performing the C–H bond cleavage (RYO₂⁻) are all coordinated to the palladium center in the transition state. Consistent with this mechanism, two types of chiral catalysts have been successfully employed to induce enantioselectivity in palladium(0)-catalyzed C(sp²)–H and C(sp³)–H activation reactions (Scheme 1b): 1. Chiral ancillary ligands, more specifically phosphorus(III) compounds[3,4] and NHCs,[5] and 2. Chiral bases, for example, carboxylates[4a,b] and Binol-derived phosphates.[6] The union of an ancillary ligand and the base in the same bifunctional molecule has not been achieved so far in the context of palladium(0)-catalyzed enantioselective C–H activation,[7] and is the subject of the work herein (Scheme 1c). Such a bifunctional ligand would possess a more organized structure, compared to the corresponding bimolecular system, and might be broadly applicable to various types of asymmetric C–H activation reactions operating by a similar mechanism.

At the onset of our work, we chose to focus on phosphine-carboxylate bifunctional ligands based on the classic binaphthalene scaffold (Schemes 1c and 2). A series of phosphine-carboxylic acid preligands (L₃–L₇), with a variable number (1–5) of methylene groups separating the carboxylic acid and the binaphthyl core, were prepared from (R)-Binol by adapting literature procedures from Uozumi, Hayashi, and co-workers (Scheme 2).[8,9] As a prototypical reaction, we chose to investigate the enantioselective C–H arylation of the...
aryl bromide 1a to give the 5,6-dihydrophenanthridine 2a. This structural motif is present in various biologically active substances, in particular, fluorogenic probes for the detection of reactive oxygen species. Related palladium(0)-catalyzed desymmetrizing C\(sp{2}\)-H arylation reactions generating carbon, phosphorus, or silicon sterocenters have been reported using a chiral phosphorus ligand and an achiral base, but such an enantioselective synthesis of 5,6-dihydrophenanthridines has not been described.

Standard reaction conditions involved the combination of the ligand (10 mol%) with Pd\(\text{dba}_{3}\), as a carbonylate-free Pd source (5 mol\% Pd), a stoichiometric amount of cesium carbonate, which is able to both deprotonate the carboxylic acid function of the ligand to generate the active carboxylate in situ, as well as regenerate it after the C–H activation step (see Scheme 1a), and DME as the solvent at 120 °C in the presence of molecular sieves to remove traces of potentially deleterious water molecules. The enantioselectivity obtained with bifunctional ligands was compared to the one obtained with the corresponding monofunctional ligands L1 (MOP)[14] and L2, containing an ethyl ester instead of the carboxylic acid. All bifunctional ligands, L3–L7, enabled the reaction in very good yield, but with various levels of enantioselectivities, thus showing the effect of the carbon spacer length (Scheme 2). The enantioselectivity was maximal for the MOP-acetic acid hybrid ligand L3 containing one methylene spacer, which furnished 2a in 91% yield and 93.5:6.5 e.r. Importantly, the enantioselectivity was much lower in control experiments performed with the monofunctional ligands L1 and L2, both in the absence and in the presence of either pivalic or acetic acid additives. Moreover, although the enantioselectivity was low with L6 and L7 bearing a longer carbon spacer, the sense of the induction was inverted compared to that of L1 and L2. All together, these results strongly indicate that the ligands L3–L7 operate in a bifunctional mode. In addition, the most selective ligand, L3, provided a much higher enantioselectivity than that of comparable bimolecular systems composed of L1 or L2 and AcOH or PivOH. Of note, we also tested other chiral ligands such as BINAP, TADDOL-derived phosphoramidites, and NHCs, which were previously employed in asymmetric palladium(0)-catalyzed C–H activation reactions[3,4] but they provided lower enantioselectivities than L3.[9]

In the search for additional improvement of the enantioselectivity, we first synthesized MOP-pivalic acid hybrids, L8 and L9, but the enantioselectivity was reduced compared to those of L3 and L5, which lack the gem-dimethyl groups. The modification of aryl substituents on the phosphorus atom turned out to be more successful (L10–L13), with dimethyl- and dimethoxy-substituted ligands (L10 and L11) affording the highest enantiomeric ratio. Further refinement of reaction conditions was performed using L10, including other carbonate bases, solvents, and temperatures.[9] These studies allowed a decrease in the amount of Cs\(_2\)CO\(_3\) to 1.5 equivalents and the temperature to 80°C, and led to an e.r. value of 98.5:1.5 with a 92% yield on a 1 mmol (fivefold) scale (Scheme 3a). Importantly, a control experiment performed with 1 equivalent of the potassium salt derived from L10, and in the absence of cesium carbonate, still furnished 2a in 92% yield with a slightly reduced e.r. value of 95.5:4.5.[9] This experiment further supports our hypothesis that this ligand is not a mere bidentate ligand, but it also acts as the base participating in the CMD mechanism (Scheme 1c). In this case the main role of the stoichiometric carbonate is to regenerate the active carboxylate ligand after the C–H activation step.

By employing these optimal reaction conditions, we studied the scope and limitations of the catalytic enantioselective synthesis of 5,6-dihydrophenanthridines using Pd/L10 (Scheme 3). For less reactive substrates, the reaction was performed at higher temperatures, as indicated. First, the optimal leaving group was found to be a bromide (Scheme 3a). Lower yields of 2a were obtained from the corresponding iodide and chloride, and the triflate underwent decomposition thus leading to none of the desired product. Next, we studied the impact of the nitrogen substituent on the reaction (Scheme 3b). The best results were obtained with alkoxycarbonyl groups (2a–c). With a tosyl group (2d), a diminished enantioselectivity was observed, whereas with...
methyl (2e) and trifluoroacetyl (2f) groups the reaction was sluggish and gave several decomposition products. With bromide as the leaving group and methoxycarbonyl as the N substituent, different types of R1 groups were introduced on the bromine-containing aromatic ring, with equally excellent yields and enantioselectivities (2g–m, Scheme 3c). Of note, the X-ray diffraction analysis of a single crystal of 2k allowed determination of its absolute configuration as R. In addition, substrates containing either an anthracene (2n) or a pyridine (2o) ring performed with similar efficiency and enantioselectivity. Similarly, the reaction was compatible with R2 substituents at various positions of the other aryl rings (2p–v, Scheme 3d). In the case of 2s, the C–H arylation occurred selectively at the most reactive position ortho to the fluorine atom, as shown by 1H-19F HOSY experiments. In contrast, a limitation was found when the connection of the rings undergoing C–C coupling was changed (Scheme 3e). A decrease in the yield and the enantioselectivity was indeed observed for 2w–y, which contain different six- or seven-membered bridging rings. Achieving efficient enantioselective syntheses of these motifs would likely require further optimization of the ligand structure. For instance, using the tBu-substituted ligand L12, instead of L10, significantly improved the enantioselectivity in the formation of 2y.

Finally, inspired from the work of Kündig and co-workers, and more recently Cramer and co-workers, in

Scheme 3. Scope and limitations of the enantioselective synthesis of 5,6-dihydrophenanthridines. [a] Yield determined by NMR spectroscopy. [b] Performed at 120 °C. [c] Performed at 100 °C. [d] Performed at 140 °C. [e] Thermal ellipsoids shown at 50% probability. [f] Using L12 instead of L10. The absolute configurations of other products were assigned by analogy to 2k. n.d. = not detected. Tf = trifluoromethanesulfonyl.
selects the same enantiotopic aryl group, two enantioenriched constitutional isomers with the same absolute configuration can be obtained with a maximum of 50% yield each. Indeed, reacting 3 and 4 under standard reaction conditions led to approximately 1:1 mixtures of the highly enantioenriched isomers 5a/5b and 6a/6b in excellent combined yields. This result is in line with previous reports,[9,17] hence tending to indicate the general character of PKR by palladium(0)-catalyzed C–H activation.

In conclusion, chiral bifunctional phosphine/carboxylate ligands based on a biphenyl scaffold showed high efficiency and enantioselectivity for a desymmetrizing C(sp²)–H arylation leading to 5,6-dihydropyridazines. In contrast, the corresponding monofunctional ligands, lacking a carboxylic acid function, induced only low enantioselectivities, thereby demonstrating the added value of bifunctionality. This new ligand type might show broad applicability to various types of asymmetric C–H activation reactions operating by the CMD mechanism.

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Conflict of interest

The authors declare no conflict of interest.

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[9] See the Supporting Information for details.


[15] CCDC 1581525 (2k) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.


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