C–H Activation

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

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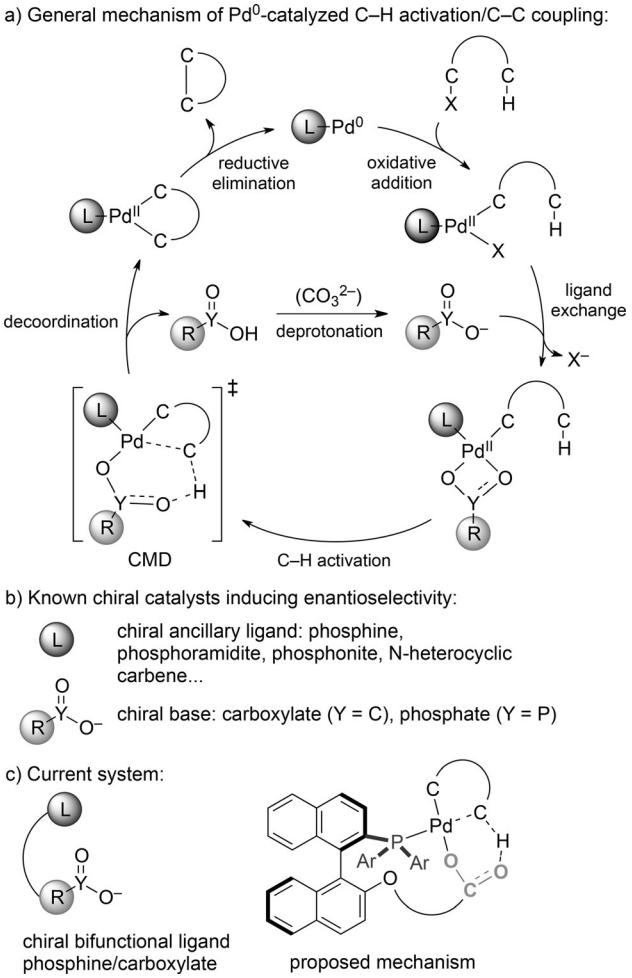
Abstract: *Previous enantioselective Pd^0-catalyzed C–H activation reactions proceeding via the concerted metalation-deprotonation mechanism employed either a chiral ancillary ligand, a chiral base, or a bimolecular mixture thereof. This study describes the development of new chiral bifunctional ligands 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 $C(sp^2)$–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 ambiphilic 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 (RYO_2^-) 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 $C(sp^2)$–H and $C(sp^3)$–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.



Scheme 1. State-of-the-art and current chiral catalysts for palladium(0)-catalyzed C–H arylation.

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

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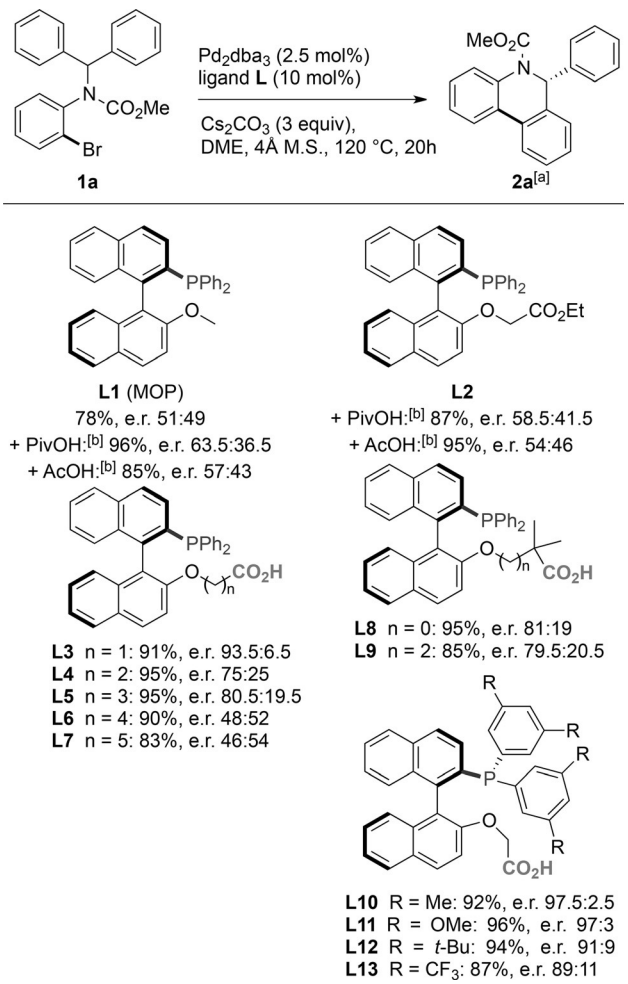


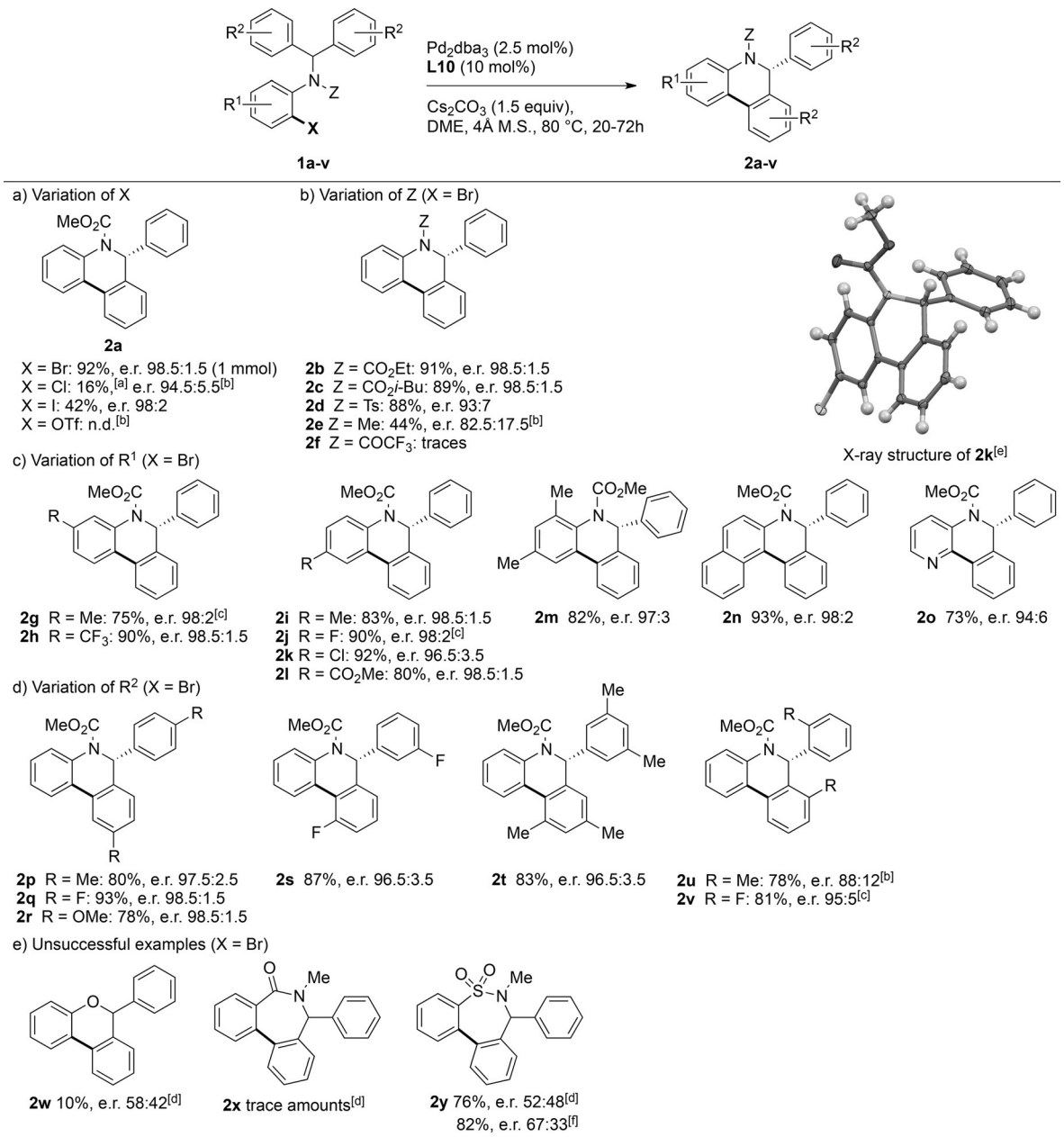
Scheme 2. Synthesized bifunctional ligands and their effect in enantioselective C(sp^2)–H arylation. [a] The absolute configuration of **2a** was deduced from the X-ray crystal structure shown in Scheme 3. [b] 15 mol%. dba = dibenzylideneacetone, DME = 1,2-dimethoxyethane, M.S. = molecular sieves.

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.[10] Related palladium(0)-catalyzed desymmetrizing C(sp^2)–H arylations generating carbon,[3a,c] phosphorus,[11] or silicon[3b,h] stereocenters 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.[12,13]

Standard reaction conditions involved the combination of the ligand (10 mol%) with Pd_2dba_3 as a carboxylate-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.[6b] 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_2CO_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

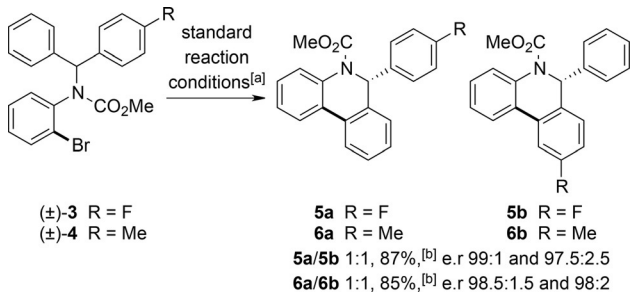


Scheme 3. Scope and limitations of the enantioselective synthesis of 5,6-dihydrophenanthridines. [a] Yield determined by NMR spectroscopy. [b] Performed at 120 °C. [c] Performed at 100 °C. [d] Performed at 140 °C. [e] Thermal ellipsoids shown at 50% probability. [f] Using **L12** instead of **L10**. The absolute configurations of other products were assigned by analogy to **2k**. n.d. = not detected. Tf = trifluoromethanesulfonyl.

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 R^1 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*.[15] In addition, substrates containing either a naphthalene (**2n**) or a pyridine (**2o**) ring performed with similar efficiency and enantioselectivity. Similarly, the reaction was compatible with R^2 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,[16] as shown by ^{1}H-^{19}F HOESY experiments.[9] 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 *t*Bu-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,[5b] and more recently Cramer and co-workers,[17] in

$C(sp^3)$–H and $C(sp^2)$–H arylation, we examined the parallel kinetic resolution (PKR) of the racemic substrates **3** and **4** (Scheme 4). This behavior is based on the fact that differently substituted aryl groups undergo C–H arylation at similar rates. Since a given enantiomer of the chiral catalyst always



Scheme 4. Parallel kinetic resolution of racemic substrates. [a] Pd_2dba_3 (2.5 mol%), **L10** (10 mol%), Cs_2CO_3 (1.5 equiv), DME, 4 Å M.S., 80°C. [b] Combined yield of the isolated mixture of inseparable isomers.

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,[5b,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 binaphthyl scaffold showed high efficiency and enantioselectivity for a desymmetrizing $C(sp^2)$–H arylation leading to 5,6-dihydrophenanthridines. 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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