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Palladium-Catalyzed Asymmetric C(sp^3)–H Allylation of 2-Alkylpyridines

Ryo Murakami,[+] Kentaro Sano,[+] Tomohiro Iwai, Tohru Taniguchi, Kenji Monde, and Masaya Sawamura*

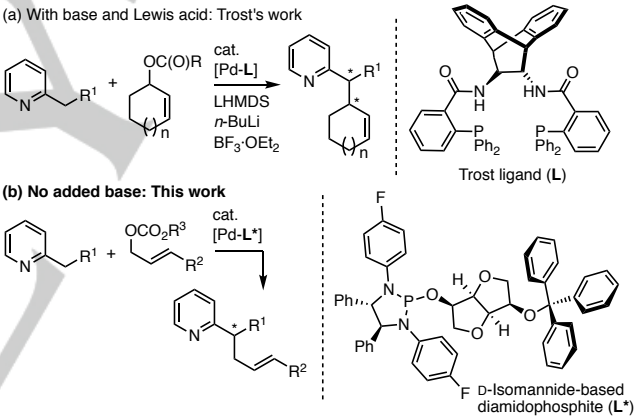
Abstract: Palladium-catalyzed asymmetric side-chain C(α)-allylation of 2-alkylpyridines without external base was developed. The high linear- and enantioselectivities were achieved using new chiral diamidophosphite monodentate ligands. Due to the no external base conditions, this catalyst system enabled chemoselective C(α)-allylation of 2-alkylpyridines containing α-carbonyl C–H bonds, which are more acidic than α-pyridyl C–H bonds.

Azaarenes with an α-stereogenic alkyl substituent at the C2 position constitute an important structure motif widely found in biologically active compounds, agrochemicals, and natural products.[1] Among methods used to access these structures,[2] asymmetric Tsuji–Trost allylation reactions with 2-alkylazaarenes as pronucleophiles to allow enantioselective C(sp^3)–C(sp^3) bond formation at the position α to the azaarene ring are promising strategies.[3] However, reported methods have required the use of stoichiometric or excess amounts of strong Brønsted bases and/or Lewis acids to activate the C(sp^3)–H bonds of the pronucleophiles (Scheme 1a).[4-6]

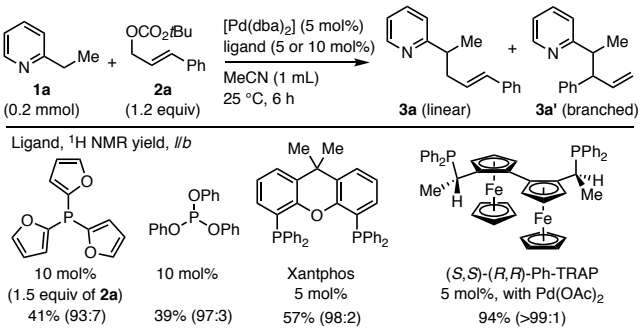
This report describes the Pd-catalyzed asymmetric C(sp^3)–H allylation of 2-alkylpyridines with primary allylic carbonates, which did not require the use of an external base. With a new chiral diamidophosphite [P(NR^1R^2)$_2$(OR^3)] monodentate ligand featuring a D-isomannide framework with a sterically demanding group at a distal position, C(sp^3)–C(sp^3) bond formation occurred cleanly with exclusive regioselectivity with respect to the allylic portion to give enantio-enriched α-stereogenic 2-alkylpyridines with no constitutional isomers (Scheme 1b). The mildness of the conditions allowed compatibility of the reaction with various functional groups,[7–9] which was site-selective toward a C(sp^3)–H bond located α to the pyridine ring in the presence of more acidic C(sp^3)–H bonds adjacent to carbonyl groups.

A preliminary screening of achiral ligands for the reaction between 2-ethylpyridine (**1a**) and cinnamyl *t*-butyl carbonate (**2a**) with 5 mol% [Pd(dba)$_2$] as a Pd source in MeCN at 25 °C for 6 h revealed that electron-deficient monophosphines and large bite-angle bisphosphines promoted side-chain C(α)-allylation (Scheme 2). Specifically, P(2-furyl)$_3$ and P(OPh)$_3$ caused moderate substrate conversion to give the linear allylation product **3a** preferentially over the branched product **3a'** (**3a**/**3a'** 93:7 and 97:3, respectively). Xantphos improved linear-selectivity, albeit with an unsatisfactory yield. Further ligand screening revealed that Ph-TRAP,[10] featuring a very large bite angle, induced complete substrate conversion to give **3a** exclusively, but with poor enantioselectivity (with Pd(OAc)$_2$, 3% ee).

This reaction occurred specifically with allylic substrates having carbonate leaving groups. Cinnamyl methyl carbonate (**2b**) also was a suitable substrate in the reaction with Ph-TRAP (95%, **3a**/**3a'** >99:1).[11]



Scheme 1. Asymmetric side-chain C(α)-allylation of 2-alkylpyridines



Scheme 2. Pd-catalyzed C(α)-allylation of **1a** with **2a**

Next, various chiral ligands were used to achieve better enantioselectivity in reaction between 5,6,7,8-tetrahydroquinoline (**1b**) and **2b** (1.3–1.5 equiv) with [Pd(dba)$_2$] (5 mol%, Pd/ligand 1:1) in MeCN at 25 °C (12 h). The results are summarized in Scheme 3.

Chiral monodentate phosphoramidite ligands and a Trost's bisphosphine ligand (**L** in Scheme 1)[4] induced no reaction. The Ph-TRAP again gave complete substrate conversion, albeit with poor enantioselectivity (19% ee). A change in the *P*-substituents

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of TRAP from Ph to *m*-terphenyl (TerPh-TRAP)[10c] improved enantioselectivity to 45%.

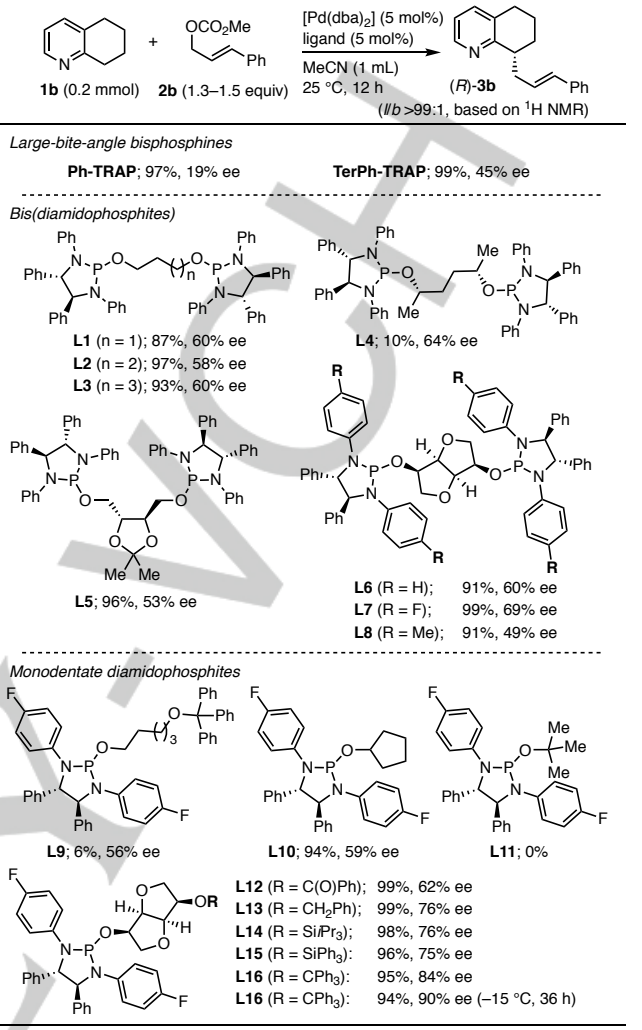
Further ligand screening revealed bis(diamidophosphite)-type ligands as promising candidates.[12] The 1,3-, 1,4-, and 1,5-alkanediol-based ligands (**L1**–**L3**) induced moderate enantioselectivity (58–60% ee) with high substrate conversion. Among bis(diamidophosphite) ligands derived from chiral 1,4-butanediols (**L4**–**L6**), the D-isomannide derivative (**L6**) with a rigid bicyclic backbone was the most favorable for both product yield and enantioselectivity (91% yield, 60% ee).[13]

An exploration of *N*-substituents on the 1,2-diamine moiety of **L6** led to further improvement in enantioselectivity (69% ee) with **L7** containing *N*-4-fluorophenyl groups. Introduction of the Me group instead of the F group decreased enantioselectivity significantly (**L8**, 49% ee).

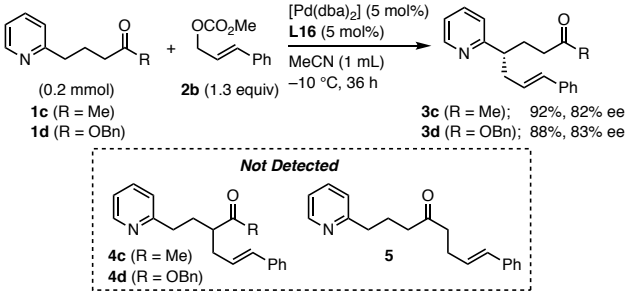
The effectiveness of the electron-poor monophosphines in the reaction of 2-ethylpyridine (**1a**) (Scheme 2) led to an exploration of monodentate diamidophosphites containing a *N,N*-(4-fluorophenyl)-1,2-diphenylethylenediamino moiety for enantioselective reaction of the tetrahydroquinoline **1b** (Scheme 3). Although primary (**L9**) and tertiary (**L11**) alcohol-based ligands induced only trace or no reaction (<6%), the ligand **L10** derived from cyclopentanol gave a high yield of **3b** with moderate enantioselectivity (94% yield, 59% ee). These results indicated that the second *P*-center was unnecessary and promoted further screening of monophosphines with mono-*O*-protected isomannide substituents.

A catalyst system prepared from [Pd(dba)$_2$] and a diamidophosphite (**L12**) having an *O*-benzoyl group (Pd/P 1:1) allowed quantitative C(α)-allylation with moderate enantioselectivity (62% ee). Interestingly, the *O*-substituent had a significant impact on the enantioselectivity regardless of its long spatial distance from the P atom. Thus, the enantioselectivity increased to 76% ee by changing the *O*-protecting group to a benzyl group (**L13**). While *O*-silyl derivatives, such as **L14** and **L15**, gave nearly the same results as the benzyl derivative **L13**, a significant increase in enantioselectivity was observed with the tritylated ligand **L16**, which afforded **3b** with 84% ee in 95% yield. The enantioselectivity with **L16** increased to 90% ee by conducting the reaction at –15 °C.[14,15] Thus, **L16** was identified as the optimal chiral ligand. The effects of the *O*-protecting groups may be due to dispersive ligand–substrate attractions.[16,17]

The synthetic utility of the present catalyst system was demonstrated in the chemoselective C(α)-allylation of 2-alkylpyridines containing α-carbonyl C–H bonds, which are more acidic than α-pyridyl C–H bonds (Scheme 4). Specifically, allylic alkylation of **1c** bearing a ketone moiety with **2b** in the presence of the Pd-**L16** system occurred cleanly to afford the side-chain C(α)-allylation product **3c** with 82% ee in 92% yield.[18] No formation of carbonyl C(α)-allylation products **4** and **5** was observed by ^{1}H NMR analysis. In contrast, the reaction between **1c** and **2b** catalyzed by the [PdCl(π-allyl)]$_2$/dppf system in the presence of LiHMDS (1.2 equiv) as a base in THF at rt did not produce **3c** at all but gave a complex mixture.[19] With the Pd-**L16** system, **1d** containing an ester moiety was also suitable.



Scheme 3. Ligand effects in asymmetric C(α)-allylation. Conditions: **1b** (0.2 mmol), **2b** (0.26–0.30 mmol), [Pd(dba)$_2$] (5 mol%), ligand (5 mol%), MeCN (1 mL), 25 °C, for 12 h. Yields of isolated product. Ee values determined by HPLC.



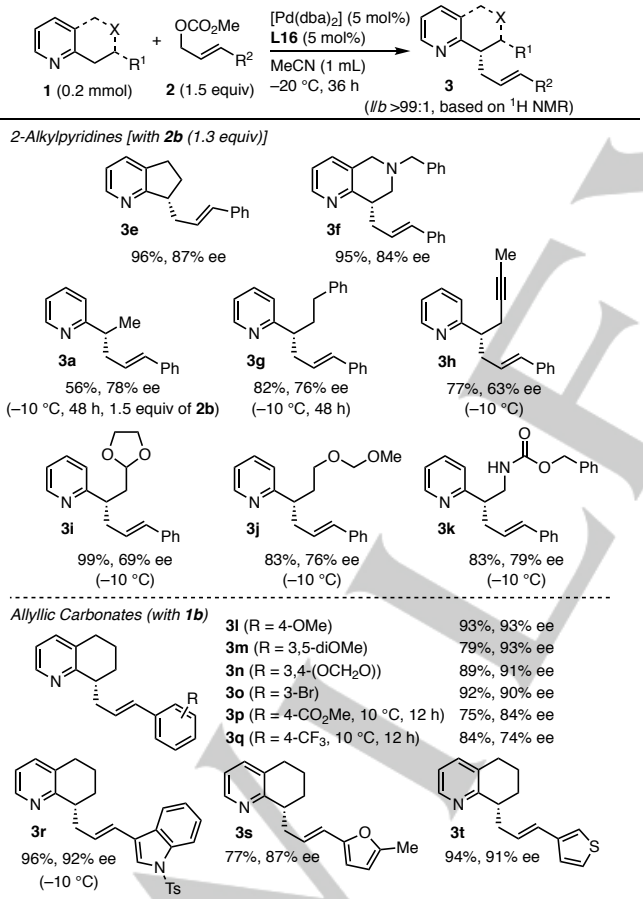
Scheme 4. Side-chain C(α)-allylation of 2-alkylpyridines containing α-carbonyl C–H bonds

Reactions with various combinations of 2-alkylpyridines **1** and allylic carbonate **2** catalyzed by Pd-**L16** system is shown in Scheme 5. The reactions occurred in the temperature range of –20 to +10 °C with exceptional linear selectivity (*l*/*b* >99:1) and good-to-high enantioselectivities (63–93% ee). The allylation of 2,3-cyclopentenopyridine with **2b** occurred with an enantioselectivity comparable to that of **1b** (**3e**, 96% yield, 87%

ee). A piperazine-fuzed substrate underwent regioselective allylation at the position β to the pyridine *N* atom with a high level of enantioselectivity (**3f**, 95% yield, 84% ee).

Acyclic alkyl substituents of pyridine substrates were also allylated with the Pd-**L16** system albeit with slightly lower enantioselectivities compared to the annulated substituent in **1b**. For instance, 2-ethylpyridine (**1a**) and 2-(3-phenylpropyl)pyridine afforded **3a** in 78% ee and **3g** in 76% ee, respectively (Scheme 5). Functional groups such as alkyne (**3h**), acetal (**3i**), methoxymethyl (**3j**), or carbamate (**3k**) with an N–H bond in the acyclic alkyl substituents did not hamper the allylation.[20,21]

Cinnamyl carbonates **2** with electron-rich or electron-neutral aromatic rings participated in asymmetric reaction of **1b** to give the corresponding C(α)-allylated products (**3l**–**o**) in high yields with enantioselectivities ranging from 90% to 93% ee. However, cinnamyl carbonates with ester- or CF_3-substituted electron-deficient aromatic rings were less reactive, and reaction at 10 °C occurred with somewhat lower enantioselectivities (**3p** and **3q**). Indole-, furan-, and thiophene-based carbonates reacted with **1b** to afford **3r**–**t** in enantioselectivities ranging from 87% to 92% ee.[22]



Scheme 5. Scope of asymmetric C(α)-allylation. Conditions: **1** (0.2 mmol), **2** (0.26–0.3 mmol), [Pd(dba)$_2$] (5 mol%), **L16** (5 mol%), MeCN (1 mL) at –20 °C for 36 h. Yields of isolated products are shown. Absolute configurations of **3e**, **3f**, and **3l**–**t** were assigned by analogy to (*R*)-**3b**. Absolute configurations of **3a** and **3g**–**k** were assigned by analogy to (*R*)-**3c**.

Reaction between **1b** with methyl (1-phenylallyl) carbonate catalyzed by the Pd-**L16** system provided the linear product **3b** with the identical absolute configuration (*R*) and enantiomeric purity as that of **2b**, but with slightly lower reaction efficiency (68% yield, 91% ee). This result strongly suggests that both reactions proceeded through a (π-allyl)palladium(II) species as a common intermediate.

The P/Pd ratio had a significant impact on the efficiency of the reaction between **1b** and **2b** catalyzed by the Pd-**L16** system (Figure 1). The reaction was conducted at –15 °C for 36 h with varying amounts of **L16** relative to Pd in the range of 0.2 to 4.0 equivalents. While no reaction occurred with 0.2 to 0.9 equivalents of **L16**, a P/Pd ratio of 0.95 gave the moderate yield (57%) and enantiomeric excess (89% ee) of product (*R*)-**3b**. The maximum yield (99%) was obtained from a P/Pd ratio of 1.0. Product yield gradually decreased to 92% as the loading of **L16** increased from 1.0 to 4.0 equivalents; however, enantioselectivity was maintained at 91% ee. These results suggest that the active species is Pd-**L16** in a 1:1 ratio (P/Pd 1:1).[23] For reactions with large-bite-angle bisphosphine ligands such as TRAPs and Xantphos, one of the two P atoms might dissociate from Pd during catalysis while bidentate coordination in the resting state may stabilize the catalytic system.

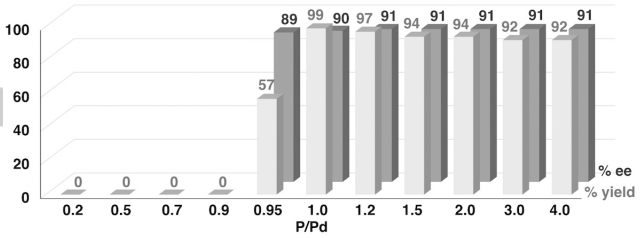
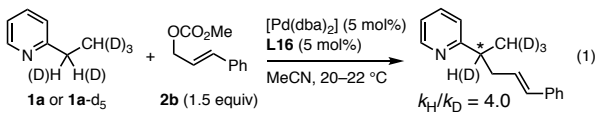


Figure 1. Effect of **L16**/Pd molar ratio in reaction between **1b** and **2b** (5 mol% Pd, in MeCN, at –15 °C, 36 h)

To have a mechanistic insight, preliminary ^{1}H NMR kinetic studies were conducted for the reaction between **1a** and **2b** with the Pd-**L16** (1:1) system in CD_3CN at rt. Thus, the rate was pseudo-first order for the Pd-**L16** catalyst, while reaction orders of 0 and 0.7 were indicated for carbonate **2b** and 2-ethylpyridine **1a**, respectively.[24] This result suggests the following mechanistic conclusions: the Pd catalyst participates in the reaction in a monomeric form; the allylic carbonate **2b** has a high affinity for the Pd catalyst; and an off-cycle species is formed upon coordination of the alkylpyridine **1a** to a catalytically active species.

Kinetic analysis of reactions using **1a** or **1a**-d_5 with **2b** catalyzed by the Pd-**L16** system in MeCN at 20–22 °C gave a significant kinetic isotope effect value [k_H/k_D = 4.0; Eq. (1)], which indicates that a turnover-limiting step of Pd catalysis involved the dissociation of a C(α)–H bond.



Based on these experimental results, a reaction pathway is proposed in Figure 2. Thus, a mono-P-ligated Pd(0) complex **A** undergoes rapid decarboxylative oxidative addition with allylic

carbonate **2**, to produce a neutral alkoxo(π-allyl)palladium(II) complex (**B**). Coordination of a 2-alkylpyridine (**1**) to **B** forms a cationic complex with an alkoxide counter anion (**C**). Further coordination of **1** to **C** forms an off-cycle species (**D**, [Pd(R^1-allyl)(P*)(**1**)$_2$]$^+$(OR^2)$^-$). Next, cleavage of a side chain C(α)–H bond produces the (η^1-enamido)(η^3-allyl)palladium(II) complex (**E**). This catalyst-turnover-limiting step should be promoted by effective acid–base cooperation between the cationic Pd(II) center bound to the N atom and the alkoxide ion interacting with one of the C(α)–H protons. Finally, diastereoselective reductive elimination of the η^1-enamido ligand and the η^3-allyl ligand, either in a direct manner or through a multi-step pathway involving η^3-to-η^1 hapticity change in the allylic ligand, furnishes the enantio-enriched C(α)-allylation product **3**.

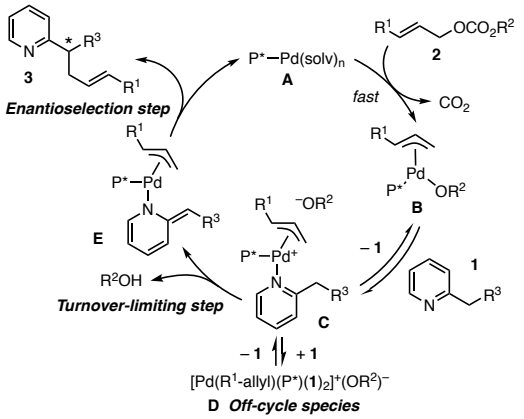


Figure 2. A possible reaction pathway

In conclusion, a Pd-catalyzed asymmetric side-chain C(α)-allylation of 2-alkylpyridines without an external base was developed. Newly synthesized D-isomannide-based monodentate diamidophosphite ligands enabled the highly linear- and enantioselective allylation with good functional group compatibility. The reaction pathway is proposed to involve formation of a (π-allyl)palladium(II) complex coordinated with a single molecule of the phosphine ligand and the 2-alkylpyridine substrate followed by side-chain C(α)-deprotonation by an alkoxide anion. Studies on extending this strategy to other alkyl azaarenes for catalytic asymmetric C–H functionalization reactions are ongoing.

Acknowledgements

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Keywords: Asymmetric catalysis · C–H functionalization · Allylation · 2-Alkylpyridines · Palladium

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[20] The reaction of papaverine, an isoquinoline alkaloid used as vasodilators, with the Pd-**L16** system gave the corresponding C(α)-allylation product with 82% ee in 18% yield (25 °C, 12 h). 1-Methyl-2-phenethyl-1*H*-benzo[*d*]imidazole did not participate in the reaction.

[21] The reaction of 2-methylpyridine and **2b** with the Pd-**L16** system at 25 °C for 12 h gave a mixture of C(α)-monoallytion (22%) and α,α-diallylation products (39%). A related work on the enantioselective Ir-catalyzed allylic substitution with 2-methylpyridines: X.-J. Liu, S.-L, You. *Angew. Chem.* **2017**, *129*, 4060–4063; *Angew. Chem. Int. Ed.* **2017**, *56*, 4002–4005.

[22] The C(α)-allylation with allyl methyl carbonate (60% yield, 67% ee; –20 °C, 36 h) or 3-cyclohexyl-2-propenyl methyl carbonate (63% yield, 39% ee; 0 °C, 12 h) were less enantioselective as compared to the reaction with aryl-substituted allylic carbonates.

[23] The non-linear dependence of the product yields on the P/Pd ratios suggests that P-uncoordinated Pd species may become a seed to induce rapid catalyst decomposition leading to total catalyst deactivation.

[24] See the Supporting Information for details of the kinetic studies.

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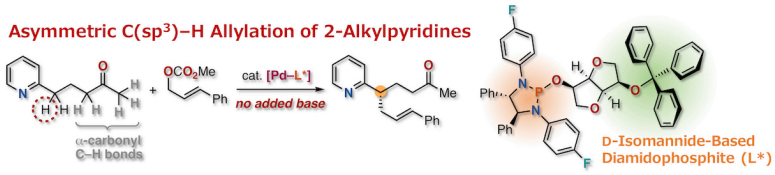

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