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A Versatile Synthesis of Vinyl-Substituted Heterocycles via Regio- and Enantioselective Pd-Catalyzed Tandem Allylic Substitution

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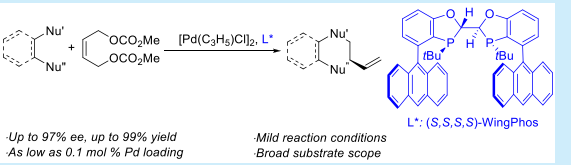
ABSTRACT: We herein report a versatile, regio- and enantioselective palladium-catalyzed tandem allylic substitution powered by a chiral bisphosphorus ligand WingPhos with the palladium loading as low as 0.1 mol %, forming a series of chiral vinyl-substituted heterocycles, including tetrahydroquinoxalines, piperazines, dihydro-2*H*-benzo[*b*][1,4]-oxazines, and morpholines, in exellent ee's and yields. The protocol features readily available starting materials, mild reaction conditions, and a broad substrate scope. Mechanistic investigation supports a tandem allylic substitution process.



Chiral substituted heterocycles such as tetrahydroquinoxalines, 3,4-dihydro-2*H*-1,4-benzoxazines, piperazines, and morpholines, exist ubiquitously in the structures of natural products and therapeutic agents (Figure 1).[1−7] Their syntheses

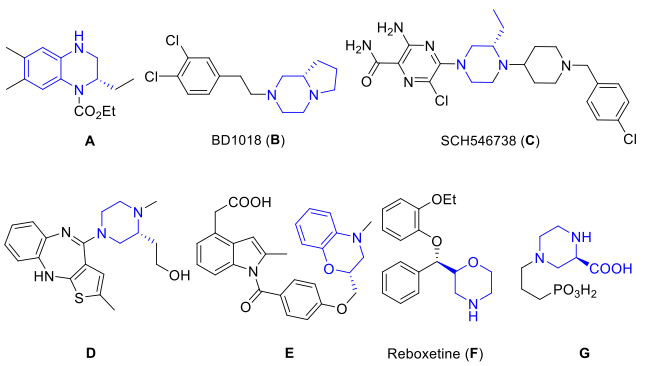
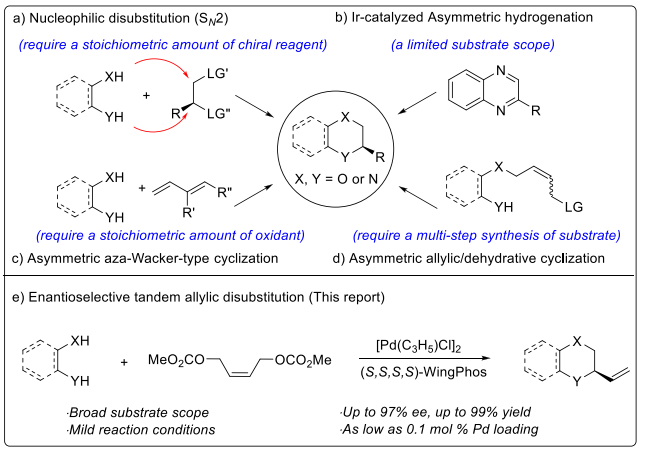


Figure 1. Therapeutic agents containing chiral substituted heterocycles.

have been subjects of extensive interests.[8] A commonly used method is the nucleophilic substitutions of a chiral functionalized building block, often derived from a chiral amino acid through a multistep synthetic sequence featuring a tedious metal hydride reduction (Scheme 1a).[8] The recent development of transition metal-catalyzed asymmetric reactions has offered attractive alternatives. Chan[9a] and Ratovelomanana-Vidal[9b] respectively reported the enantioselective construction of tetrahydroquinoxalines by Ir-catalyzed asymmetric hydrogenation, albeit with a limited substrate scope (Scheme 1b). An elegant asymmetric Wacker-type aminohydroxylation of 1,3-dienes was developed by Gong and co-workers, forming a series of chiral dihydro-2*H*-benzo[*b*][1,4]-oxazines in good to excellent enantioselectivities, although the addition of a stoichiometric amount of oxidant is required (Scheme 1c).[10]

Scheme 1. Enantioselective Synthesis of Chiral Substituted Heterocycles



Additionally, asymmetric Au-catalyzed dehydrative cyclizations,[11] Pd-catalyzed carboaminations,[12] and intramolecular allylic cyclizations[13] were also developed and high enantioselectivities were reported (Scheme 1d). Despite various asymmetric methods, limitations such as high catalyst loadings have significantly hampered their applications and development of a practical asymmetric catalytic method remains an important goal. The enantioselective palladium-catalyzed tandem allylic substitution employing readily available starting

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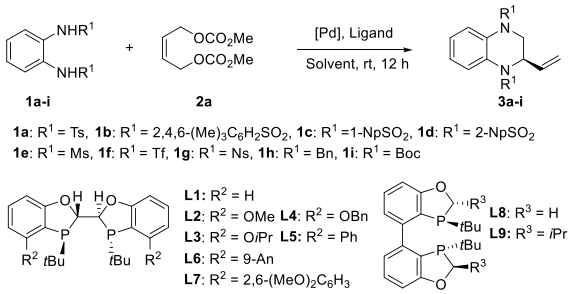
Table 1. Palladium-Catalyzed Tandem Allylic Substitution between 1,2-Phenylenediamine Derivatives (1a−i) and 2-Butenylene Dicarbonate (2a)[a]



entry	Pd precursor	ligand	solvent	substrate **1**	yield (%)[b]	ee (%)[c]
1	$Pd_2(dba)_3$	**L1**	THF	**1a**	99 (**3a**)	20
2	$Pd_2(dba)_3$	**L2**	THF	**1a**	99 (**3a**)	60
3	$Pd_2(dba)_3$	**L3**	THF	**1a**	99 (**3a**)	30
4	$Pd_2(dba)_3$	**L4**	THF	**1a**	99 (**3a**)	0
5	$Pd_2(dba)_3$	**L5**	THF	**1a**	99 (**3a**)	63
6	$Pd_2(dba)_3$	**L6**	THF	**1a**	99 (**3a**)	74
7	$Pd_2(dba)_3$	**L7**	THF	**1a**	50 (**3a**)	13
8	$Pd_2(dba)_3$	**L8**	THF	**1a**	99 (**3a**)	36
9	$Pd_2(dba)_3$	**L9**	THF	**1a**	70 (**3a**)	60
10	$Pd(dba)_2$	**L6**	THF	**1a**	99 (**3a**)	32
11	$Pd(OAc)_2$	**L6**	THF	**1a**	99 (**3a**)	17
12	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1a**	99 (**3a**)	84
13	$[Pd(C_3H_5)Cl]_2$	**L6**	dioxane	**1a**	99 (**3a**)	47
14	$[Pd(C_3H_5)Cl]_2$	**L6**	toluene	**1a**	98 (**3a**)	73
15	$[Pd(C_3H_5)Cl]_2$	**L6**	Me-THF	**1a**	70 (**3a**)	86
16	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1b**	99 (**3b**)	50
17	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1c**	85 (**3c**)	81
18	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1d**	99 (**3d**)	91
19[d]	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1d**	99 (**3d**)	95
20[e]	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1d**	50 (**3d**)	89
21	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1e**	99 (**3e**)	88
22	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1f** or **1g**	NR	–
23	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1h**	99 (**3h**)	45
24[f]	$[Pd(C_3H_5)Cl]_2$	**L6**	THF	**1i**	87 (**3i**)	87

[a]Unless otherwise specified, all reactions were performed at rt for 12 h in the selected solvent (2.0 mL) with **1** (0.2 mmol), **2** (0.22 mmol), Pd precursor (0.5 mol %), and ligand (1.0 mol %). The absolute configuration of **3d** was determined by the X-ray structure. [b]Isolated yields. [c]Determined by chiral HPLC. [d]T = 15 °C. [e]T = 10 °C. [f]T = 50 °C.

materials under mild conditions offers an attractive solution for the synthesis of chiral vinyl-substituted heterocycles (Scheme 1e). Pioneering work by Hayashi and co-workers reported low enantioselectivities and yields in the formation of 2-vinylpiperazine and 2-vinylmorpholine with chiral BINAP as the ligand.[14] By employing BHMP, Achiwa and co-workers reported the synthesis of dihydro-2*H*-benzo[*b*][1,4]-oxazines in modest yields and enantioselectivites.[15] Improved yields and ee's were reported independently by Nakano group[16] and Ito group[17] by using chiral P,N-ligands. A modest or low ee was observed on a tetrahydroquinoxaline with MeO-BIPHEP[18] or Feiphos[19] as the ligand. Despite the employment of various chiral ligands, a palladium-catalyzed tandem allylic substitution with high enantioselecivity, low catalyst loading (<1 mol %), and a broad substrate scope, is yet to be realized. Moreover, excellent ee's and yields have not been achieved on tetrahydroquinoxalines. Herein we report a WingPhos-powered palladium-catalyzed tandem allylic substitution that has provided a series of enantioenriched vinyl-substituted heterocycles, including tetrahydroquinoxalines, piperazines, dihydro-2*H*-benzo[*b*][1,4]-oxazine, and morpholines in high enantioselectivities and yields, with the palladium loading as low as 0.1 mol %.

We have developed a series of electron-rich and sterically hindered P-chiral bisphosphorus ligands. The chiral BIBOP-type ligands are structurally unique and highly tunable in terms of both electronic and steric properties, proving to be efficient for various asymmetric catalytic reactions.[20] The palladium-catalyzed reaction between *N*,*N*′-(1,2-phenylene)bis(4-methylbenzenesulfonamide) (**1a**) and 2-butenylene dicarbonate (**2a**) was thus studied by employing chiral BIBOP-type ligands. The reactions were performed in THF at rt for 12 h with **1a** (0.1 mmol), **2a** (0.1 mmol), palladium precursor (0.5 mol %), and a chiral ligand (1.0 mol %), without adding an additional base or oxidant. As shown in Table 1, BIBOP (**L1**) provided an almost perfect yield, albeit with merely 20% ee (entry 1). A more electronic-rich ligand MeO-BIBOP (**L2**) also provided an excellent yield (99%) with a much improved ee (60%, entry 2). Further increase of the bulkiness of the alkoxy groups (R^2) in the ligand structure (**L3** or **L4**) led to a poor enantioselectivity, although the yield was not compromised (entries 3−4). When phenyl groups were installed at R^2

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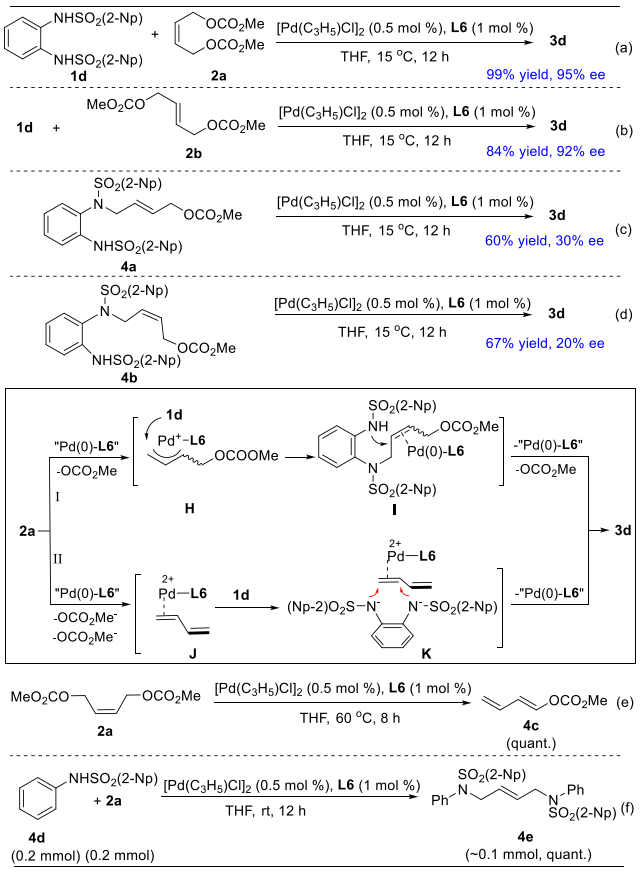
positions of the ligand, 60% ee was obtained (entry 5). When WingPhos (**L6**) was employed with anthracenyl groups at R^2 positions, a much improved ee (74% ee) was achieved (entry 6). Both the reactivity and enantioselectivity decreased when DI-BIDIME (**L7**) was employed, indicating the importance of the anthracenyl structures for the high enantioselectivity (entry 7). BABIBOP-type ligands[21] (**L8**, **L9**) were also tested, leading to moderate enantioselectivities (entries 8−9). Among various palladium precursors screened, $[Pd(C_3H_5)Cl]_2$ proved to be the best in terms of both yield and enantioselectivity (entries 9−12). Solvent screening showed that the enantioselectivity diminished substantially in dioxane and toluene, albeit with acceptable yields (entries 12−15). Furthermore, substrates **1a**−**h** with various *N*-protecting groups were tested. Bulky aryl sulfonamides such as 2,4,6-$(CH_3)_3C_6H_2SO_2$ or 1-$NpSO_2$ led to diminished ee's (entries 16−17). To our delight, excellent results were achieved (99% yield, 90% ee) when 2-$NpSO_2$ was employed as the *N*-protecting group (entry 18). The ee was promoted to 95% by reducing the reaction temperature to 15 °C (entry 19). A further decrease of the reaction temperature led to an inferior yield and ee (entry 20). Interestingly, a good isolated yield and enantioselectivity (99% yield, 88% ee) were achieved when *N*-Ms protecting groups were employed (entry 21). A more electron-deficient substrate with *N*-Tf or *N*-Ns protecting groups showed no reactivity under similar reaction conditions (entry 22). A substrate with *N*-Bn protecting groups led to a moderate ee (45%) albeit with an excellent yield (99%). A Boc-protected substrate **1i** also provided a good yield (87%) and a decent ee (87%) (entry 24). It should be noted that tetrahydroquinoxaline derivatives were formed for the first time in excellent yields and ee's by palladium-catalyzed tandem allylic substitution.

In order to gain mechanistic insight of the reaction, a series of experiments were performed using Pd-WingPhos (Pd-**L6**) as the catalyst. First, both (*Z*)- and (*E*)-but-2-ene- dimethyl bis(carbonate) (**2a** and **2b**) were subjected to the transformation under similar reaction conditions, respectively (Scheme 2, entries a−b). The fact that both reactions provided similarly high ee's indicated that the two reactions were likely to proceed through the same reaction intermediate. Their presumed intermediates **4a** and **4b** after the first allylic substitution were also prepared and further subjected under similar reaction conditions (entries c−d). We were surprised that both reactions were incomplete under similar reaction conditions, and the formed product **3d** was isolated in low ee's (20−30%). The vastly different results between entries a−b and entries c−d raised a question about the true mechanism of the palladium-catalyzed nucleophilic substitution. Trost and co-workers reported that the enediol dicarbonates underwent elimination under reduced conditions to form conjugated dienes.[22] Besides a previously proposed tandem allylic substitution pathway I which goes through palladium intermediates **H** and **I**, we pondered the possibility of an alternate mechanism II involving a dicationic diene-bound palladium species **J**, which could also undergo two consecutive nucleophilic attacks to form the product **3d** (CCDC 1964498). To determine whether the palladium species **J** is formed, stoichiometric amounts of $[Pd(C_3H_5)Cl]_2$, **L6**, and **2a** were mixed in THF at rt for 12 h; no change was observed according to ^1H and ^{31}P NMR. No consumption of **2a** was observed when $Pd_2(dba)_3$ instead of $[Pd(C_3H_5)Cl]_2$ was employed as the precursor. However, when **2a** was stirred at 60 °C in THF in the presence of a catalytic amount of

Scheme 2. Mechanistic Investigation



$[Pd(C_3H_5)Cl]_2$ (0.5 mol %) and **L6** (1 mol %), (*E*)-buta-1,3-dien-1-yl methyl carbonate (**4c**) was formed in an almost quantitative yield, which was presumably generated through oxidative addition followed by *β*-hydride elimination from **2a** (entry e). The formation of **4c** excluded the presence of a palladium species **J** in the allylic substitution process, further supporting the credibility of a tandem allylic substitution pathway. Interestingly, a stoichiometric mixture of $Pd_2(dba)_3$, **L6**, and (*E*)-1,4-dichloro-2-butene (**2c**) led to the formation of 1,3-butadiene in 80% yield along with Pd(**L6**)Cl_2, whose structure was characterized by X-ray diffraction (CCDC 1964492) (see Supporting Information).

Further experiments between **1d** and **2a** or **2b** with a stoichiometric amount of $[Pd(C_3H_5)Cl]_2$ and **L6** revealed no formation of an intermediate **4a** or **4b** by ^{1}HNMR. We also performed the allylic substitution between *N*-phenylnaphthalene-2-sulfonamide (**4d**) and **2a** at equal mole ratio, and the substitution product **4a** was formed in almost quantitative yield (entry f). No formation of a monosubstitution product was observed either at reaction end point or in the middle of the transformation, which suggested that a continuous coordination of the palladium catalyst after the first allylic substitution leads to a facile second allylic substitution. These experiments well explained the vastly different results between entries a−b and entries c−d. The relative fast reaction rates in the former cases could be attributed to the relative facile oxidative addition of **2a** and **2b** followed by a tandem substitution process, while slow reaction rates in the latter cases could be due to the slow oxidative addition rates of **4a** and **4b**. The

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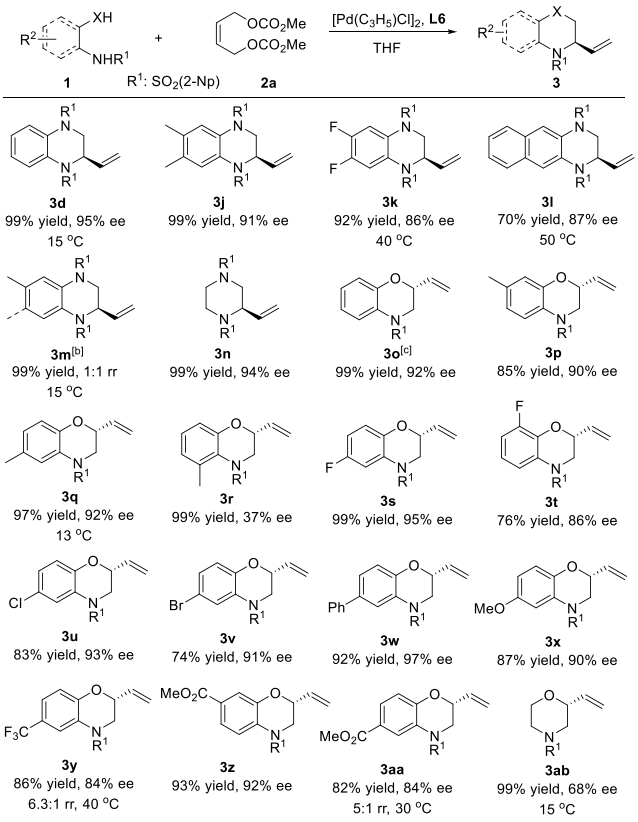
varied enantioselectivities indicated a different enantioselectivity-determining step between entries a–b and entries c–d.

We then looked into the substrate scope of the asymmetric tandem allylic substitution process. As shown in Scheme 3, a

Scheme 3. Substrates Scope[a]

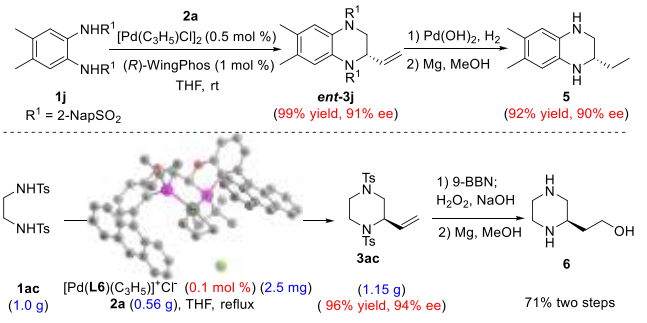


[a]Unless otherwise specified, all reactions were performed at rt for 12 h in THF (2.0 mL) with **1** (0.2 mmol), **2** (0.22 mmol), $[Pd(C_3H_5)Cl]_2$ (0.5 mol %), ligand (1.0 mol %). The absolute configuration of **3d** was determined by X-ray crystallography, the rests were assigned by analogy. Isolated yields and ee values were determined by chiral HPLC, regioselectivities were determined by ^1H NMR. [b]Ee's were not determined. [c]The absolute configuration was confirmed by transforming to a known Ts-protected derivative according to the sign of optical rotation.[10]

series of substituted *ortho*-diaminoarene substrates were applicable, providing a series of chiral 2-vinyl tetrahydroquinoxalines **3d–l** in excellent yields and ee's. Elevated reaction temperature was required for relatively electron-deficient substrates, and hence the enantioselectivities of **3k** and **3l** dropped slightly. A regioselectivity issue arose from an unsymmetrical *ortho*-diaminobenzene substrate, and a 1:1 regio-isomeric mixture of **3m** was isolated. Pleasingly, a 2-vinylpiperazine derivative **3n** was synthesized in excellent yield and ee. Various substituted *ortho*-aminophenol substrates were suitable substrates to form substituted 2-vinyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **3o–3aa** in good to excellent yields, enantioselectivities, and regioselectivities. Both 7-methyl and 6-methyl-substituted products **3p** and **3q** were obtained in excellent yields and ee's, while 5-methyl product **3r** was isolated in only 37% ee possibly due to a steric effect. Various halogen substituents including fluorine, chlorine, and bromine atoms were well-tolerated (**3s–3v**). Phenyl- and methoxy-substituted products **3w** and **3x** were also formed in excellent yields and ee's. For substrates with electron-withdrawing substituents *para* to the phenol functionality, both the regioselectivity and enantioselectivity of the products decreased slightly (**3y** and **3aa**). However, product **3z** containing an ester functionality at the 7 position was obtained with an excellent ee (92%) and yield (93%). A 2-vinyl morpholine derivative **3ab** was also obtained in 99% yield with a moderate ee (68% ee).

To demonstrate the synthetic utility of this methodology, the key chiral intermediates of two bioactive molecules were synthesized efficiently (Scheme 4). Compound **A** (Figure 1) is

Scheme 4. Synthetic Applications of the Reaction Products



a cholesteryl ester transfer protein (CETP) inhibitor developed by Pfizer for the treatment of atherosclerosis and obesity.[1] Its chiral dihydroquinoxaline skeleton was constructed from *ent*-**3j**, which was prepared from **1j** and **2a** in the presence of a Pd-WingPhos catalyst (1 mol %) in 99% yield and 91% ee. A simple hydrogenation over $Pd(OH)_2$ followed by deprotection of sulfonamide under conditions of Mg/MeOH gave the key chiral intermediate **5** in 90% ee and 92% yield. Compound **D** is an antipsychotic agent.[4] Its chiral piperazine structure was prepared from ditosyl-protected ethylenediamine **1ac**. In the presence of an ionic Pd species $[Pd(\mathbf{L6})(C_3H_5)]Cl$ (CCDC 1964490) (0.1 mol %), a gram-scale reaction between **1ac** and **2a** proceeded smoothly to provide **3ac** (1.15 g) in 96% yield and 94% ee. The excellent yield, ee, and turnover number (1000) proved the practicality of this transformation for industrial applications. Subsequent hydroboration–oxidation and deprotection of the Ts groups yielded the key piperazine intermediate in 71% yield.

In conclusion, we have developed a general and enantioselective palladium-catalyzed tandem allylic substitution of butenylene dicarbonate powered by a chiral bisphosphorus ligand Wingphos, forming a series of chiral substituted heterocycles including tetrahydroquinoxalines, piperazines, dihydro-2*H*-benzo[*b*][1,4]oxazine, and morpholines in exellent ee's and yields. The method features mild and simple reaction conditions, broad functional group compatibility, and the use of readily available starting materials. Mechanistic investigations have excluded a pathway involving a dicationic diene-bound palladium species and supported a tandem allylic substitution process. The high turnover number (up to 1000) proved its practicality for industrial applications. The method is expected to be widely applicable in both drug discovery and process chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01490.

Experimental procedures, characterization data, crystallographic data, NMR Experiments, HPLC traces, and NMR spectra (PDF)

Accession Codes

CCDC 1964490, 1964492, and 1964498 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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