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An Unprecedented Access to Chiral Tetrahydropyrimidines via Palladium-Catalyzed Asymmetric Allylic C-H Amination

Pu-Sheng Wang, Meng-Lan Shen, Tian-Ci Wang, Hua-Chen Lin, Liu-Zhu Gong*

Abstract: A chiral phosphoramidite ligand-controlled palladium-catalyzed asymmetric intramolecular allylic C-H amination has been established to prepare various substituted chiral tetrahydropyrimidines in high levels of yields and enantioselectivities. Particularly, dienyl sodium N-sulfonyl amides bearing an arylethene-1-sulfonyl group underwent sequential allylic C-H amination and intramolecular Diels-Alder (IMDA) reaction to produce chiral fused tricyclic tetrahydropyrimidine frameworks in high yields and stereoselectivities. Significantly, an asymmetric synthesis of letermovir has been accomplished by using this method as the key step.

Chiral tetrahydropyrimidine has frequently been encountered in numerous complex bioactive molecules as a core skeleton,[1] which possess a diverse spectrum of remarkable biological properties and thereby prompt the invention of innovative pharmaceuticals (Figure 1). For instance, DPC-083 is a potent reverse transcriptase inhibitor for the treatment of HIV infection,[1a] and KCP10043F is a selective T-type Ca^{2+} channel blocker,[1f] which can inhibit the growth of the human lung cancer cells. Among them, letermovir shows great potential in the next-generation human cytomegalovirus (HCMV) infection treatment without observation of dose-dependent toxicity,[1c] and has already been approved for the phase III clinical trials. Therefore, the development of unprecedented synthetic methods, which are not only able to efficiently access chiral tetrahydropyrimidines frameworks,[2] but enable a divergent and flexible modulation of these structures and thereby allow building up a chemical library holding a structurally diverse range of molecules for high-throughput screening, turns out to be essential for drug discovery.

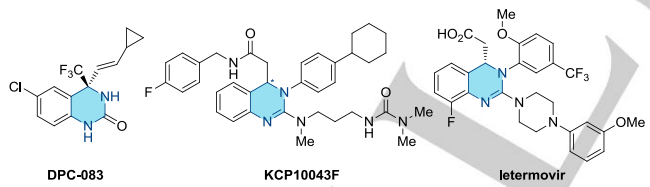
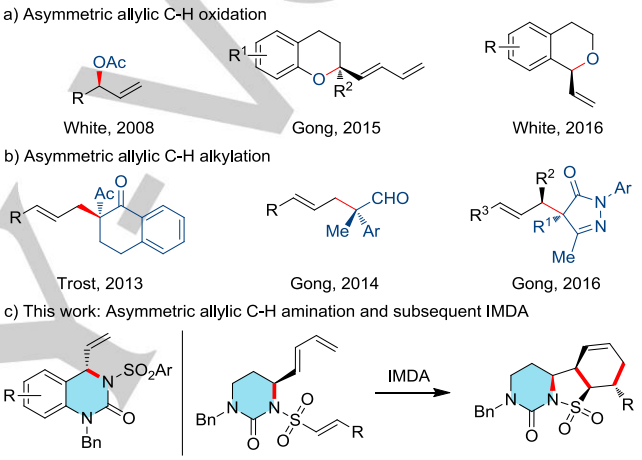


Figure 1. Representative biologically active molecules containing tetrahydropyrimidine scaffold.

Palladium-catalyzed asymmetric allylic substitution is one of the most popular and widely applicable chemical reactions for assembling chemical bonds.[3] Since pioneering reports by Tsuji and Trost,[4] this reaction has been intensively studied to address issues concerning chemo-, regio-, and stereoselectivity with excellent tolerance of various nucleophiles.[5] Basically, the Tsuji−Trost type reactions require pre-oxidized allylic substrates, such as allylic halides, esters, and carbonates to complicate the whole synthetic process during installation of these functional groups.



Scheme 1. Pd-catalyzed asymmetric allylic C-H functionalization

In sharp contrast, the direct oxidative allylic C-H functionalization of simple alkenes[6] appears to be a more straightforward approach to provide unprecedented retrosynthetic disconnections for chemical synthesis. As such, the establishment of enantioselective variants for the allylic C-H functionalization continues to receive a broad range of research interest.[7-10] In recent years, the enantioselective formation of C−O[7] and C−C[8f,9,10] bonds via allylic C−H activation-based substitution has been successfully established (Scheme 1a and 1b). White and co-workers found that a chiral Lewis acid reversibly coordinated ligand[7a] was able to offer modest enantioinduction to the allylic C-H oxidation. Subsequently, chiral phosphoramidite ligands[7c] and chiral aryl sulfoxide-oxazoline ligands[7d,11] were respectively found capable of inducing high enantioselectivity in intramolecular asymmetric allylic C-H oxidation reactions. In particular, Trost[9,12] and our group[10] indicated that both triphenylphosphine and chiral phosphoramidite ligands were not only suitable for the regeneration of Pd(II) from Pd(0) under suitable oxidation conditions, but also able to accelerate the asymmetric allylic C−H alkylation with acidic carbon nucleophiles, therefore providing unusual opportunities to create enantioselective allylic C-H alkylation reactions. However, a palladium-catalyzed direct asymmetric allylic C-H amination to generate highly synthetically useful chiral amine derivatives has not been reported, yet. Herein, we will present an approach to access pharmaceutically interesting chiral tetrahydropyrimidine deriva-

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tives via palladium-catalyzed asymmetric intramolecular allylic C−H amination (Scheme 1c), and its application in a concise enantioselective synthesis of an optically pure drug candidate, letermovir.

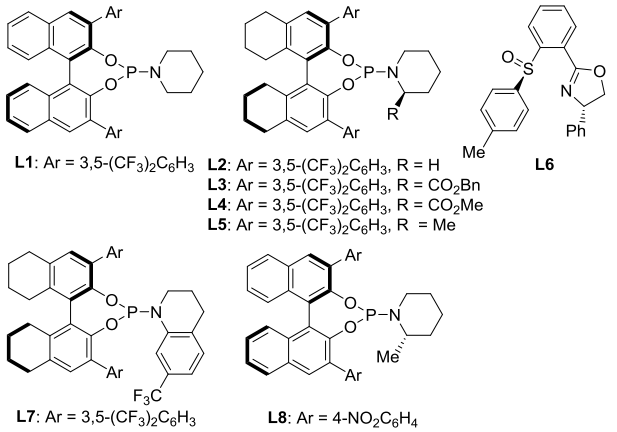
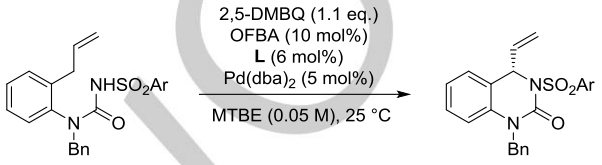


Figure 2. Chiral ligands used in this study

As shown in our previous reports,[7c,10c] chiral phosphoramidite ligands (Figure 2) were beneficial for both the palladium-catalyzed allylic C−H activation and the subsequent substitution process. Therefore, chiral phosphoramidite ligand **L1** was initially used in our preliminary optimization of conditions for the intramolecular asymmetric allylic C−H amination reaction of **1a** (Table 1). Encouragingly, the desired product tetrahydropyrimidine **2a** was furnished in nearly quantitative yield, albeit with a modest enantioselectivity (entry 1). Particularly, the use of H_8-BINOL-derived phosphoramidite ligand **L2** could offer a higher enantioselectivity (entry 2). Fine-tuning of the amine moiety in the phosphoramidite ligands found that α-substitution of the cyclic piperidine moiety would slightly improve the enantioselectivity (entries 3-5). Further optimization of the reaction conditions revealed that a higher concentration, lower reaction temperature and the absence of OFBA turned out to be beneficial to the stereochemcial control (entries 6-8), and thereby enabled the reaction to give 97% yield and 94.5:5.5 er (entry 8). Notably, either chiral aryl sulfoxide-oxazoline ligand **L6** or the absence of the phosphoramidite ligand under otherwise identical conditions resulted in a trace amount of **2a** and nearly quantitative recovery of the starting material **1a** (entries 9-10), implying that a pivotal role of the phosphoramidite ligand was played in this asymmetric allylic C−H amination.

Under the optimized reaction conditions, we next explored the generality of the asymmetric allylic C−H amination reaction (Table 2). Significantly, a broad scope of aromatic substitutions was nicely tolerated, with both electron-donating and -withdrawing substituents at either 4- or 5-position of the benzene ring, affording the desired products in moderate to high yields and good enantioselectivities (**2b**-**k**). Notably, both bromide and chloride substituents were well tolerated, which could provide additional reactivity to increase structural complexity by undergoing easily preformed reactions for building up chemical library (**2g**-**h**). Unfortunately, the installation of a fluoride at 6-position on the benzene ring led to a diminished enantioselectivity (**2l**), but the results could be slightly improved by using ligand **L7** in lieu of **L5**. Particularly, the absence of the benzyl group could also result in the formation of the allylic C-H amination product **2m** in a high yield and modest enantioselectivity, which strongly demonstrated that the phosphoramidite ligands could regulate the property of Pd(II) species to activate the allylic C-H bond, rather than to promote a Wacker process reported previously furnishing the oxidative alkene diamination product.[13]

Table 1. Optimization of the reaction conditions [a]

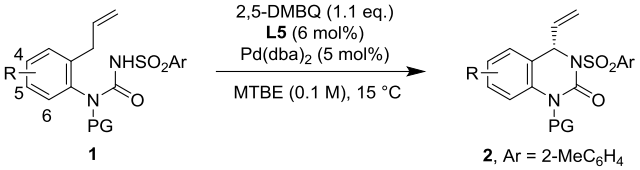


1a **2a**, Ar = 2-MeC_6H_4

entry	L	T / °C	yield (%)[b]	e.r. [c]
1	**L1**	25	99	86:14
2	**L2**	25	97	90.5:9.5
3	**L3**	25	92	91:9
4	**L4**	25	93	91.5:8.5
5	**L5**	25	92	92.5:7.5
6[d]	**L5**	25	96	93.5:6.5
7[d]	**L5**	15	98	94:6
8[d,e]	**L5**	15	97	94.5:5.5
9[d,e]	**L6**	15	<1[f]	--
10[d,e]	**--**	15	<1[f]	--

[a] Reaction conditions: **1a** (0.05 mmol), $Pd(dba)_2$ (5 mol %), **L** (6 mol %), and 2,5-DMBQ (1.1 equiv), MTBE (1 mL), 24 h, under N_2. [b] Isolated yield. [c] Determined by HPLC. [d] 0.1 mmol scale of **1a** in 1 mL MTBE, 48 h. [e] without 10 mol % OFBA. [f] >99% **1a** was recovered. 2,5-DMBQ = 2,5-dimethylquinone. OFBA = 2-fluorobenzoic acid. The absolute configuration of **2a** was assigned by the X-ray analysis of its single crystal (see the Supporting Information).

Table 2. Substrate scope for N-((2-allylphenyl)carbamoyl)sulfonamides **1**[a]



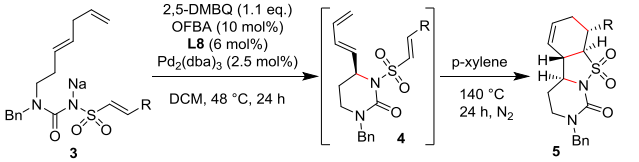
1 **2**, Ar = 2-MeC_6H_4

entry	R	PG	2	yield (%)[b]	*er* (%)[c]
1[d]	4-Me	Bn	**2b**	98	95.5:4.5
2	4-^{i}Pr	Bn	**2c**	90	94.5:5.5
3[e]	4-MeO	Bn	**2d**	91	94.5:5.5
4	4-CF_3	Bn	**2e**	95	94.5:5.5
5	4-F	Bn	**2f**	94	93:7
6[e]	4-Cl	Bn	**2g**	96	94:6
7[e]	4-Br	Bn	**2h**	88	95:5
8	5-Me	Bn	**2i**	44	91:9
9	5-CF_3	Bn	**2j**	81	93:7
10	5-CF_3O	Bn	**2k**	91	92.5:7.5
11[f]	6-F	Bn	**2l**	91	91:9
12[g]	H	H	**2m**	92	84:16

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(dba)_2$ (5 mol %), **L5** (6 mol %), and 2,5-DMBQ (1.1 equiv), MTBE (1 mL), 15 °C, 48 h, under N2. [b] Isolated yield. [c] Determined by HPLC. [d] With 10 mol % OFBA, 25 °C, 72 h. [e] With 10 mol % OFBA, 25 °C, 48 h. [f] **L7** was used instead of **L5**, with 10 mol % OFBA, 25 °C, 48 h. [g] With 10 mol % OFBA, 45 °C, 48 h.

Dienyl sodium N-sulfonyl amides bearing an arylethene-1-sulfonyl group **3**, after undergoing the allylic C-H amination reaction, will generate products **4**, which can provide additional 1,3-diene functionality and are capable of participating in a subsequent diastereoselective intramolecular Diels-Alder (IMDA) reaction,[14] allowing for a feasible synthesis of chiral polycyclic heterocycles **5** (Table 3). Since the simple extension of the standard conditions failed to give good results, the reaction conditions were re-optimized and identified that the phosphoramidite **L8** was the best ligand (See Table S1 in Supporting Information for detail). The expansion of the re-optimized reaction conditions to different substrates found that the presence of an aryl group bearing either an electron-donating or -withdrawing substituent at either *ortho*- or *para*-position was allowed to undergo the sequential asymmetric allylic C−H amination and IMDA to give chiral fused tricyclic products **5** in moderate to good yields and with good diastereo- and enantioselectivities (entries 1−9).

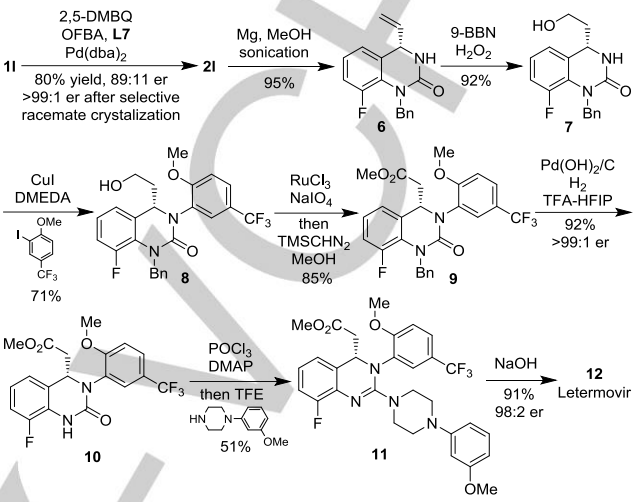
Table 3. Substrate scope for dienyl sodium *N*-sulfonyl amides **3**[a]



entry	R	5	yield (%)[b]	*er* (%)[c]	*exo*/*endo*[d]
1	phenyl	**5a**	75	91:9	7:1
2	2-MeC_6H_4	**5b**	75	88:12	8:1
3	2-MeOC_6H_4	**5c**	71	91.5:8.5	8:1
4	2-FC_6H_4	**5d**	54	89.5:10.5	7:1
5	2-ClC_6H_4	**5e**	62	90.5:9.5	6:1
6[e]	2-BrC_6H_4	**5f**	50	91:9	8:1
7	4-MeC_6H_4	**5g**	74	88:12	6:1
8	4-MeOC_6H_4	**5h**	70	89.5:10.5	7:1
9	4-BrC_6H_4	**5i**	77	90.5:9.5	7:1

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(dba)_2$ (5 mol %), **L8** (6 mol %), OFBA (10 mol%) and 2,5-DMBQ (1.1 equiv), DCM (1 mL), 25 °C, 48 h, under N_2; **4** was purified by flash chromatography and then heated in *p*-xylene at 140 °C for 24 h. [b] Overall isolated yield. [c] Determined by HPLC. [d] Measured by ^{1}H NMR. [e] For 96 h in the first step. The absolute configuration of **5i** was assigned by the X-ray analysis of its single crystal (see the Supporting Information).

To showcase the utility of this reaction in the enantioselective preparation of pharmaceutical compounds, a concise enantioselective synthesis of letermovir was conducted (Scheme 3). A scale-up reaction of **1l** under the optimized reaction conditions gave **2l** in synthetically useful yield and enantioselectivity, which could be obtained in optically pure form by selective racemate crystallization (>99:1 *er*) from Et_2O. The arenesulfonamide group of **2l** was readily removed by magnesium reduction under ultrasonic conditions[15] to afford **6** in a high yield. A subsequent regioselective hydroboration-oxidation of **6** furnished an alcohol **7** in 95% yield. A regioselective Ullmann-type N-arylation reaction[16] of **7** and 2-iodo-1-methoxy-4-(trifluoromethyl)benzene underwent smoothly to provide **8** in a 71% yield. The Sharpless oxidation[17] of the primary alcohol **8** with $RuCl_3$/$NaIO_4$ followed by methylation with trimethylsilyl–diazomethane gave rise to the corresponding ester **9** in 85% yield. The benzyl group of the intermediate **9** could be cleanly cleaved by the $Pd(OH)_2$/C catalyzed hydrogenolysis in the presence of TFA[18] to give a urea **10**. A Vilsmeier-type condensation[19] of the urea **10** and 1-(3-methoxyphenyl)piperazine in TFE[20] was able to provide the highly enantioenriched dihydroquinazoline **11**, which was finally hydrolyzed in the presence of aqueous NaOH at 60 °C to give letermovir **12** as a white solid.



Scheme 2. Total synthesis of letermovir.

In summary, we have established an unprecedented palladium-catalyzed asymmetric intramolecular allylic C-H amination reaction, leading to a variety of substituted chiral tetrahydropyrimidines in high yields and stereoselectivity. More interestingly, a sequential protocol consisting of asymmetric allylic C-H amination and intramolecular Diels-Alder (IMDA) reaction has been created to allow for stereoselective construction of chiral fused tricyclic frameworks. Moreover, capitalizing on the current reaction, a concise and enantioselective synthesis of letermovir has been accomplished to further demonstrate the great potential of this method in the pharmaceutical chemistry.

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Keywords: Palladium catalysis • C-H activation • Asymmetric allylic amination • Diels-Alder reaction • Letermovir

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[20] Epimerization was observed in the subsequent Vilsmeier-type condensation with piperazine, which could be alleviated by the use of TFE as solvent, see ref. 2c.

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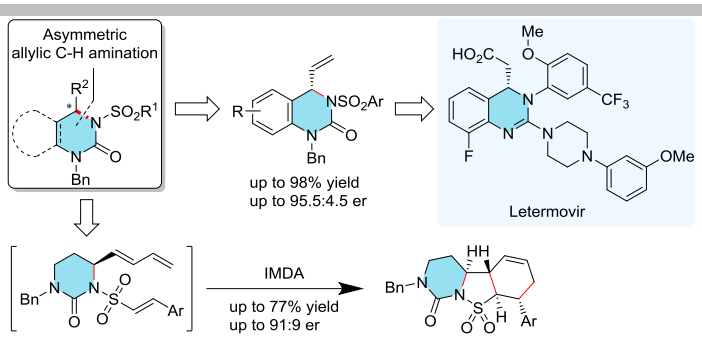

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An Unprecedented Access to Chiral Tetrahydropyrimidines via Palladium-Catalyzed Asymmetric Allylic C-H Amination

A chiral phosphoramidite ligand-controlled asymmetric palladium-catalyzed intramolecular allylic C-H amination has been introduced to access various substituted chiral tetrahydropyrimidines in high yields and enantioselectivities. Moreover, this methodology was successfully applied to the asymmetric total synthesis of letermovir.