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Pd-Catalyzed regio- and enantioselective allylic substitution with 2-pyridones†

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An efficient method for the asymmetric synthesis of *N*-substituted 2-pyridones *via* Pd-catalyzed regio- and enantioselective allylic substitution of hydroxyl-containing allylic carbonates with 2-pyridones has been developed. By using a palladium complex *in situ* generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphoramidite L2 as a ligand, the process allowed rapid access to *N*-substituted 2-pyridones with complete chemo- and regioselectivities and good to high enantioselectivities.

Chiral *N*-substituted 2-pyridones are prevalent motifs in a variety of important medicinally relevant agents and biologically active natural products, such as rhinovirus 3C-protease inhibitors (Fig. 1).[1] Although several synthetic protocols from chiral amines are available,[2] the catalytic asymmetric approaches to directly access this skeleton are largely underdeveloped.[3] Only a few examples of asymmetric catalytic methods have been documented to date. In 2010, Batey and co-workers reported a Pd(II)-catalyzed asymmetric [3,3] sigmatropic rearrangement of 2-allyloxy pyridines to afford *N*-substituted 2-pyridones with high enantioselectivities.[3a] Breit[3b,c] and You[3d] reported recently the Rh- and Ir-catalyzed asymmetric allylic substitution of 2-pyridones respectively to furnish *N*-substituted 2-pyridones in high chemo-, regio- and enantioselectivities (Scheme 1a). Therefore, the development of new asymmetric catalytic methods for the construction of chiral *N*-substituted 2-pyridones from readily accessible starting materials is highly appealing.

The Pd-catalyzed asymmetric allylic substitution is one of the most powerful methods for carbon–carbon and carbon–heteroatom bond formation.[4] However, for unsymmetric mono-substituted allylic substrates, Pd-catalyzed allylic substitution generally gave linear products.[5] Even so, several approaches have been achieved in the Pd-catalyzed branch-selective allylic substitution with high enantioselectivities by ligand control.[6] Since Trost and co-workers reported the Pd-catalyzed regio- and enantioselective allylic alkylation of vinylepoxide with phthalimide,[7] the branch-selective control by hydrogen-bond interactions between nucleophiles and allylpalladium intermediates has been exploited.[8] Most recently, our group reported the Pd-catalyzed asymmetric decarboxylative allylic cycloaddition of vinylethylene carbonates (VECs) with unsaturated electrophiles to afford versatile oxo-heterocycles with complete branch-selectivities.[9] The branch-selective control has also been achieved by the cooperative catalysts of the palladium and boron reagent.[10] Based on our continuous efforts for the development of Pd-catalyzed branch- and enantioselective allylic substitution, we are interested in allylic substitution with 2-pyridones to construct enantioenriched

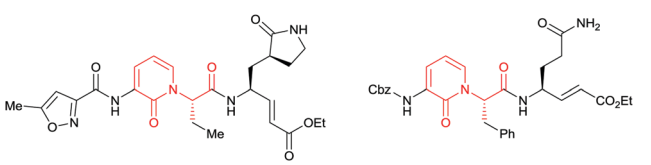

Fig. 1 Examples of rhinovirus 3C-protease inhibitors with a 2-pyridone ring.

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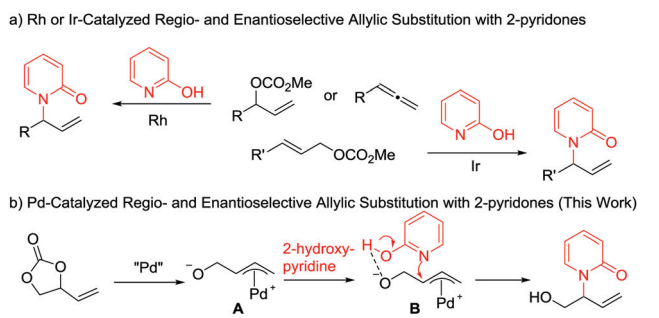
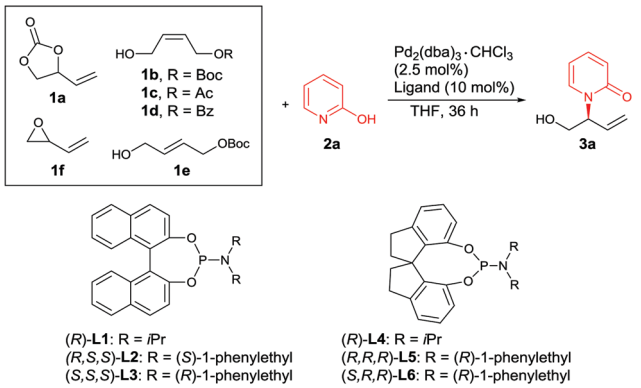


Scheme 1 Chemo-, regio- and enantioselective allylic substitution with 2-pyridones.

N-substituted 2-pyridones. To the best of our knowledge, there is no report on Pd-catalyzed branch-selective allylic substitution with 2-pyridones. Based on our previous research results, we envisioned that a zwitterionic allylpalladium intermediate **A** could be obtained by the reaction of the palladium catalyst with VEC (Scheme 1b). The branch-selective control would be possible by the hydrogen-bond interactions between the proton of 2-hydroxypyridine and oxygen anion of intermediate **A** to produce the desired branch-substituted allylic product. Herein, we report the successful execution of these ideas and present H-bond directed Pd-catalyzed regio- and enantioselective allylic substitution with 2-pyridones, a practical and efficient approach which allows rapid access to *N*-substituted 2-pyridones with complete chemo- and regioselectivities and good to high enantioselectivities.

Based on our previous studies,[9] the initial investigations focused on the examination of the allylic substitution of H-VEC **1a** and hydroxypyridine (**2a**) as standard reaction partners using a palladium catalyst bearing phosphoramidite as a ligand (Table 1).

Table 1 Condition optimization[a]



Entry	1	Ligand	*T* (°C)	Yield[b] (%)	er[c] (%)
1	**1a**	**L1**	20	88	70 : 30
2	**1a**	**L1**	0	83	75.5 : 24.5
3	**1a**	**L1**	−20	52	80.5 : 19.5
4	**1a**	**L1**	−40	57	81.5 : 18.5
5	**1a**	**L2**	−40	91	59 : 41
6	**1a**	**L3**	−40	81	48 : 52
7	**1a**	**L4**	−40	93	60.5 : 39.5
8	**1a**	**L5**	−40	62	60 : 40
9	**1a**	**L6**	−40	28	38 : 62
10	**1b**	**L1**	−40	81	75.5 : 24.5
11	**1b**	**L2**	−40	87	95 : 5
12	**1b**	**L3**	−40	89	21 : 79
13	**1b**	**L4**	−40	31	69.5 : 30.5
14	**1b**	**L5**	−40	Trace	—
15	**1b**	**L6**	−40	Trace	—
16	**1b**	**BINAP**	−40	Trace	—
17	**1b**	**Trost**	−40	26	31 : 69
18	**1c**	**L2**	−40	42	80 : 20
19	**1d**	**L2**	−40	30	76 : 24
20	**1e**	**L2**	−40	92	94.5 : 5.5
21	**1f**	**L2**	−40	82	57.5 : 42.5

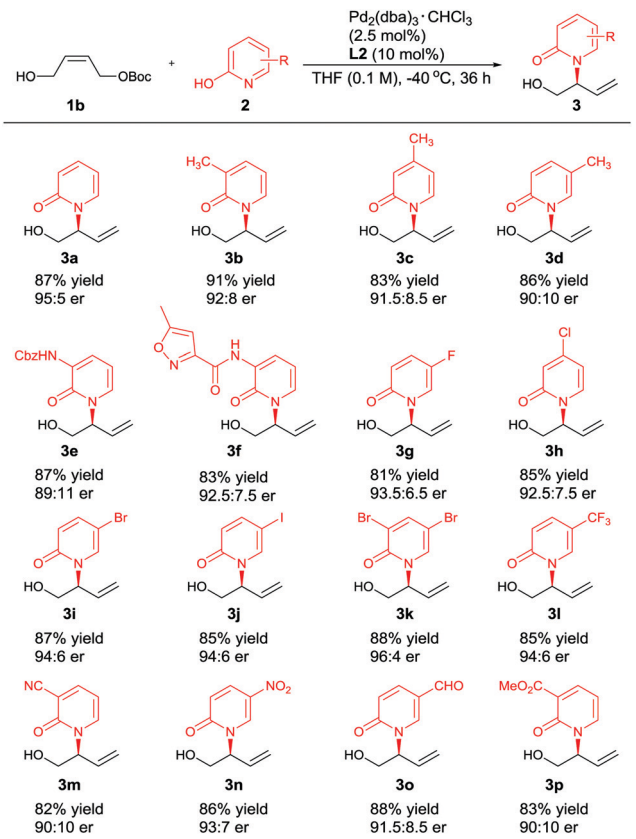
[a] Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), ligand (10 mol%), **1** (0.2 mmol), **2a** (0.2 mmol), solvent (2.0 mL), 36 h. [b] Isolated yields. [c] Determined by HPLC using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation with that reported.[3a]

To our delight, the reaction proceeded smoothly in the presence of a catalyst generated *in situ* from the $Pd_2(dba)_3{\cdot}CHCl_3$ and Feringa's phosphoramidite[11] **L1** as a ligand in THF at 20 °C to afford the desired product **3a** in 88% yield with complete chemo- and branch-selectivities, albeit a low enantioselectivity was observed (entry 1). We next found that the enantioselectivity could be increased with the decrease of the reaction temperature (entries 2–4). Thus, the enantioselectivity could be improved to 63% when the reaction was conducted at −40 °C (entry 4). However, further improvement in the enantioselectivity was not observed upon reacting with other phosphoramidite ligands[12] (entries 5–9), even though high yields could be obtained in some cases (entries 5–7). Next, we examined the allylic substitution of (*Z*)-hydroxyl-containing allylic carbonate **1b** using palladium catalysts bearing different phosphoramidites in THF at −40 °C (entries 10–15). Surprisingly, the reactions of allylic carbonate **1b** gave very different results in comparison with that of H-VEC **1a**. Thus, the reactions with phosphoramidites derived from Binol proceeded smoothly to afford the allylic product **3a** in high yields with complete chemo- and regioselectivities (entries 10–12), and the reaction with ligand **L2** showed the best enantioselectivity (95 : 5 er, entry 11). The reactions were not effective when BINAP or a Trost ligand was used (entries 16 and 17). The reaction efficiency was remarkably decreased when the reactions were conducted with corresponding allylic acetate **1c** and benzoylate **1d** (entries 18 and 19). Although the reaction of vinylepoxide **1f** with **2a** proceeded smoothly under the identical conditions with entry 11, poor enantioselectivity was observed (entry 21). The allylic substitution of (*E*)-allylic carbonate **1e** gave almost the same results with that of (*Z*)-isomer **1b** (entries 20 *versus* 11). We finally examined the reaction of allylic carbonate **1b** with **2a** in the different solvents (see ESI†). However, the enantioselectivity could not further improve. Notably, when the reaction of **1b** with **2a** was performed in MeOH, a 3.7 : 1 branch/linear ratio was observed. These results implied that the hydrogen-bond interaction between 2-hydroxypyridine and the allylpalladium intermediate played an important role for the regioseletive control. Although the allylic donors **1a**, **1b**, **1e** and **1f** should give the same allylpalladium intermediate **A** as described in Scheme 1, these results indicated that the reaction efficiency was highly affected in the leaving group of the allylic donors.[4]

With optimal conditions (Table 1, entry 11) in hand, the reaction scope of the protocol was evaluated by the allylic substitution of allylic carbonate **1b** with various substituted 2-pyridones. As shown in Table 2, a variety of substituted 2-pyridones bearing different electronic and steric properties was tolerated under the reaction conditions to afford the corresponding allylic pyridones **3** in high yields (81–91%) with complete chemo- and regioselectivities and acceptably high enantioselectivities (89 : 11 to 96 : 4 er). A wide range of functional groups, such as halogen, protected amine, nitro-, cyanide, aldehyde, and ester groups, could be successfully installed with a high efficiency. Notably, the compounds **3e** and **3f** would be useful intermediates for the synthesis of medicinally interesting rhinovirus 3C-protease inhibitors.[1d]

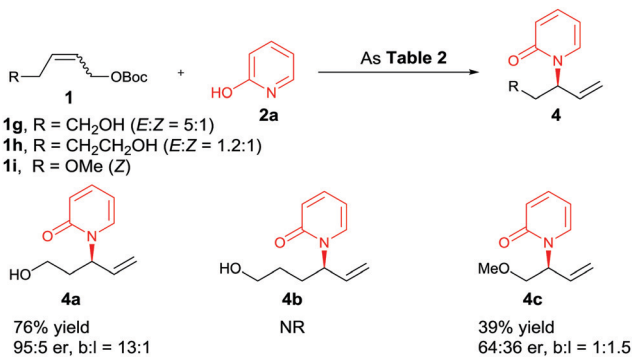
We next turned our attention toward the examination of the Pd-catalyzed allylic substitution of longer hydroxyl-containing

Table 2 Pd-Catalyzed allylic substitution of **1b** with various substituted 2 pyridones **2**[a]



[a] Reaction conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), **L2** (10 mol%), **1b** (0.2 mmol), **2** (0.2 mmol), THF (2.0 mL), 36 h. The yields are of isolated materials. The enantiomeric excesses were determined by HPLC using a chiral stationary phase.

allylic carbonates with 2-pyridone **2a**. As revealed in Scheme 2, the allylic substitution of hydroxylethyl allylic carbonate **1g** also proceeded smoothly to afford the product **4a** in 76% yield with 95 : 5 er, albeit the branch-selectivity was slightly decreased (b : l = 13 : 1). However, the allylic substitution of hydroxylpropyl allylic carbonate **1h** did not work at all under the reaction conditions, even when the reaction was carried out



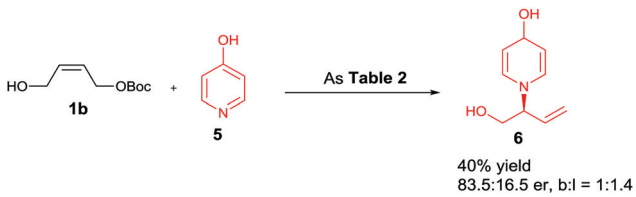
Scheme 2 Pd-Catalyzed allylic substitution of allylic carbonates **1g–1i** with 2-pyridone **2a**.

at 40 °C. The reaction of methoxyl allylic carbonate **1i** showed a poor branch selectivity (b : l = 1 : 1.5) to afford the branch-product **4c** in 39% yield with a low enantioselectivity (28% ee). These results implied that the hydrogen-bond interaction between 2-hydroxypyridines and the allylpalladium intermediate as revealed in Scheme 1 played an important role not only for the regioselectivity control, but also for the reactivity. The allylpalladium intermediates generated from hydroxymethyl and hydroxyethyl allylic carbonates could build an effective hydrogen-bond interaction with 2-hydroxypyridines, thus the corresponding allylic products could be given in high yields with high levels of regioselectivities.

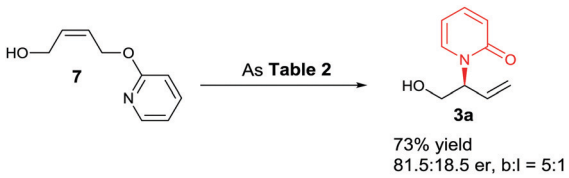
The reaction conditions were also tolerated for the allylic substitution of **1b** with 4-hydroxypyridine **5** to afford the *N*-alkylated product **6** in 40% yield with 83.5 : 16.5 er, but low regioselectivity was observed (b : l = 1 : 1.4, Scheme 3).[13]

To gain more information on the reaction pathway, we conducted the reaction of the possible *O*-alkylated product **7** under the standard reaction conditions (Scheme 4). The reaction proceeded smoothly to give *N*-alkylated product **3a** in 73% isolated yields with 63% ee and 5 : 1 branched to linear selectivity, which were quite different to the results obtained from the reaction of **1b** with **2a**. These results indicated that the *O*-alkylation followed by the rearrangement or rapid retroreaction of the *O*-alkylated product is unlikely to be involved.[3b,d]

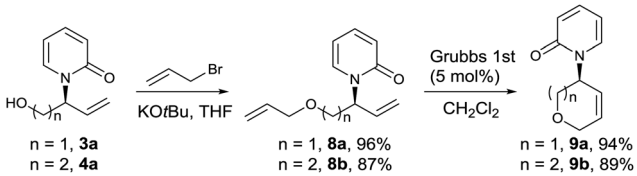
The utility of the present process was demonstrated by the product derivatization (Scheme 5). Dihydropyran **9a** and tetrahydrooxepine **9b** could be obtained in high yields by the



Scheme 3 Pd-Catalyzed allylic substitution of allylic carbonate **1b** with 4-pyridone **5**.



Scheme 4 Conversion of the *O*-allylated product **7** to the *N*-allylated product **3a**.



Scheme 5 The elaboration of **3a** and **4a**.

alkylation of **3a** and **4a** with allyl bromide respectively followed by ring-close metathesis.

In conclusion, we have developed an efficient method for the asymmetric synthesis of *N*-substituted 2-pyridones *via* a Pd-catalyzed regio- and enantioselective allylic substitution of hydroxyl-containing allylic carbonates with 2-pyridones. By using a palladium complex *in situ* generated from $Pd_2(dba)_3 \cdot CHCl_3$ and phosphoramidite **L2** as a ligand, the process allowed rapid access to *N*-substituted 2-pyridones with complete chemo- and regioselectivities and good to high enantioselectivities. The reaction pathway has been rationalized by the control experiments, and the synthetic utility was demonstrated by the product derivatization. Further studies on extending the scope of the hydrogen-bond directed regioselective allylic substitution with other nucleophiles are currently underway, and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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