Asymmetric Catalysis

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Enantioselective Iridium-Catalyzed Allylic Substitution with 2-Methylpyridines

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Abstract: *An enantioselective iridium-catalyzed allylic substitution with a set of highly unstabilized nucleophiles generated in situ from 2-methylpyridines is described. Enantioenriched 2-substituted pyridines, which are frequently encountered in natural products and pharmaceuticals, could be easily constructed by this simple method in good yields and excellent enantioselectivity. The synthetic utility of the pyridine products is demonstrated through the synthesis of a key intermediate of a reported Na^+/H^+ exchanger inhibitor and the total synthesis of (−)-lycopladine A.*

Pyridines are among the most prevalent heterocyclic structural moieties in biologically active natural products, pharmaceuticals, and agrochemicals.[1] For example, twelve small molecules containing a pyridine motif were listed in the top 200 pharmaceutical products in 2012, including the top entry, Nexium.[2] Therefore, diverse functionalization of pyridine derivatives could lead to wide applications in many fields.[3] One aspect of our ongoing efforts to develop methods to build complex and biologically active molecules is the application of iridium-catalyzed allylic substitution reactions with heteroaromatic compounds as nucleophiles.[4]

Iridium-catalyzed enantioselective allylic substitution reactions have become a powerful tool for constructing carbon–heteroatom and carbon–carbon bonds, and they have found extensive application in the total synthesis of natural products and the preparation of bioactive compounds.[5] Although a wide range of nucleophiles can be employed in these reactions, unstabilized carbon-type nucleophiles have been much less studied and have been mainly limited to enolates, organoborons, and aryl- or alkylzinc bromides[6] owing to challenges relating to reactivity and controlling the regio- and enantioselectivity. The exploration of unstabilized nucleophiles in iridium-catalyzed asymmetric allylic substitution is thus still of great importance.

Recently, transition-metal-catalyzed allylic alkylation reactions of unstabilized benzylic nucleophiles have attracted interest because of their applications in the synthesis of a broad diversity of complex molecules.[7] Pioneering works from the groups of Trost[7a] and Walsh[7h] have led to impressive palladium-catalyzed processes for asymmetric allylic alkylation with 2-methylpyridine derivatives ($pK_a \approx 34$[8a]) and toluene derivatives ($pK_a \approx 44$[8b]), respectively. In these studies, elegant strategies have been developed that involve the addition of activating agents to stabilize the resulting anionic charge. To date, there are only a few examples of these reactions in a catalytic asymmetric version, and the reaction scope is very limited. Inspired by these studies, we envisaged that the alkyl nucleophiles generated in situ from 2-methylpyridines might be compatible with iridium-catalyzed asymmetric allylic substitution reactions. Under iridium catalysis, complementary selectivity and substrate scope would facilitate the utility of the methods in the synthesis of natural products and bioactive molecules (Figure 1).[9] Herein, we describe the first iridium-catalyzed asymmetric allylic substitution reaction with highly unstabilized alkyl nucleophiles derived in situ from 2-methylpyridines.

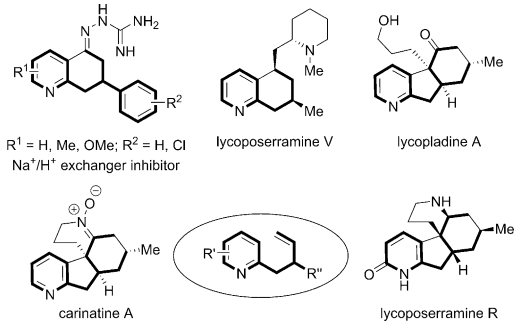

Figure 1. Selected bioactive compounds and natural products that contain the circled structural motif.

We began our study by testing the reaction of *tert*-butyl cinnamyl carbonate with the complex generated in situ from 2-methylpyridine and $BF_3{\cdot}OEt_2$ with different ligands (Table 1). It is proposed that $BF_3{\cdot}OEt_2$ coordinates to pyridine nitrogen to increase the acidity of the proton of the methyl group and stabilize the resulting carboanion. The Feringa ligand and its variants (**L1**, **L2**, **L3**, and **L4**) afforded the desired product in varied yields and enantioselectivity. To our delight, the Alexakis ligand **L2** gave **3a** in 71% yield and 95% *ee*. The reactions with **L5** or **L6** only led to a trace amount of product. The reaction outcomes of ligands **L7**, **L8**, and **L9** were unsatisfactory, and only **L7**, which contains a methoxy group, afforded **3a** in 27% yield and 84% *ee*. Further optimization of the reaction conditions revealed that LiHMDS is the optimal base, but multiple equivalents

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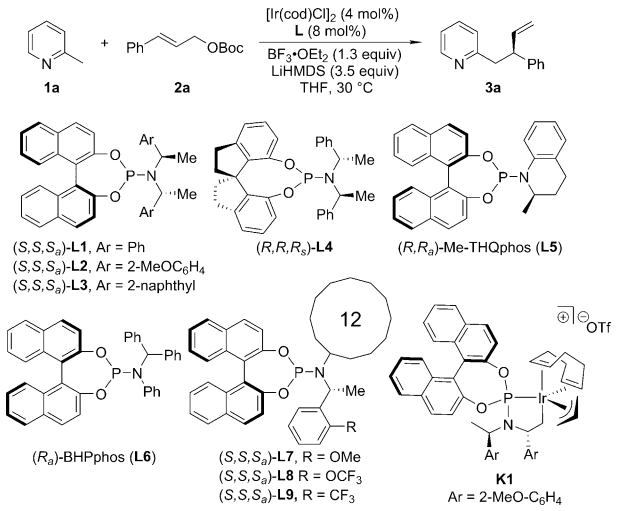
Table 1: Optimization of the reaction conditions.[a]



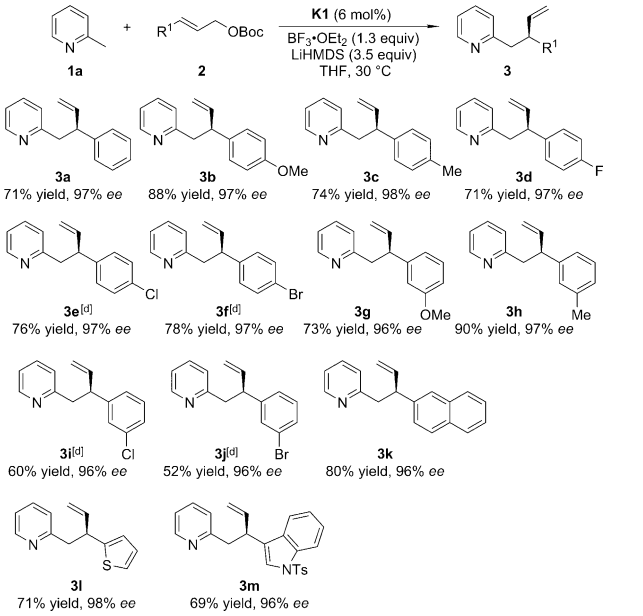
Entry	L	Yield [%][b]	*ee* [%][c]
1	**L1**	23	84
2	**L2**	71	95
3	**L3**	20	80
4	**L4**	42	−77
5	**L5**	trace	–
6	**L6**	trace	–
7	**L7**	27	84
8	**L8**	trace	–
9	**L9**	trace	–
10[d]	**L2**	73	97
11[e]	**L2**	71	97
12[f]	**L2**	54	97

[a] Reaction conditions: $[Ir(cod)Cl]_2$ (4 mol%), **L** (8 mol%), **1a** (0.3 mmol), **2a** (0.2 mmol), $BF_3{\cdot}Et_2O$ (0.26 mmol) and LiHMDS (0.7 mL, 1 M in THF) in THF (2 mL) at 30 °C. THF = tetrahydrofuran. Catalyst was prepared through $^nPrNH_2$ activation.[11] [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] **K1** (8 mol%) as catalyst. [e] **K1** (6 mol%) as catalyst. [f] **K1** (4 mol%) as catalyst.

(3.5 equiv) were required for full conversion. Next, solvents were surveyed and THF was found to be the optimal one (see the Supporting Information for details). To simplify the operational procedure, the iridium complex **K1**[10] (8 mol%), prepared from the optimal ligand **L2**, was used directly. The reaction gave a similar yield with an increased enantioselectivity (97% *ee*). To our delight, it was found that 71% yield was obtained in the presence of 6 mol% catalyst without any effect on enantioselectivity. However, the reaction did not proceed to full conversion when 4 mol% of **K1** was used. Based on these results, the optimal reaction conditions were established as described in Table 1, entry 11.

With the optimal reaction conditions in hand, we undertook studies on the scope and limitations of the allylic alkylation reaction. As depicted in Table 2, with **1a** as the nucleophile, allyl carbonates containing 4-MeO, 4-Me, 4-F, 3-MeO, and 3-Me substituents on the phenyl ring were examined and were found to be well tolerated, delivering the corresponding products efficiently (**3b**, **3c**, **3d**, **3g**, **3h**, 71–90% yields, 96–98% *ee*). Although substrates bearing 4-Cl or 4-Br were less reactive, reactions in the presence of 8 mol% of the catalyst delivered the products in moderate yields with excellent enantioselectivity (**3e**, **3f**, 76–78% yields, 97% *ee*).

Table 2: Substrate scope with respect to the allyl carbonates.[a,b,c]



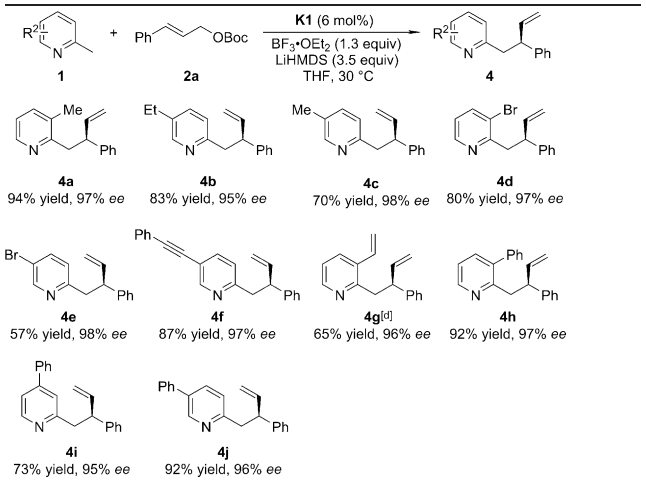
[a] Reaction conditions: **K1** (6 mol%), **1** (0.3 mmol), **2a** (0.2 mmol), $BF_3{\cdot}Et_2O$ (0.26 mmol) and LiHMDS (0.7 mL, 1 M in THF) in THF (2 mL) at 30 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] **K1** (8 mol%) as catalyst.

Excellent enantioselectivity was obtained for substrates bearing 3-Br or 3-Cl substituents (**3i**, **3j**, 52–60% yields, 96% *ee*). However, the reaction with *tert*-butyl crotyl carbonate occurred to give only trace amounts of product with a low branch-to-linear ratio. These results suggest that the reaction with the unstabilized carbon nucleophiles is more sensitive to the electronic and steric properties of the allyl carbonates compared to reactions with soft carbon nucleophiles. To our delight, heteroaryl allylic carbonates, such as those derived from 2-thienyl and 3-indolyl, were compatible under the optimized conditions (**3l**, **3m**, 69–71% yields, 96–98% *ee*).

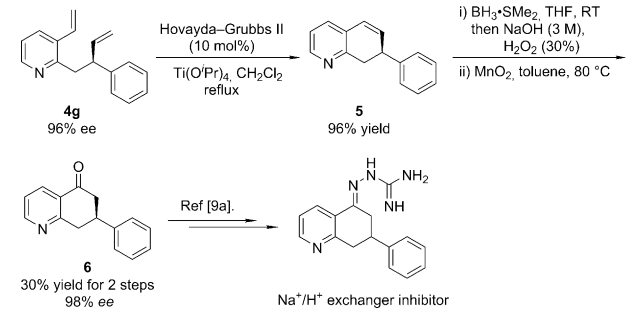
Subsequently, we set out to investigate the scope with respect to the nucleophiles. A variety of 2-methylpyridines with diverse substituents were examined (Table 3). Alkyl or phenyl substituents at the 3-, 4-, or 5-positions of pyridine were tolerated, delivering the desired products smoothly (**4a**–**c**, **4h**–**j**, 70–94% yields, 95–98% *ee*). It is worth noting that vinyl and alkynyl groups were also well tolerated (**4f**, **4g**, 65–87% yields, 96–97% *ee*). Gratifyingly, the allylation reactions of 2-methyl pyridines bearing a bromide group at the 3- or 5-position occurred smoothly to give products in excellent enantioselectivity (**4d**, **4e**, 97–98% *ee*).

To demonstrate the utility of the current method, it was applied in the synthesis of biologically interesting compounds and natural products. Product **4g** was converted into the corresponding olefin compound through ring-closing metathesis (RCM). Hydroboration and oxidation yielded the corresponding alcohol, and oxidation with MnO_2 then generated the key intermediate **6** with high enantiopurity. The latter compound can be converted into a previously described Na^+/H^+ exchanger inhibitor by following the reported procedure (Scheme 1).[9a]

Table 3: Substrate scope with respect to 2-methylpyridines.[a,b,c]

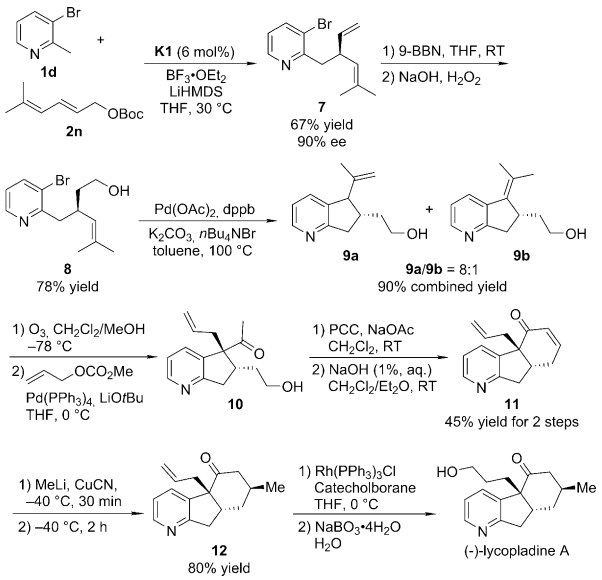


[a] Reaction conditions: **K1** (6 mol%), **1** (0.3 mmol), **2a** (0.2 mmol), $BF_3{\cdot}Et_2O$ (0.26 mmol) and LiHMDS (0.7 mL, 1 M in THF) in THF (2 mL) at 30 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] **K1** (8 mol%) as catalyst.



Scheme 1. Preparation of a key intermediate of an Na^+/H^+ exchanger inhibitor.

Next, an asymmetric total synthesis of (−)-lycopladine A was carried out. Lycopladine A is a tricyclic alkaloid featuring a pyridyl-fused hydrindanone core and three stereocenters, including an all-carbon quaternary center. It shows modest but selective cytotoxicity toward murine lymphoma L1210 cells ($IC_{50} = 7\ \mu g\,mL^{-1}$).[7c,9c] The unusual structure and interesting biological activity of lycopladine A have aroused the interest of several synthetic groups, which has led to successful total syntheses by Toste, Martin, Hiroya, Yang and Meng.[12] Our synthesis of lycopladine A by the current method is summarized in Scheme 2. Asymmetric allylic alkylation of **1d** with **2n** generated **7** in 67% yield and 90% *ee*. Hydroboration of the terminal alkene in **7** provided primary alcohol **8** in 78% yield, and **9a** was then obtained through a palladium-catalyzed Heck reaction. Cleavage of the double bond in **9a** by ozonolysis and subsequent allylic alkylation under palladium catalysis afforded compound **10** in 79% yield. Compound **10** was subjected to pyridinium chlorochromate (PCC) oxidation, followed by treatment with NaOH (1%, aq.) to yield tricyclic intermediate **11** (45% yield over two steps). Installation of the methyl group at the β-position of the carbonyl through treatment with $[Me_2Cu(CN)Li_2]$ led to **12** in 80% yield with perfect stereoselectivity. Finally, the terminal alkene was transformed



Scheme 2. Total synthesis of (−)-lycopladine A. LiHMDS = lithium hexamethyldisilazide, 9-BBN = 9-borabicyclo[3.3.1]nonane, dppb = 1,4-bis-(diphenylphosphino)butane.

into an alcohol to accomplish the total synthesis of lycopladine A. The absolute configuration of the synthetic sample of lycopladine A could be assigned through comparison of the sign of the optical rotation with the reported value.[9c,12a] It is noteworthy that this route is the first total synthesis of (−)-lycopladine A through a catalytic asymmetric method.

In summary, we have successfully developed the first iridium-catalyzed asymmetric allylic alkylation of 2-methylpyridine derivatives with high enantioselectivity. With an iridium-catalyst derived from a commercially available iridium precursor and the Alexakis ligand, the allyl alkylation reaction can tolerate a broad range of allyl carbonates and nucleophiles derived from 2-methylpyridines. The synthetic utility of the pyridine products has been demonstrated through the synthesis of a key intermediate of an Na^+/H^+ exchanger inhibitor with high enantiopurity and the total synthesis of (−)-lycopladine A. Further extension of the scope to benzylic nucleophiles and the development of more efficient catalytic systems are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · homogeneous catalysis · iridium · pyridines · unstabilized nucleophiles

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Communications

Asymmetric Catalysis

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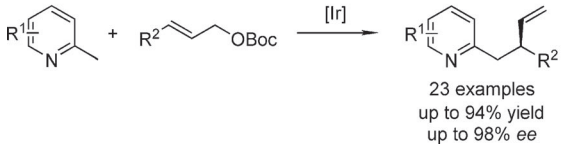
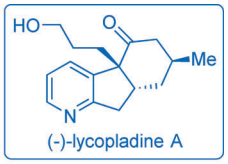
Enantioselective Iridium-Catalyzed Allylic Substitution with 2-Methylpyridines





An enantioselective iridium-catalyzed allylic substitution with a set of highly unstabilized nucleophiles generated in situ from 2-methylpyridines was developed. Enantioenriched 2-substituted pyridines, which are frequently encountered in natural products and pharmaceuticals, could be easily constructed by this simple method in good yields and excellent enantioselectivity. The pyridine products were applied in the total synthesis of (−)-lycopladine A.