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# Recoverable Resin-Supported Pyridylamide Ligand for Microwave-Accelerated Molybdenum-Catalyzed Asymmetric Allylic Alkylations: Enantioselective Synthesis of Baclofen

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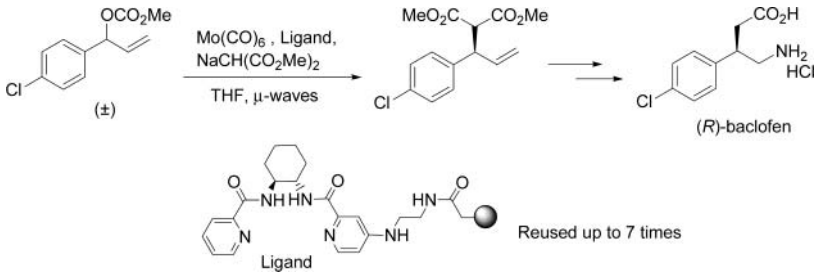
## ABSTRACT




**The syntheses of a series of 4-monosubstituted pyridylamides and a resin-supported pyridylamide are described. The ligands were evaluated in the microwave-accelerated molybdenum-catalyzed asymmetric allylic alkylation. The reaction afforded the product in high yield and with high regio- and enantioselectivity. The heterogeneous ligand could be reused several times with no change in the reaction outcome. The asymmetric allylic alkylation was employed as the key step in the enantioselective synthesis of (*R*)-baclofen.**

The development of immobilized catalysts has been a growing area during the past years.[1] Due to the increased demand for robust, reliable, and economic synthetic methods to prepare chiral compounds, heterogeneous asymmetric catalysis has been a field of interest for many research laboratories. Thus, solid-supported chiral ligands have been synthesized and used for a number of classes of asymmetric catalytic organic transformations including oxidations, reductions, and C−C bond formations among others.[2] Some advantages of using solid-supported ligands are the ease of removing the ligand after reaction and the possibility to reuse the recovered ligand without loss of performance.[3]

Since the discovery by Trost and Hachiya[4] that pyridylamide **1a** (Figure 1) served as an efficient ligand for the molybdenum-catalyzed asymmetric allylic alkylation, some effort has been made to gain a deeper understanding of the operating reaction mechanism,[5] and new classes of ligands have been synthesized and employed successfully.[6] We

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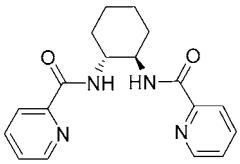


1a

**Figure 1.** Parent bis-pyridylamide.

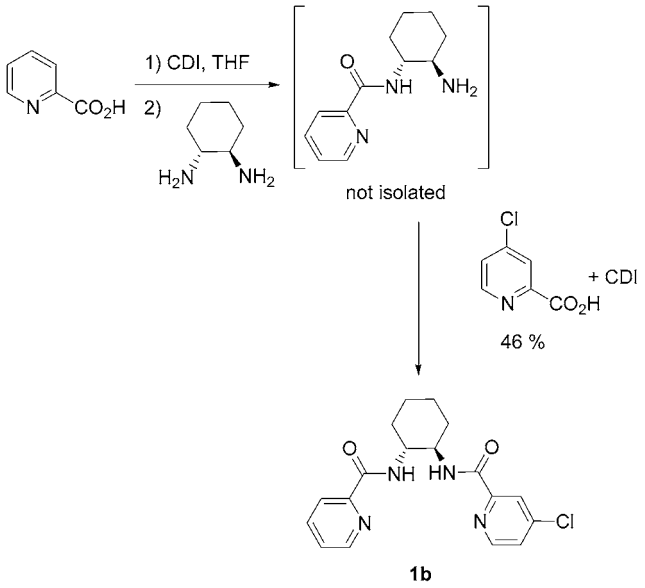
developed a convenient and robust procedure for the reaction of cinnamyl methyl carbonate with sodium dimethyl malonate using $Mo(CO)_6$, ligand **1a**, and *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) under air that afforded the product with high regio- and enantioselectivity.[7] We were also interested in the influence of the electronic and steric properties of the ligand on the outcome of the reaction and synthesized several substituted pyridylamides and evaluated them as ligands for the allylation reaction with different model substrates.[8] Our results showed that electron-donating groups in the 4-position of the pyridine rings of the ligand improved the regioselectivity in favor of the branched product.

Previously in our group, we have made resin-supported pyridyloxazolines[9] and bis(oxazolines)[10] for use in the complementary palladium-catalyzed allylic alkylation reaction. Herein, we report the preparation and use of a recyclable polymer-supported pyridylamide for the microwave-accelerated molybdenum-catalyzed allylic allylation.

For the immobilization of pyridylamide **1a**, methods involving the reaction of a derivative of **1a** substituted either in the diamine part of the molecule or in a pyridine ring with a suitably functionalized solid support were considered. The former method, which may retain the $C_2$ symmetry of the molecule, was recently utilized for the heterogenization of the Trost diphosphane.[11] However, the attachment via a pyridine ring allows for a higher flexibility, and the functionalization can at the same time be employed for tuning of the electronic properties of the ligand. In addition, it has recently been demonstrated that 2-fold symmetry is not a requirement for high selectivity in the catalytic reaction under study.[5b,6d]

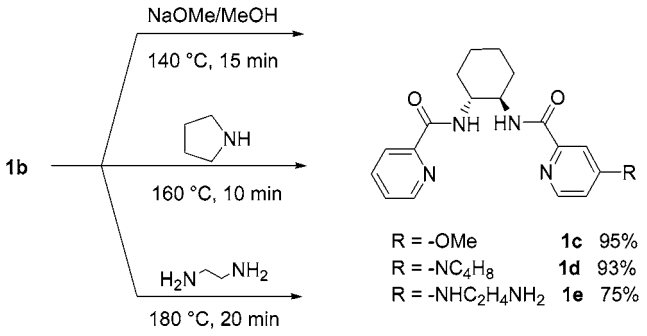
To study the behavior of ligands containing only one substituted pyridine ring, some monofunctionalized ligands were prepared. Our previous investigations showed that pyridylamides substituted in the 4-position of the pyridine rings could be conveniently prepared from the bis(4-chloropyridine) derivative by nucleophilic aromatic substitution.[8b] Pyridylamides containing two different aromatic nuclei have been made before by stepwise formation of the monoamide and then further reaction to form the diamide.[5c] However, this procedure affords mixtures of compounds if the reaction conditions are not carefully controlled. We observed that when slowly adding a 0.05 M solution of picolinic acid activated with carbonyl diimidazole (CDI) to a 0.05 M solution of (1*R*,2*R*)-1,2-diaminocyclohexane, the monoamide was formed almost exclusively. Further reaction with activated 4-chloropicolinic acid gave the desired monosubstituted precursor **1b** in 46% yield after chromatography (Scheme 1).

**Scheme 1.** Synthesis of the Monofunctionalized Ligand **1b**




With **1b** in hand, we prepared a series of monosubstituted ligands by treatment of **1b** with a suitable nucleophile under microwave heating to give the corresponding derivative (**1c**−**e**) in high yields (Scheme 2).

**Scheme 2.** Synthesis of Monofunctionalized Ligands by Nucleophilic Aromatic Substitution of **1b**

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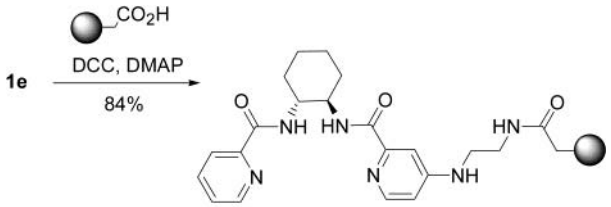
**Scheme 3.** Preparation of the Solid-Supported Ligand **1f**

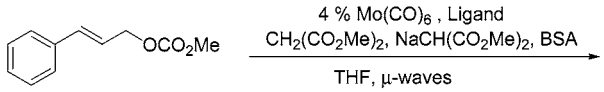



**1f**

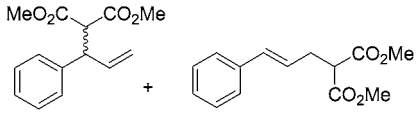
Furthermore, the primary amino group in ligand **1e** could be utilized as an attachment point to a carboxylic acid functionalized resin by simple amide formation. Thus, reaction of the ligand with a TentaGel HL-COOH resin in the presence of DCC and DMAP in dichloromethane for 24 h at room temperature gave the desired immobilized ligand in 84% yield based on elemental analysis (Scheme 3).

The ligands were evaluated in the allylation reaction of dimethyl malonate with 3-phenylprop-2-enyl methyl carbonate (**2**) (Table 1). Catalysts showing high regio- and enantioselectivity were produced when the monosubstituted bispyridylamides **1b**−**d** were used. Very high regioselectivity (98:1) was observed when the 4-methoxy-monosubstituted ligand (**1c**) was used, while the 4-chloro-substituted ligand (**1b**) afforded the product in nearly the same branched-to-linear ratio as the 4-pyrrolidine substituted ligand (**1d**) (74:1 and 75:1, respectively). These ligands **1b**−**d** also afforded the branched product with high selectivity (97% ee for **1b** and **1c** and 99% ee for **1d**). On the other hand, the reaction was very slow when ligand **1e**, having a free primary amino group, was used. Even after 12 min at 160 °C, only small amounts of product were detected by GC−MS, and the branched-to-linear ratio and % ee could not be determined accurately. When using polymer-supported ligand **1f**, the reaction was also slower, presumably because of the heterogeneous nature of the catalyst. However, when the reaction was run with double concentration of the reagents (1.54 M for the nucleophile and 1.42 M for **2**), no starting material could be detected after 30 min and the product exhibited a branched-to-linear ratio of 35:1 and an enantiomeric excess of 97%. Furthermore, the resin-supported ligand could be recovered by filtration from the reaction mixture and reused as ligand, after washing with different solvents and vacuum-drying, for at least seven times with no significant change in the reaction outcome.

**Table 1.** Results of the Catalytic Reaction Using Ligands **1b**−**f**




**2**



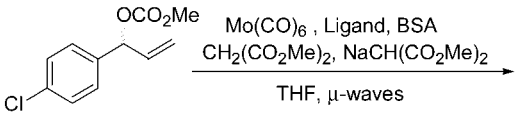

**3** **4**

| entry | ligand | *T* (°C) | *t* (min) | yield of **3**[a] (%) | **3**/**4**[b] | % ee[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 160 | 6 | 80 | 19:1 | 98 |
| 2 | **1b** | 160 | 6 | 89 | 74:1 | 97 |
| 3 | **1c** | 160 | 6 | 90 | 98:1 | 97 |
| 4 | **1d** | 160 | 6 | 89 | 75:1 | 99 |
| 5 | **1e** | 160 | 12 | traces | | |
| 6[d] | **1f** | 160 | 20 | 90[b] | 35:1 | 97 |
| 7[d] | **1f** | 160 | 25 | 95[b] | 35:1 | 97 |
| 8[d] | **1f**[e] | 160 | 30 | 82 | 35:1 | 97 |

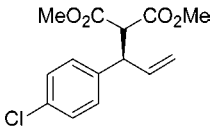
[a] Isolated yield. [b] Determined by GC−MS. [c] Determined by chiral HPLC. [d] Concentration of the reagents was doubled. [e] The ligand could be reused at least seven times without change in the reaction outcome.

The molybdenum-catalyzed allylic alkylation has high synthetic potential.[5a,12] We wanted to apply our convenient procedure for the allylation reaction in the synthesis of (*R*)-baclofen (**8**). The racemic form of **8** is used as a muscle relaxant (antispasmodic) lipophilic derivative of $\gamma$-aminobutyric acid (GABA). Pharmacological studies have shown that the (*R*)-enantiomer is the therapeutically useful agonist of the $GABA_B$ receptor.[13] Therefore, several efforts have been made to prepare enantiomerically pure **8**.[14] Allylic carbonate **5** was easily prepared by the addition of vinylmagnesium chloride to 4-chlorobenzaldehyde and subsequent treatment with methyl chloroformate.[15] Alkylation with malonate afforded **6**[16] (Table 2) in good yield and enantioselectivity (96% ee when using ligand **1a**). The polymer-supported ligand **1f** also afforded the product in good yield, but with drastically lower enantioselectivity, probably as a result of

**Table 2.** Preparation of Intermediate (*R*)-**6**




(±)-**5**

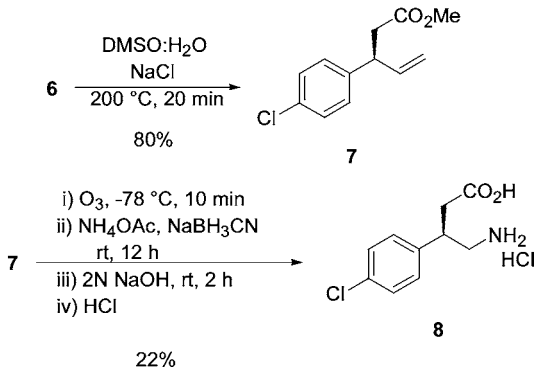



(*R*)-**6**

| entry | ligand | THF (mL) | PhMe (mL) | *T* (°C) | *t* (min) | yield[a] (%) | b/l[b] | % ee[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | (*S*,*S*)-**1a** | 2 | 0 | 160 | 6 | 78 | 26:1 | 96 |
| 2 | (*S*,*S*)-**1f** | 1 | 0 | 160 | 30 | 95[b] | 27:1 | 48 |
| 3 | (*S*,*S*)-**1f** | 0.5 | 0.5 | 160 | 30 | 98[b] | 24:1 | 76 |
| 4 | (*S*,*S*)-**1f**[d] | 0.1 | 0.9 | 160 | 30 | 76 | 25:1 | 89 |

[a] Isolated yield. [b] Determined by GC−MS. [c] Determined by chiral HPLC. [d] The ligand could be reused at least seven times without change in the reaction outcome.

**Scheme 4.** Synthesis of (*R*)-Baclofen from **6**




a memory effect.[5a] As shown by Hughes et al.[5a] for the parent ligand, running the reaction in toluene minimized the memory effect, and in our case the enantioselectivity increased to 89% ee when the reaction was run in that solvent.

Decarboxylation of the geminal diester (Scheme 4) was achieved when a solution of **6** and NaCl in DMSO/water was heated in the microwave cavity for 20 min.[17] Oxidation of the double bond in **7** with ozone at −78 °C for 10 min and cleavage of the ozonide with $Me_2S$ produced the corresponding aldehyde[18] that was immediately treated with $NH_4OAc$ and $NaBH_3CN$[19] at room temperature for 12 h. Then addition of 2 N NaOH to the reaction mixture at room temperature afforded **8** (Scheme 4), after workup and formation of the hydrochloric salt in 22% yield overall (from **7**).

In summary, we have synthesized new monosubstituted pyridylamide ligands and developed a new resin-supported pyridylamide ligand for the microwave-accelerated molybdenum-catalyzed allylic alkylation reaction. The ligands were evaluated in the reaction and yielded the product in high yields and with high selectivity. The resin-supported ligand could easily be recovered and reused several times without significant loss in the outcome of the reaction. A short enantioselective synthesis of (*R*)-baclofen was achieved using the allylation reaction as the key step.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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