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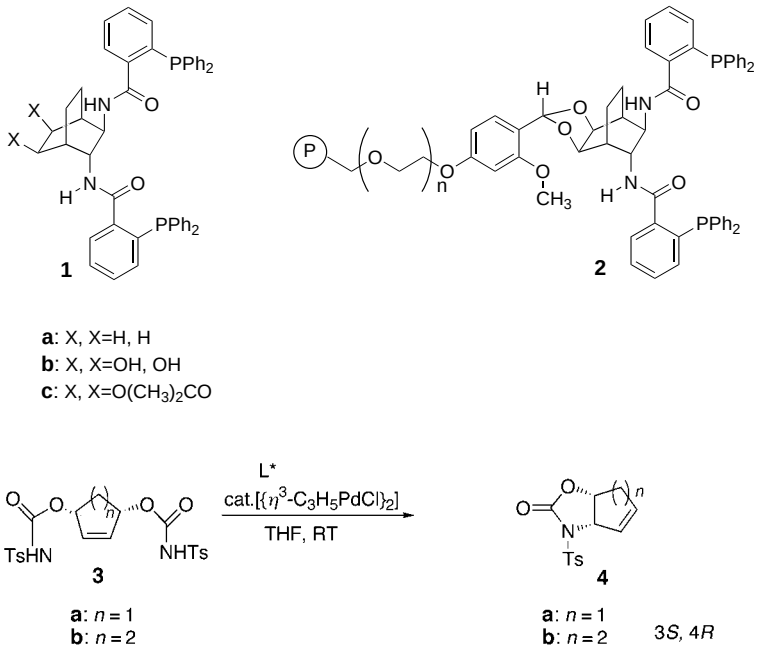

Polymer-Supported C_2-Symmetric Ligands for Palladium-Catalyzed Asymmetric Allylic Alkylation Reactions**

Barry M. Trost,* Zhengying Pan, Jorge Zambrano, and Christof Kujat

Development of immobilized ligands/catalysts for asymmetric synthesis is a rapidly growing field.[1] Because of palladium's broad applications in organic synthesis,[2] many types of supported ligands have been reported for allylic,[3] alkylation,[4] amination, and cross-coupling reactions.[5] However, there are surprisingly few successful polymer-bound ligands for palladium-catalyzed asymmetric allylic alkylations.[6,7] In the late 1970s, we demonstrated the use of polymer-bound phosphane ligands in Pd-catalyzed transformations.[8] We here report a competent, easily prepared, recyclable chiral ligand for asymmetric allylic alkylation (AAA) reactions.

Initially, we examined the supported ligand **2**, which was derived from the rigid bicyclic templates **1**[9] to minimize any perturbation of the chiral pocket. The supported ligand **2** formed readily by reacting the diol **1b** with ArgoGel-CHO catalyzed by *p*-toluenesulfonic acid (TsOH) in dichloromethane. Cyclization of the bisurethane **3a** to the oxazolidin-2-one **4a**[10,11] was examined as the test reaction [Eq. (1)]. As a baseline, the reaction was performed in normal solution phase with the simple ligands **1a** and **1b**. Table 1, entries 1 and 2, reveals the effectiveness of this class of ligands. It is somewhat surprising that a small dip in enantiomeric excess (*ee*) occurs on introducing electronegative oxygen atoms into the remote bridge (91 to 87% *ee*). The supported ligand **2** was effective in performing the reaction but there was a more significant drop in enantiomeric excess (Table 1, entry 3) although it was still reasonable. Simply decanting the reaction mixture from the solid support and washing the beads with fresh THF prepared the beads for the next cycle. No additional palladium was loaded after the initial charge. The yield dipped in the second cycle but subsequently stabilized at 60 ± 5%. Thus, the supported catalyst was quite robust remaining highly active even after seven cycles (Table 1, entries 3–9). The enantiomeric excess also remained quite constant through most of the cycles at 70 ± 1%. In earlier experiments with normal solution ligands, addition of triethylamine led to a significant enhance-

Table 1. First-generation bicyclic ligands.[a]

Entry	Ligand	Run	Yield of **4a** [%]	*ee*[b] [%]
1[c]	**1a**	–[d]	69	91
2[c]	**1c**	–[d]	79	87
3	**2**	1	81	73
4	**2**	2	74	71
5	**2**	3	70	70
6	**2**	4	63	71
7	**2**	5	63	69
8	**2**	6	60	70
9	**2**	7	66	69
10	**2**	–[d]	78	68

[a] All reactions were performed with 10 mol% [{η³-C_3H_5PdCl}$_2$] and 25 mol% ligand in THF at room temperature; the vessel was shaken for mixing unless otherwise indicated. [b] Determined by chiral HPLC in an AD chiralpak column. [c] Performed with 2.5 mol% [{η³-C_3H_5PdCl}$_2$], 7.5 mol% ligand in THF at room temperature with normal magnetic stirring for mixing. [d] Not applicable. [e] Triethylamine added.

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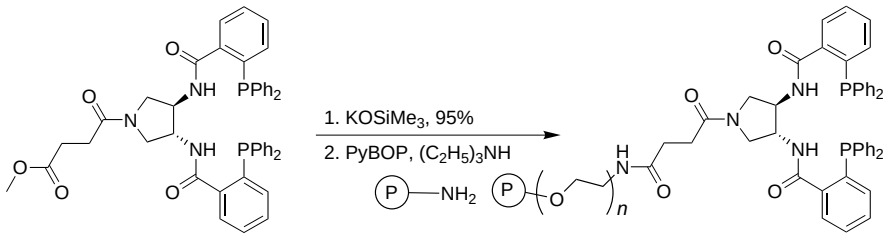
ment of the enantiomeric excesss. That effect was not observed with this supported ligand (Table 1, entry 10). In related experiments, ArgoPore or Merrifield resins proved less efficacious; immobilizing the ligand in the solid support had no effect on the absolute configuration of the major enantiomer produced.

While the reactivity of the supported catalyst was satisfactory, less loss of enantiomeric excess was desired. Speculation that the polar amide linkages may be interacting with the polyether polymer led us to envision an amide tether. Consequently, we examined ligand **5**, which was generated from the known corresponding diamide bis(Boc-pyrrolidine) compound (Boc = *tert*-butyloxycarbonyl),[12] and its supported version **6** derived from ArgoGel-NH_2 and **5** (Scheme 1).



5 **6**

Scheme 1. Synthesis of the supported compound **6** from the ligand **5**. PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

Hydrolysis of the ester **5** with $KOSiMe_3$ (95% yield) followed by coupling of the resulting acid with ArgoGel-NH_2 using PyBOP and triethylamine (quantitative yield; the disappearance of free NH_2 groups was monitored by Kaiser and chloranil tests)[13] gave the desired supported ligand (0.37 mmol g^{-1}). Once again, cyclization of the bisurethane **3b** to the oxazolidin-2-one **4b** [Eq. (1)] was examined as the test reaction. As entry 1 in Table 2 indicates, the pyrrolidine ligand **5** performs superbly.

Loading the polymer with $[(dba)_3Pd_2]\cdot CHCl_3$ as the palladium source proved problematic and required the presence of substrate to be successful. On the other hand, using $[\{\eta^3\text{-}C_3H_5PdCl\}_2]$ was straightforward. Furthermore, comparison of entries 2 and 3 to those of entries 4 and 5 in Table 2 suggests that the π-allylpalladium chloride precatalyst generates a somewhat better catalyst and therefore this was adopted as the standard palladium source. In this case, addition of one equivalent of triethylamine has a noticeable effect (Table 2, entry 2 versus 3 and 4 versus 5) of improving the enantiomeric excess but slowing the reaction somewhat as observed in the solution phase with the standard ligand.[10a] Further addition of the triethylamine was not beneficial (Table 2, entry 6), and switching to dichloromethane (Table 2, entry 7) or toluene (Table 2, entry 8) proved quite deleterious. On the other hand, increasing the concentration of the substrate to 1M had little effect (Table 2, entries 9 and 10). The reaction in Equation (1) was equally effective in the case of the five-membered-ring substrate **4a**, whereby the oxazolidin-2-one **4b** was formed in 63% yield with 93% *ee*. The absolute configuration of the product was the same for the same chiral scaffold generated by using the soluble and supported catalysts. The key question was the ability to recycle the catalyst. Table 3 summarizes the results. In each recycle step, no additional loading of palladium after the initial charge was performed. After 1 h, the reaction mixture was decanted off by using a cannula, and the solution of the reactants for the next cycle was then added to the beads. Over four cycles, no significant differences in either yield or enantiomeric excess were observed.

Table 2. Second-generation pyrrolidine-based ligands.[a]

Entry	Ligand	$(C_2H_5)_3N$ [equiv]	Conc. [M]	Solvent	Yield **4b** [%]	*ee* **4b** [%]
1[b]	**5**	1	0.2	THF	97	> 99
2[b]	**6**	1	0.2	THF	70	87
3[b]	**6**	none	0.2	THF	54	71
4	**6**	none	0.2	THF	93	80
5	**6**	1	0.2	THF	78	90
6	**6**	2	0.2	THF	64	89
7	**6**	1	0.2	CH_2Cl_2	35	50
8	**6**	1	0.2	$PhCH_3$	–[c]	–
9	**6**	1	0.5	THF	72	86
10	**6**	1	1.0	THF	77	85

[a] All reactions were performed with 5 mol% catalyst at room temperature overnight using $[\{\eta^3\text{-}C_3H_5PdCl\}_2]$ as the palladium precatalyst (ratio of bound ligand to palladium 1.5:1) unless otherwise noted. [b] For this run, $[(dba)_3Pd_2]\cdot CHCl_3$ used as precatalyst (dba = *trans,trans*-dibenzylideneacetone. [c] No reaction.

Table 3. Recycling experiments with catalyst **6**.[a]

Entry	Reaction time [h]	Yield [%]	*ee* [%]
1	1	81	92
2	1	81	92
3	1	77	91
4	1	77	92

[a] All reactions were run with 20 mol% catalyst and one equivalent of $(C_2H_5)_3N$ at 0.2M in THF at room temperature.

The results herein demonstrate that polymer-supported chiral catalysts can function for palladium-catalyzed asymmetric allylic alkylations. The more solution-like environment of the ArgoGel resins make them more efficacious than the other polymeric supports such as the Merrifield or ArgoPore resins. Nevertheless, the choice of the scaffold and the bond type for tethering is critical. While reactivities were normally not an issue, the impact of the solid support on enantiomeric excess was significant. The degree of loss of enantiomeric excess was dependent upon both parameters. The use of an amide tether and a pyrrolidine scaffold gave a solution and a supported catalyst that closely resembled each other and kept the *ee* value $\geq$ 90%. In all the cases examined, good recyclability of the catalyst (up to seven recycles were examined) was observed as long as the reaction mixtures were thoroughly degassed to ensure that the oxygen content was as low as possible. The readily available supported catalyst generated from ligand **6** should prove to be generally useful for palladium reactions.[14] The ability to produce

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oxazolidin-2-ones with high enantiomeric excesses has already proved to be useful in generating a number of biologically significant targets such as mannostatin A,[15a] allosamizoline,[15a] and swainsonine.[15b]

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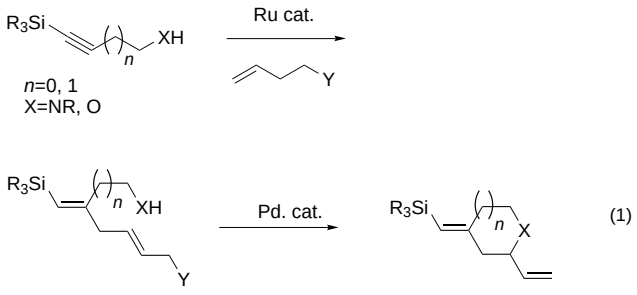
An Efficient One-Pot Enantio- and Diastereoselective Synthesis of Heterocycles**

Barry M. Trost* and Michelle R. Machacek

Heterocycles comprise the core of many complex natural products. The most common method for their formation is based on intramolecular ring closure. However, in most intramolecular closure strategies it is necessary to synthesize and then isolate the open-chain precursor. On an industrial scale the environmental and economic costs of the isolation step are considerable. In contrast, a more efficient strategy utilizes a domino alkylation–cyclization[1] to form the ring without isolation of the acyclic intermediate. For the development of ideal syntheses, processes are sought that generate multiple bonds in one pot.[2]

We aimed to design a one-pot heterocyclization process that was both efficient and permitted control of the stereochemistry of our products. We therefore focused on the Pd-catalyzed asymmetric allylic alkylation (AAA)[3,4] for the critical stereochemical determining step. This was combined with the Ru-catalyzed ene–yne coupling[5] to create the proper juxtaposition of functionality for the second step. Recently we have shown that in the presence of $[CpRu(CH_3CN)_3PF_6]$,[6] silyl-substituted alkynes form 1,4-dienes with complete regio- and stereoselectivity.[7] If the ene partner is a homoallylic group, the resulting 1,4-diene will contain a *newly formed allylic* group as illustrated in Equation (1). This intermediate



(1)

may then *without isolation* be subjected to Pd-catalyzed asymmetric allylic alkylation. An additional feature of this strategy is that the resulting vinylsilanes offer a pathway for further structural elaboration[8] and permit differentiation of the two resulting double bonds.

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