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A study of catalyst selectivity with polymer bound palladium phosphine complexes on various solid phase synthesis supports

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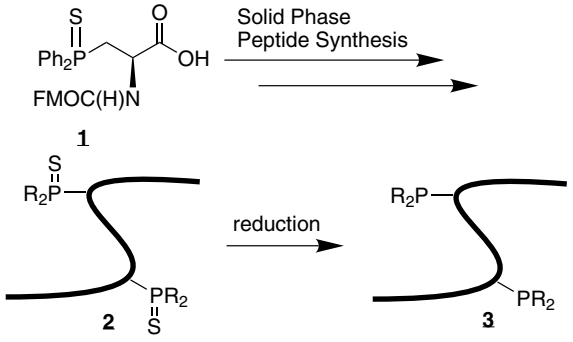
Abstract—A peptide based ligand system is synthesized on six different supports and then examined for the ability of its palladium complex to catalyze the addition of dimethylmalonate to 3-acetoxycyclopentene in six different solvents. The results on support are correlated to the results observed with the catalyst system dissolved in solution.

For a number of years we have been involved in the development of parallel methods for the synthesis of chiral phosphine ligands. A series of phosphine-sulfide amino acids have been developed that allows the production of phosphine ligands through solid phase peptide synthesis followed by reduction of the phosphine sulfide (**2**) to a phosphine (**3**) (Scheme 1).[1,2] In addition, to facilitating the synthesis of libraries of phosphines, this approach allows the synthesis of ligands that possess stable peptide secondary structures such as α-helix and β-turn motifs.[3–6] Since the goal of this research is the development of a system that allows for the rapid synthesis and evaluation of catalysts exhibiting high enantioselectivity, chemistry has been developed that allows for the synthesis and screening of the catalysts while they are attached to the polymer support the ligand was synthesized on.[4] One might expect that some supports may perform better than others in this unique application. A complicating factor in the use of solid supports for catalysis is that the optimal solvent for a given catalyst may not be the optimal solvent for swelling the support the catalyst is attached to. While the performance of different supports may vary depending on the given catalyst that is attached, it should be useful to examine a series of supports and solvents with a given reaction. This paper reports a study of the selectivity of a palladium-catalyzed allylation with a variety of supports and different solvents. Palladium catalyzed allylation is a widely studied reaction and as such should represent a good model for the study of different supports.



Scheme 1.

For some time we have been investigating the reaction of dimethyl malonate (**5**) with 3-acetoxycyclopentene (**4**) (Fig. 1). Cyclic allyl acetates have been difficult substrates for asymmetric allylation. There are only a selective number of ligand systems that perform this reaction in high enantiomeric excess.[7–13] In previous studies, libraries of catalysts were screened with the goal of identifying ligands that performed this reaction with high selectivity.[6] The method used to identify selective catalysts was to perform the catalytic reaction with the complex immobilized on the support the ligands were

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synthesized on and then analyzing the reaction products. Since running the reaction and then analyzing the selectivity of each catalyst was necessary, a spatially addressable system for library synthesis was required. The original choice was the SynPhase™ system from Mimotopes.[14–16]

While we were quite successful in finding a system that gave excellent selectivity with the peptide attached to the synthesis support,[17] we felt it would be useful to examine other supports and other solvent systems. In this study the peptide sequence was kept constant while changing the support and the solvent. To facilitate synthesis, a simple peptide sequence (support-Gly-Pps-D-Ala-Pro-Pps-D-Ala-Ac) was chosen rather than the sequence that had been shown to give the absolute highest selectivity. The sequence chosen provides moderate selectivity for the allylation reaction. With this peptide six different synthesis supports or linkers were examined; SynPhase™ lanterns, polystyrene Rink resin, JandaJel™, ArgoPore, NovaGel™ and NovaSyn TGR. Additionally, a homogeneous variant of the catalyst was also screened. Each support was tested with a series of solvents. Reactions were run with dichloromethane, toluene, THF, acetonitrile, 1,4-dioxane and acetone. The data in Table 1 and Chart 1 illustrates the selectivities that were observed. In a number of cases the support-solvent combinations that gave higher conversions also tended to provide the products with greater selectivity. ArgoPore using dichloromethane as solvent provided the product in 63% ee and 64% conversion. While not providing the highest selectivity, ArgoPore provided consistent results in all of the solvents tested. One would expect this resin to be less sensitive to solvent, given that it is highly crosslinked

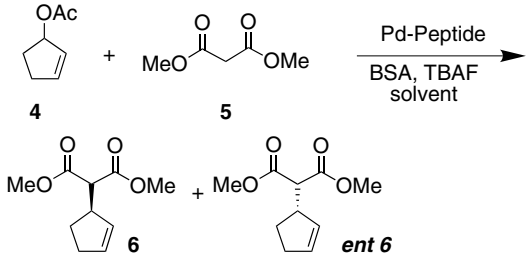

Figure 1.

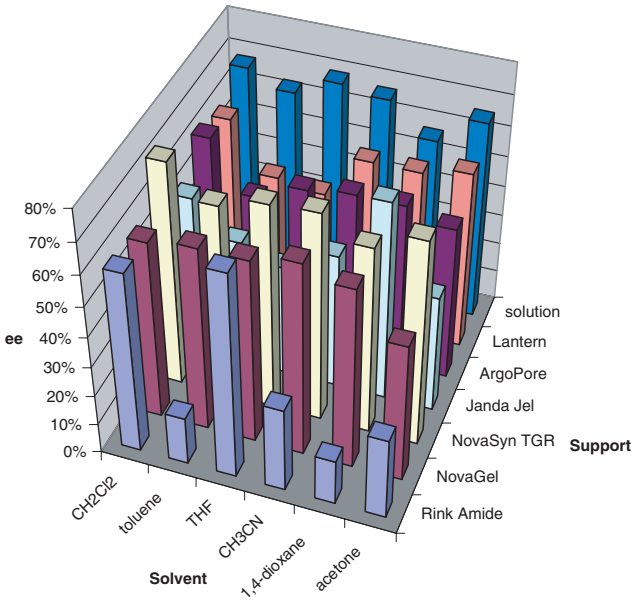

Chart 1. Enantiomeric excess versus support and solvent.

(10% cross linked with divinyl benzene) polystyrene and consequently should be less prone to different degrees of swelling in various solvents. The results with NovaGel™, a resin designed to swell well in a variety of solvents are also insensitive to the solvents examined, with the highest selectivity coming in acetonitrile (64% ee, 60% conversion). This result may be related to our observation that in the homogenous system acetonitrile is often the best solvent for this reaction. Good selectivity and conversion were also observed in dioxane and THF, solvents that should swell this resin. In the case of JandaJel™ the conversions varied with solvent, as did the selectivities. Dioxane, a solvent expected to solvate this resin, provided the highest selectivity (66% ee) and the highest conversion (59%). The system that was used in the original study, SynPhase™ lanterns, provided good as well as consistent selectivity with a variety of solvents. NovaSyn TGR provided the results that most closely mirrored the results observed with the catalyst in solution. Giving nearly the same selectivities as the homogeneous system in all six solvents examined. All of the resins tested provided more consistent results than Rink amide linked polystyrene, which provided the

Table 1. Convertion (%[a])/enantiomeric excess (% ee[b]) on various supports

	CH_2Cl_2	Toluene	THF	CH_3CN	1,4-Dioxane	Acetone
SynPhase™ lantern[c]	34/60	14/44	26/42	38/56	44/56	26/59
Rink amide[c]	35/60	32/16	48/68	26/28	38/15	37/27
JandaJel[c]	55/53	33/42	31/37	31/45	59/66	37/39
ArgoPore[c]	64/63	78/47	86/53	63/55	78/55	71/51
NovaGel™[c]	70/59	58/61	52/61	60/64	64/60	65/46
NovaSyn TGR[c]	58/74	71/64	49/68	72/69	74/62	66/68
Solution[d]	100/68	100/63	100/69	100/67	53/57	88/66

Reactions were run at rt, using *N*,*O*-bis(trimethylsilyl)acetamide, TBAF and dimethylmalonate.
[a] Conversions were determined by ^{1}H NMR.
[b] Enantiomeric excess was determined by ^{1}H NMR analysis using [Eu(hfc)$_3$] shift reagent.
[c] Peptide sequence support-Gly-Pps-D-Ala-Pro-Pps-D-Ala-Ac.
[d] Peptide sequence H_2N-Gly-Pps-D-Ala-Pro-Pps-D-Ala-Ac.

lowest selectivities and the largest variations with changes in solvent.

In order to examine the catalysis with a homogeneous system a peptide was synthesized in solution and capped on the carboxy terminus as the amide (H_2N-Gly-Pps-D-Ala-Pro-Pps-D-Ala-Ac). The reaction under homogenous conditions with the catalyst in solution proved to be less dependent on the solvent used for the reaction with CH_2Cl_2, toluene, THF, CH_3CN and acetone all giving selectivities higher than 60% ee.

While the results with the catalyst in solution provided the most consistent outcome, it is important to note that a number of support systems provided selectivities that were equal to the results in solution. This correlation is critical if one plans to use screening of support bound catalysts to find selective homogeneous catalysts. The ability to perform catalysis with the metal complex immobilized on a solid support is important for the rapid synthesis and evaluation of libraries of catalysts. Consequently, it is important to be able to find supports that do not interfere with the selectivity of a given catalyst. The palladium catalyzed allylation reaction is a very complex reaction. Not only are there issues with formation of the intermediate palladium complex but there is also the requirement for control of the attack by a charged nucleophile and its associated counter ion. These issues combine to make this reaction a formidable test for a support bound catalyst system. While it may be difficult to make generalizations from the examination of just one reaction some useful trends were observed that are likely to hold. What can be seen from this study is that standard polystyrene with a Rink linker is a poor support to use for this type of catalysis. This is significant since this is still one of the most common resins and one that researchers are likely to try first. While many supports provided selectivities that tracked to those obtained with the catalyst in solution, the key is to match the solvent used for the reaction with the swelling and solvation properties of the various supports. This was particularly true with Rink resin where the highest selectivities were observed with the solvents that also are the best at swelling this particular resin, CH_2Cl_2 and THF. In most cases, when a solvent that is known to swell the resin is used, it was found that the selectivities obtained were comparable to those obtained with that solvent using a soluble metal complex. Lastly, it is notable that at least for this application NovaSyn TGR provided selectivities that most closely mirrored those obtained with the catalyst in solution.

In conclusion, if the proper match between solvent and support is possible, polymer-supported catalysts can be used to screen for selectivity with the corresponding ligand in homogeneous reaction conditions. In cases other than when there is extreme incompatibility between the solvent and support, selectivities that correlate with the results in solution are observed. While some supports appear to be relatively insensitive to different solvent systems, ultimately to obtain maximum selectivity, it is necessary to optimize the reaction conditions for a catalyst in a homogeneous environment.

Resins tested: The following resins where examined; SynPhase™: MD Crown Type I series Rink amide linker (8.0 μmol loading) from Mimotopes, Wang resin from Novabiochem #04-12-2053, 100–200 mesh (0.65 mmol/g loading), Rink amide resin from Novabiochem #01-64-5026, 100–200 mesh (0.62 mmol/g loading), NovaGel™ from Novabiochem #01-64-0286, 100–200 mesh (0.56 mmol/g loading), NoraSyn® TGR resin from Novabiochem #01-64-0060, 90 μm beads (0.20 mmol/g loading), JandaJel™ NH_2 beads from Aldrich #52,461-1, 100–200 mesh (1.0 mmol/g loading) ArgoPore-NH_2 beads from Aldrich #48,249-8, 60–140 mesh (0.6–1.1 mmol/g loading).

Heterogeneous catalysis: The bisphosphine was treated with up to 5-fold excess of $[Pd(allyl)Cl]_2$ for 30 min in acetonitrile. After an extensive washing with 6 aliquots of acetonitrile the support was dried in vacuo and transferred to individual 20 mL scintillation vials sealed under N_2. We have found that the results in terms of selectivity are not sensitive to the exact metalation procedure. The metalations have been performed with quantities of $[Pd(allyl)Cl]_2$ ranging from 1 to 5 equiv with little change in the selectivity. To the metallated support under N_2 was added 1–2 mL of solvent and 200 μmol of substrate. In a separate flask under N_2 600 μmol bistrimethylsilyl acetamide was added drop wise to 600 μmol of dimethyl malonate and 600 μmol TBAF (1 M in THF). This exothermic reaction is allowed to cool to room temperature and is then added drop wise to the catalyst and substrate. The reactions were monitored by TLC using $KMnO_4$ stain. After 12 h the reactions were concentrated and chromatographed on silica gel with 10% EtOAc in hexane. Samples for evaluating enantioselectivity were prepared by adding 0.5–0.6 mL of C_6D_6 to ~5 mg of product and 10–15 mg of $Eu(hfc)_3$. Enantiomeric excesses were determined by integrating the two pairs of singlets (4.1–4.6 ppm for the 3-acetoxycyclopentene adduct) corresponding to the malonate methyl esters.

Acknowledgements

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