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Experimental design and the optimization of a polymer supported palladium complex for use in the Heck reaction

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Abstract—Optimization of the Heck reaction of 4-bromoacetophenone with styrene by a polymer supported, sulfur-containing palladacycle, varying 6 factors at a total of 28 different levels, corresponding to 5760 different possibilities was undertaken. Conversion improved from 34%, with large observable leaching to 88% with no leaching. This was accomplished using a Design of Experiments approach facilitated by the Statistical Design Package, MODDE 7.0$^{\text{TM}}$.

Combinatorial chemistry has been one of the most rapidly expanding areas of chemistry in the past decade, enabling the rapid, parallel synthesis and screening of hundreds of thousands of compounds.[1] However, the optimization of a specific library synthesis, which can involve numerous possibilities of reagents and reaction conditions can often be far more time consuming than carrying out the actual process of library synthesis itself.[2]

Traditionally, chemists have addressed the issue of optimizing a reaction by varying factors randomly or more logically in a sequential, parallel fashion, sometimes entitled the OVAT (one variable at a time) or the COST (changing one single factor at a time) approach. These techniques are limited in that consecutive, one-dimensional analyses do not completely utilize the full, multi-dimensional experimental domain and cannot efficiently account for interactions between factors.[3] For this reason various groups have reported the application of Design of Experiments (DoE) to optimize reactions.[4] This approach, which involves the systematic variation of variables over a series of experimental stages, aims to yield the maximum amount of information from the minimum number of experiments, in a rational, statistical fashion and various software packages have been designed to facilitate the use of this methodology in a wide range of applications.[5]

The use of polymer supported catalysts and reagents has been thoroughly reviewed[6] and their use often facilitates work-up and eradicates the need for time-consuming purification steps. The possibility of recycling can also appreciably reduce the cost and time of synthesizing, or purchasing expensive or synthetically challenging ligands.

In order to combine DoE with polymer supported catalysis a system, which has been shown to work effectively with scope for optimization was sought. Such a system would be required to be affected by several factors, which could be straightforwardly set at required levels, and would require facile attachment of the catalytic moiety onto a solid support. Soluble poly(ethyleneglycol) (PEG) supported sulfur-containing palladacycles, reported in 1999 by Bergbreiter et al. represent such a catalytic system,[7] which provide a range of ligands in which the sulfur pincer, the resin type and the incorporation of a spacer group between the resin and the catalytic moiety could be varied and readily prepared. In addition to these 'support' characteristics a variety of reaction conditions such as: solvent, type of base, equivalents of base and the incorporation of a tetraalkylammonium halide, phase transfer catalyst[8] were all open to optimization.

Keywords: Design; Polymer; Supported; Palladium.

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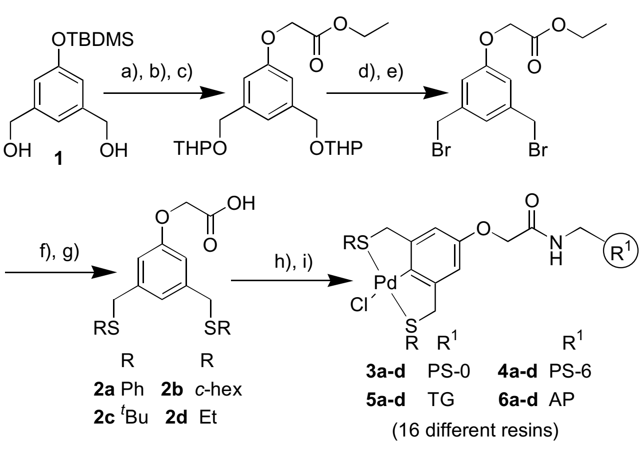
Bergbreiter has shown that tridentate, sulfur-containing palladacycles with a phenyl, thiol pincer group attached to PEG by an ether linkage were active catalysts in the Heck reaction of aryl iodides with alkene acceptors, although decomposition of the catalytic moiety was observed. Ligands attached via an amido linkage were also prepared, which also showed good activity in the Heck reaction, this time with no observable decomposition. Soluble counterparts of the PEG supported catalysts were however found to be ineffective in promoting the reaction with aryl bromides.

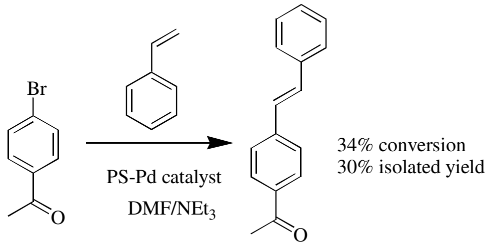
With this in mind, four different thiol pincer groups (phenyl, cyclohexyl, *t*-butyl and ethyl) attached to four different resins (polystyrene (PS-0), polystyrene with a six carbon chain spacer (PS-6), Tentagel (TG) and Argopore (AP)) were synthesized as shown in Scheme 1, from diol **1**, which was synthesized in three steps from 5-hydroxy-isophthalic acid as previously described by Van Veggel and co-workers.[9] Complexation with palladium was achieved by reaction with $Pd(MeCN)_2$ $(BF_4)_2$, formed in situ from palladium chloride and silver tetrafluoroborate.

Resin **3a** was used as the catalyst in the Heck reaction of bromoacetophenone with styrene in NEt_3/DMF, which initially proceeded with only 34% HPLC conversion with a large amount of observable palladium leaching (Scheme 2).

To seek an improvement of this reaction an extensive DoE investigation varying 6 factors at a total of 28 different levels, corresponding to 5760 different possibilities was undertaken (if each quantitative variable represented three levels). As such a large number of factors were to be studied, it was decided to carry out the optimization in three stages, two screening experiments and one optimization study with a smaller set of conditions.



Scheme 1. Synthesis of polymer supported palladacycles: (a) DHP, *p*-PTS, DCM, 2.5h, quant; (b) TBAF, THF, 18h, 76%; (c) $BrCH_2CO_2Et$, K_2CO_3, KI, MeCN, reflux, 6h, 68%; (d) i. *p*-ToSH, EtOH, rt, 18h, ii. Amberlyst A-15 EtOH, reflux, 18h, 67%; (e) i. MsCl, Et_3N, DCM, 0°C, 50min, ii. LiBr, acetone, reflux, 18h, 69%; (f) RSH, K_2CO_3, DMF, reflux, 18h, 82–100%; (g) LiOH, THF/H_2O (4/1), 2h, 82–95%; (h) resin, DIC, HOBt, DCM, o/n; (i) i. $Pd(MeCN)_2(BF_4)_2$, MeCN, reflux o/n, ii. brine, DCM, 30min.



Scheme 2. Heck reaction of 4-bromoacetophenone and styrene.

In addition to the thiol and resin type other factors shown in Table 1 were varied. Type of base was included as a qualitative factor and the levels selected were considered to encompass the range of strong, medium and weak inorganic, as well as soluble, bases.

Quantification of solvent is a major obstacle in DoE. For example, the most common descriptor is the dielectric constant, but often this is not sufficient, for example, two solvents with very different properties such as heptane and dioxane, have very similar values of 1.92 and 2.22, respectively. For this reason, in this study, an alternative approach where a large number of solvents were incorporated as qualitative factors was undertaken. This meant that model coefficients would not be associated with a ‘weighting value’ and predictions on the optimum solvent and base could be made with results in hand, post experiment rather than before. Equivalents of base and the incorporation of the phase transfer catalyst—tetrabutylammonium bromide—were also included as quantitative factors.

Solvents were selected by plotting the lipophilicity of 27 common laboratory solvents versus the dielectric constant using values reported by Musumarra and co-workers[10] and classing each according to the type of functional group. Ten were then selected encompassing all areas of the plot and functional group type (see supporting information).

The factors and response (conversion) were entered into the design wizard in MODDE 7.0,[5c,11] which generated a D-Optimal, screening design with a total of 40 experiments, including three replicated centre points. Reac-

Table 1. Factors to be varied in the first screening experiment

Factor	Type	Levels	
Resin	Qualitative	4	PS-0, PS-6, TG, AP
Thiol	Qualitative	4	Ethyl, *c*-hexyl, *t*-butyl, phenyl
Base	Qualitative	4	NaOH, Na_2CO_3, NaOAc, NEt_3
Solvent	Qualitative	10	Heptane, dibutyl ether, $CHCl_3$, ethyl acetate, 1,4-dioxane, 1-pentanol, 3-methyl-2-butanone, NMP, DMF, MeCN
Base eq	Quantitative		1 and 4
PTC[a] eq	Quantitative		0 and 2

[a] PTC = phase transfer catalyst.

tions were conducted in a Radleys Carousel with modified thinner tubes, in random order at 70 °C. A leaching assessment screen, which involved assigning a value according to the observable leaching, was also formulated. Results from this initial screening experiment (see supporting information for full table of results and coefficient overview plot) showed conversions after 24 h ranged from 1% to 94% and a wide range of leaching was observed. MODDE fitted a model to the data, which gave an R^2 of 0.83 and 0.82 for conversion and leaching, respectively. The normal effect plots for both responses are shown in Figure 1, which indicate that the most positive significant factor on conversion was the use of DMF, however this corresponded to the second largest negative effect on leaching. NaOH as base gave the worst response, with high levels of leaching.

Contour plots (see supporting information) indicated that the presence of a phase transfer catalyst (PTC) had a positive effect on the conversion but no effect on leaching. In contrast the equivalents of base had no effect on conversion but led to increased leaching.

Although minor, the effect of the thiol pincer group showed that the electron rich, bulky *c*-hexyl and *t*-butyl thiols gave better conversions than their smaller, ethyl counterparts, with the lowest levels of leaching observed for the *c*-hexyl moiety. Finally Argopore and Tentagel supported catalysts gave higher conversions than those immobilized on polystyrene however, these also gave the highest levels of leaching. PS-6 gave the least leaching but also the lowest conversion response.

For the second screening experiment it was decided to retain all levels of thiol pincer group and resin but PS-6 was excluded as it had the worst effect on conversion. As it had no effect on the conversion but a negative effect on leaching the equivalents of base was fixed at 1. Analysis of the results from the first screening experiment indicated that the presence of the phase transfer catalyst had a positive effect on the conversion although for this experiment the levels had been set at 0 and 2 therefore, except for in the case of the centre points, it had been used in excess (2 equiv). It was deemed desirable to investigate the use of this material at lower levels and for the second screening stage this factor was set at levels of 0.1 and 2.

By considering the solvent as a qualitative factor it had been hoped that correlations between the model coefficients and their physio-chemical properties could be established in order that predictions for the desirable parameters could be made. Unfortunately no such relationships could be detected although some conclusions could be drawn including; the reaction proceeded in a wide range of solvents with different functionalities, except for $CHCl_3$, the only chlorinated solvent. The worst leaching was observed for nitrogen-containing solvents with high dielectric constants.

For the second screening stage it was decided to select 5 out of the initial 10 solvents; chloroform, pentanol, ethyl acetate and MeCN were disregarded because of their negative effect on conversion. DMF was retained because of its positive effect on conversion although NMP was omitted because it was considered similar to DMF.

Heptane, dibutyl ether, methyl-butanone, dioxane and DMF were therefore selected as the five solvents for further investigation. The factors and their levels for the second screening experiment are summarized in Table 2.

Again the factors and responses were entered into MODDE, which generated 28 necessary experiments to fulfil the design criteria. The experiments were carried out in blocks of 12, again in random order, (see supporting

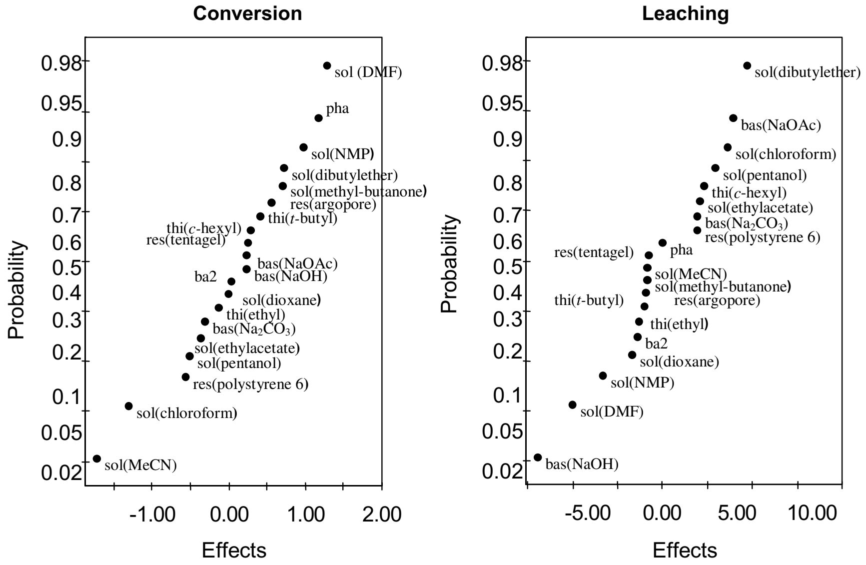


Figure 1. Normal effect plot for the first screening experiment (res = resin, sol = solvent, bas = base, pha = equivalents of phase transfer catalyst, ba2 = equivalents of base).

Table 2. Factors varied in the second screening experiment

Factor	Type	Levels	
Resin	Qualitative	4	PS-0, TG, AP
Thiol	Qualitative	4	Ethyl, *c*-hexyl, *t*-butyl, phenyl
Base	Qualitative	4	NaOAc and NEt_3
Solvent	Qualitative	10	Heptane, dibutyl ether, 1,4-dioxane, 3-methyl-2-butanone, DMF
PTC (eq)	Quantitative		0 and 2

information for results and coefficient overview plot). A model was fitted, with an R^2 of 0.79 and 0.82 for conversion and leaching, respectively (Fig. 2).

For this experiment, the most significant positive effect on conversion was the use of a phase transfer catalyst, closely followed by the use of the cyclohexyl thiol pincer group. The most significant, positive effect on leaching was the use of heptane as solvent followed by the use of dioxane. Of the three resins the only positive response for conversion was for polystyrene, Tentagel gave a positive effect on leaching. With regard to the four thiols only cyclohexyl and ethyl had positive effects, on conversion and leaching, respectively, the others showed negative effects. Interestingly the phenyl pincer, which is the most commonly used had the most negative effect on both responses.

Due to the higher number of experiments required, for response surface designs it is desirable to minimize the number of factors and their levels. It was thus decided, for the final experimental phase to vary three factors at two levels.

From the results of the second screening experiment it was clear that the quantity of the phase transfer catalyst had to be further investigated. It was decided to fix the resin as polystyrene as this gave the most positive effect on conversion (pleasing as this resin is considerably less expensive and has a superior loading to the other two). It was also decided to fix the use of NaOAc as base as this had the most positive effect on both responses. Thus the other two factors varied were solvent and thiol and two levels for each were then decided upon, these were cyclohexyl and *t*-butyl due their positive effect on conversion. With regard to solvent, dioxane and heptane were retained as these had positive effects on conversion.

The factors investigated in the response surface modeling experiment are shown in Table 3. This gave 16 experiments to fulfil the design criterion, in these experiments no leaching assessment was undertaken as almost none was observed. This time the R^2 for the model was 0.81 (Table 4).

The normalized coefficient plot for these results is shown in Figure 3, which shows that the *c*-hexyl thiol pincer group and the use of dioxane as solvent gave superior conversions while the reaction showed curvature with regard to phase transfer catalyst that is it had a quadratic dependence and conversion peaked at intermediate levels. The normalized coefficient plot also shows that the effect of the phase transfer catalyst depended on the solvent, in that increased levels caused conversion levels to increase more with heptane than with dioxane.

From the optimization experiments it was clear that the best conditions were with the cyclohexyl thiol pincer lig-

Table 3. Factors varied in the response surface modeling experiment

Factor	Type	Levels	
Thiol	Qualitative	+1	*c*-Hexyl
		−1	*t*-Butyl
PTC	Quantitative	+1	1
		−1	0.1
Solvent	Qualitative	+1	Dioxane
		−1	Heptane

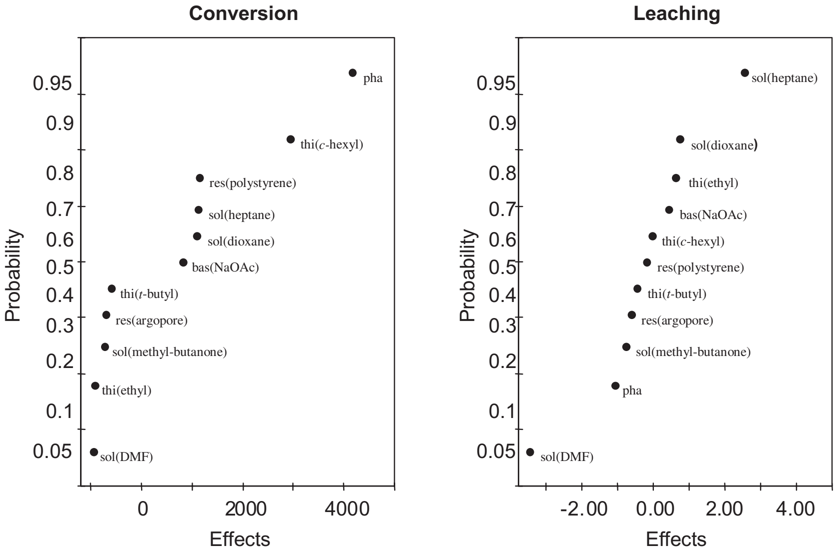


Figure 2. Normal effects plot for the second screening experiment.

Table 4.

Run	Thiol	PTC eq[a]	Solvent	Conversion (%)
1	*c*-Hexyl	0.55	Heptane	76
2	*c*-Hexyl	0.55	Heptane	70
3	*c*-Hexyl	0.1	Dioxane	61
4	*t*-Butyl	1	Heptane	69
5	*c*-Hexyl	0.1	Heptane	50
6	*c*-Hexyl	0.55	Dioxane	91
7	*t*-Butyl	0.55	Dioxane	85
8	*c*-Hexyl	1	Dioxane	73
9	*c*-Hexyl	1	Heptane	85
10	*t*-Butyl	0.55	Heptane	79
11	*c*-Hexyl	0.55	Heptane	69
12	*t*-Butyl	1	Dioxane	48
13	*c*-Hexyl	0.1	Dioxane	42
14	*c*-Hexyl	0.55	Heptane	88
15	*t*-Butyl	0.1	Dioxane	25
16	*t*-Butyl	0.1	Heptane	7

[a] PTC = phase transfer catalyst.

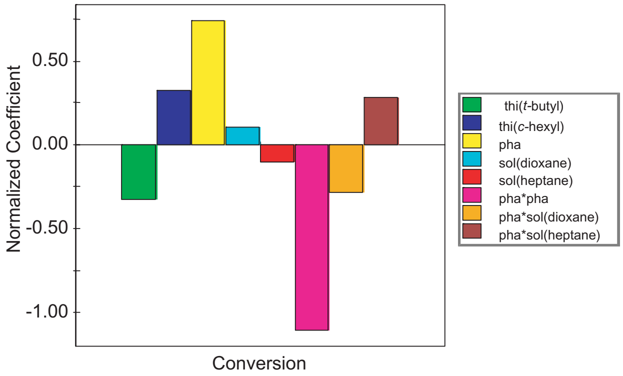


Figure 3. Normalized coefficient plot for the optimization experiment.

and in dioxane. MODDE predicted the optimum equivalents of phase transfer catalyst to be 0.65 and under these conditions the predicted yield was 89%.

The reaction was repeated three times under the following conditions: resin—polystyrene 0; thiol—*c*-hexyl; base—NaOAc; equivalents of base—1, equivalents of phase transfer catalyst 0.65 and solvent—dioxane. Yields obtained were 87%, 88% and 91% with no observable leaching.

In conclusion, an extensive DoE investigation varying 6 factors at a total of 28 different levels, corresponding to 5760 different possibilities, resulted in the Heck reaction of 4-bromoacetophenone with styrene being improved from 34% conversion in a DMF/NEt_3 system with large observable leaching of catalyst to 88% with no observable leaching in a dioxane/NaOAc system. Although overall fairly insignificant the choice of resin was polystyrene and the incorporation of the cyclohexyl thiol pincer group proved far superior to the phenyl counterpart, the reaction showed a quadratic dependence concerning the level of phase transfer catalyst. Consideration of the factors using this approach not only afforded substantially improved conditions but also led to an overall, greater understanding of the reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.016.

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