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Optimization of variables for screening solid-supported metal complexes as oxidation catalysts

Amarnath Natarajan and Jose S. Madalengoitia*

Department of Chemistry, University of Vermont, Burlington, VT 05405, USA

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Abstract

Evaluation of polymer-supported metal complexes as oxidation catalysts revealed that product distribution is not dependent on metal stoichiometry, or resin but is dependent on the oxidant, oxidant stoichiometry and the metal incubation times. The model systems investigated under the optimized conditions afforded highly reproducible results, indicating that this methodology can be used to reliably screen libraries of metal complexes.

Keywords: supported reagents/reactions.

Since the introduction of combinatorial chemistry as a tool for the generation and identification of lead compounds, the use of molecular diversity techniques in the discovery and optimization of novel catalysts has held much interest. Accordingly, a number of reports on combinatorial catalysis have appeared in the literature.[1–5] We were particularly intrigued in the synthesis of peptide libraries as ligands for redox active metals. In discovering new systems for catalysis using combinatorial chemistry we envisioned a two-step process: (1) optimization of conditions to establish a highly reproducible screening method; and (2) library evaluation using the established methodology. In this first paper we address the first step: how experimental variables affect the reliability of an 'on bead assay'. Specifically, we explore the effects of metal incubation time, metal/ligand stoichiometry, and substrate/oxidant stoichiometry on oxidation reactions using four model ligands **1**, **2**, **3** and **4** (Fig. 1).

Ligands **1**, **2**, **3** and **4** were synthesized on aminomethyl polystyrene (AMP) resin using Fmoc chemistry and standard peptide coupling conditions.[6–10] The first objective was to identify an active catalyst system which could then be used to optimize reaction conditions. To this end, a small library was generated by incubating ligands **1** and **2** with different metal salts ($Fe(ClO_4)_3{\cdot}6H_2O$, $RuCl_3{\cdot}H_2O$, $Ni(OAc)_2{\cdot}4H_2O$, $CoCl_2{\cdot}6H_2O$, $Mn(OAc)_2$ and $Mn(OAc)_3{\cdot}6H_2O$) in degassed DMF under N_2 for 1 h. The resin-bound metal complexes were then assayed for their ability to catalyze

* Corresponding author.

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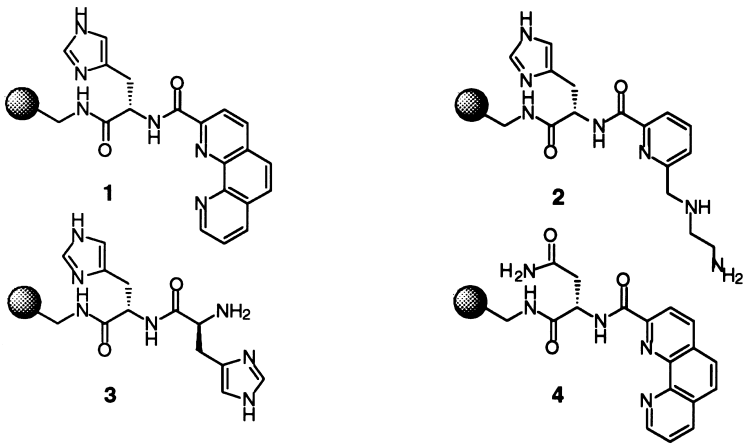


Figure 1. Ligand structures synthesized on polystyrene support (0.5 mmol/g loading, 100–200 mesh particle size)

the oxidation of *cis*-stilbene (300 equiv.) with *t*-BHP (100 equiv.) in degassed CH_2Cl_2 at rt for 5 h. Results from these experiments are summarized in Fig. 2. The turnover number for these complexes was not particularly impressive, however, the study indicated that the Ru complex with ligands **1** and **2** afforded significantly higher amounts of *cis*-epoxide than either the other metal complexes or the control (PhIO/*cis*-stilbene). Although this study identified rutheniun as a potentially active metal for these systems we did not pursue the use of *t*-BHP as an oxidant because the observed gas evolution (most likely O_2) and the formation of *trans*-stilbeneoxide suggested radical processes.

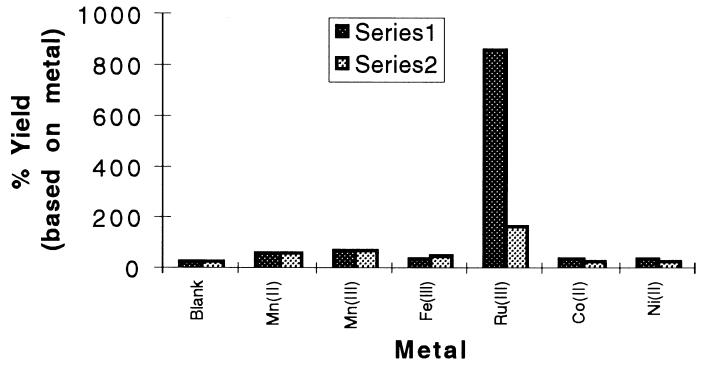


Figure 2. Evaluation of ligands **1** and **2** with metal salts [$Fe(ClO_4)_3{\cdot}6H_2O$, $RuCl_3{\cdot}H_2O$, $Ni(OAc)_2{\cdot}4H_2O$, $CoCl_2{\cdot}6H_2O$, $Mn(OAc)_2$ and $Mn(OAc)_3{\cdot}6H_2O$]

Identification of ruthenium as an active metal allowed us to optimize the time dependence of metal complexation (Fig. 3). In this series of experiments, ligand **3** was incubated with $RuCl_3{\cdot}H_2O$ in degassed DMF under N_2 over different times. The resin bound material was then assayed for its ability to catalyze the oxidation of *cis*-stillbene with iodosobenzene (oxidant) in degassed CH_2Cl_2 at rt for 48 h. The results from these experiments are summarized in Fig. 2. This study showed that *cis*-stilbene was not completely consumed with catalyst generated from less than a 24 h metal incubation. Likewise, the amounts of *cis*-stilbeneoxide and benzaldehyde products

increases and plateaus between 24 and 72 h. Interestingly, the amount of *trans*-stilbeneoxide formation goes from ~19% to background level when the metal incubation time is increased from 1 h to 72 h. These data suggest that with a 1 h incubation not only is there little metal complexation but also the complex(es) formed have not fully equilibrated and might represent weakly bound metal. Clearly Ru(III) complexation will be slower than other metals because Ru(III) has a slow ligand exchange rate; however, these results indicate that longer incubation times should minimize missing potentially active complexes.

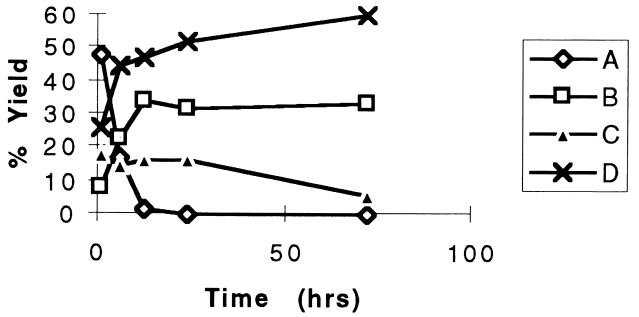
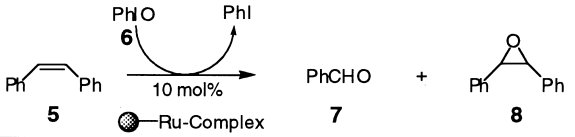


Figure 3. Evaluation of ligand **3** at different metal complexation times. A = recovered *cis*-stillbene; B = *cis*-stillbeneoxide; C = *trans*-stilbeneoxide; D = benzaldehyde

We then studied if the metal to ligand stoichiometry has an effect on the product distribution. This could arise if, for example, different complexes (with differential reactivity) were formed from alternate metal/ligand (M/L) ratios. The ligands were then incubated with 1, 0.5 and 1.5 equiv. of $RuCl_3 \cdot H_2O$ in degassed DMF under N_2 for 3 days. The complexes were then assayed for their ability to catalyze the oxidation of *cis*-stillbene with PhIO in degassed CH_2Cl_2 at rt for 48 h. Table 1 summarizes the results from these experiments. Entries 1–3 (Table 1), in which resin-bound ligand is incubated with variable amounts of Ru, exhibit essentially the same product distribution (~2:1 oxidative cleavage/epoxidation). These data are indicative that irrespective of the M/L stoichiometry, a unique ruthenium complex is formed which gives rise to a unique product distribution. This information illustrates that the results of a high throughput screen will not be subject to small errors in ligand weighting or metal delivery.

We next turned our attention to the effects of the oxidant/substrate ratio on product distribution. Entries 4–6 (Table 1) show the results from experiments in which the quantity of iodosobenzene is varied. Interestingly, the product distribution is sensitive to the amount of PhIO. At a lower loading of PhIO, epoxide formation is favored (entry 4) while at a higher loading, oxidative cleavage is favored (entry 6). The substrate is completely consumed at a 4:1 oxidant/substrate ratio. These results indicate that to obtain the most consistent results in a high throughput screen, the catalyst evaluation is best performed at a high PhIO loading. We next investigated if the reaction performed at a low PhIO loading could be driven to completion by addition of PhIO aliquots at 12 h intervals. Entry 7 now shows that indeed the reaction may be driven to completion by addition of PhIO portions and that epoxide formation is favored by the addition of PhIO in small amounts (60%). The isolated yield (entry 8) is consistent with the product distribution obtained by NMR and validates the observed results. Evaluation of the Ru-complex formed with ligand **4** reveals that this complex now strongly favors oxidative cleavage affording an 87% yield

Table 1
Evaluation of ruthenium complexes as heterogeneous catalysts



Entry	Ligand	M/L	6/5	% Yield[c] 7	8
1	**3**	1.0	4	57	34
2	**3**	0.5	4	58	34
3	**3**	1.5	4	61	31
4	**3**	1	1	11	14
5	**3**	1	2	44	33
6	**3**	1	3	59	32
7	**3**	1	4[a]	33	60
8	**3**	1	4[a]	25[b]	55[b]
9	**4**	1	4	87	9
10	**4**	1	4[a]	64	31
11	**4**	1	4[a]	51[b]	27[b]

[a] 10 eq. PhIO was added every 12 h. [b] Isolated yields. M/L = $RuCl_3 \bullet H_2O$/ligand. [c] Yields were determined by NMR using N,N-dimethylacetamide as an internal standard.

of benzaldehyde and a 9% yield of epoxide. Since another complex exhibits a different product profile the oxidation is not due to some non-specific effect.

We next investigated different solid supports. Ligand **3** was synthesized on four different resins (ClTrt, Wang, AMP, MBHA). Metal complexation and complex evaluation was carried out with the optimized conditions. Results from these studies are summarized in Table 2. Examination of the data indicates that the epoxide yield is essentially not affected by the steric crowding around the linking site. Furthermore, upon treatment of the AMP resin–$RuCl_3$ complex (Entry 5) 1% TFA/CH_2Cl_2 (ClTrt resin cleavage conditions) the catalytic activity of the complex remained unaffected. This experiment shows that after identification of an active metal complex in a high throughput screen, the complex may be synthesized on ClTrt resin and liberated under conditions that do not affect the catalytic activity of the complex.

Table 2
Effect of solid support on product distribution

Entry	resin bound Ru-**3**	% Yield[a] *cis*-stilbeneoxide	benzaldehyde
1	AMP	33	44
2	Wang	30	47
3	ClTrt	29	61
4	MBHA	30	57
5	AMP[b]	32	52

[a] %yield based on both *cis*-stilbeneoxide and benzaldehyde. [b]Resin bound ruthenium complex was treated with 1% TFA prior to assay.

In conclusion, we have investigated the potential sources of error in evaluating peptide-derived metal complexes as oxidation catalysts. Our results indicate that at least in the systems investigated, catalyst evaluation is not dependent on metal stoichiometry, or resin but is dependent on the oxidant, oxidant stoichiometry and metal incubation time. Finally, it should be noted that our

results are reproducible within ±5% of the values reported, thus indicating that this method of catalyst evaluation should not miss potentially active catalysts or give rise to false-positives. The following paper describes the results of evaluating a small combinatorial library using the methods described.

General procedure for the synthesis and evaluation of the Ru complexes: Resin bound ligand (0.1 g, 0.05 mL) was placed in a reaction vial equipped with a fritted stopcock. Resin swelling (DMF) was followed addition of $RuCl_3 \cdot H_2O$ (0.02 M in DMF) and agitation under N_2 for 48 h. The polymer-supported Ru complexes were isolated via filtration. The resulting resin was rinsed with 9:1 DMF:CH_2Cl_2 (3×5 min). The final rinsing solutions were colorless. Evaluation: resin-bound complex (10 mg, 5 μmol), PhIO (0.2 mmol), and *cis*-stilbene (1 mL 0.05 M in CH_2Cl_2) in CH_2Cl_2 were stirred for 48 h. An aliquot of the resulting solution was evaporated by blowing N_2 over the sample. Conversion and yield were determined by NMR.

Acknowledgements

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