Using Intelligent/Random Library Screening To Design Focused Libraries for the Optimization of Homogeneous Catalysts: Ullmann Ether Formation

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Abstract: A 96-member "pyridine" library consisting of both rationally chosen and "random" members was used to screen Ullmann ether forming reactions. The reaction of 2-bromo-4,6-dimethylaniline and other substrates with a variety of alkoxides was investigated under different conditions with the aid of an automated liquid handler. From the results of the 96-member library screening, a structure activity profile was determined which led to the design of smaller "focused" ligand libraries. The focused libraries produced a higher frequency of hits compared to the original 96-member library. Some of the more effective ligands discovered in this work were found to be generally useful for alkoxylation of a variety of substrates, and also functioned in intramolecular ether forming reactions. This work demonstrates for homogeneous catalysis the analogy to the pharmacological model of drug discovery. By using a large library to screen for a lead compound followed by screening the diversity space closest to the lead, a larger fraction of increased performance ligands was discovered.

Introduction

Combinatorial chemistry is now routinely used for lead discovery in pharmaceutical and agrochemical companies.[1] Combinatorial chemistry techniques have more recently been applied for the discovery of materials[2] and catalysts.[3−7] For catalysis, the strategy usually relies on optimization of reaction conditions using different temperatures, pressures, additives, ligands, and/or metal ions. Most of the ligand synthesis effort to date has focused on the use of polymer-bound ligands.[6] Borrowing from the early work directed at pharmaceutical discovery, ligand libraries have been derived from building blocks of amino acids with a few notable exceptions.[5,6j,n] In some catalyst studies, the libraries were biased with cases that were already known to work well to demonstrate principle.

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With the goal of discovering the best catalyst for an Ullmann alkoxylation reaction, we used a strategy that parallels enzyme inhibitor optimization. To our knowledge, this approach has not yet been reported to be successful for the *discovery and optimization* of homogeneous catalysts. Our strategy was to screen a parent set of ligands that were designed to contain both rationally and randomly chosen members. After screening this library and discovering successful hits, smaller focused libraries were created based on ligand structure−activity relationships. These daughter libraries were screened, and resulted in a higher "hit frequency" than the parent library. This method of screening an intelligent/random parent library followed by focused libraries was demonstrated to be a fast and logical approach for optimization of the ligand component of the catalytic Ullmann reactions studied here.

The discovery of the best *heterogeneous* catalyst for a reaction by combinatorial methods is fraught with difficulties and renders the process of rational library design challenging. Library catalyst synthesis, history, characterization, and reproducible performance are important and sometimes difficult to control experimental parameters.[8] However, for homogeneous catalysts that combine a ligand and a metal, the factors that control catalyst performance at the molecular level are better defined and easier to incorporate when creating a ligand library. We felt that the design of a ligand library for homogeneous catalysis need not be as random or exhaustive in parameter space as the heterogeneous catalyst case. Incorporating molecular parameters important to most homogeneous catalyst functions was a natural way to cover ligand diversity space as completely as possible with a relatively small parent library.[9] For our particular study, we considered the following as important parameters to vary when preparing the "intelligent" portion of the parent library: (1) electron-donating and -withdrawing abilities of the ligands (σ and π); (2) sterics around the donating atom on the ligands;[10] (3) monodentate or multidentate donation, (4) for multidentate ligands, ligand bite angles;[11] and (5) second coordination sphere effects (molecular recognition potential).[12] Taking these parameters into account, we attempted to maximize the chance of discovering the best ligand with a minimum set. Although the bulk of the library members were chosen with these parameters in mind, we also took the opportunity for serendipity by incorporating ligands that were not expected to work for any particular reason. By a combination of intelligent and random experimentation, we hoped to attain our goal of finding the best "pyridine-containing" ligands for the Ullmann reactions in this study. Having found these lead ligands, we then would prepare and screen a focused library whose members contained structural elements resembling the discovered lead compounds.

We selected the Ullmann ether forming reaction because it constitutes a practical approach to form aryl ethers, a structure common to many agrochemical and pharmaceutical lead compounds. These reactions couple aryl halides and alkoxides and are usually carried out using Cu(I) or Cu(II) salts in the presence of ligands (or a solvent that can serve as a ligand). Recent advances have been made for certain types of Ullman reactions,[13−17] and novel Pd-based catalytic systems have been shown to be efficient at carrying out C−O and other C−X bond forming reactions.[18] General trends indicate that electron-deficient aryl halides typically work best in Ullmann chemistry, but yields and/or rates can rapidly decrease with increasing electron density on the aromatic ring, increasing steric bulk, or the presence of deleterious unprotected functionality. An additional problem especially encountered in the methoxylation reaction of haloarenes is the formation of the reduced arene byproduct; one of our goals was to minimize this side reaction. In general, the detailed mechanistic steps of copper-catalyzed Ullmann reactions are poorly understood and dependent on many variables; this is exactly the type of experimental situation where combinatorial methods are best suited.

Copper(I)-catalyzed C−O bond-forming reactions have been reported in the presence of pyridine-type ligands.[14,16c] Numerous pyridine-containing compounds are commercially available and

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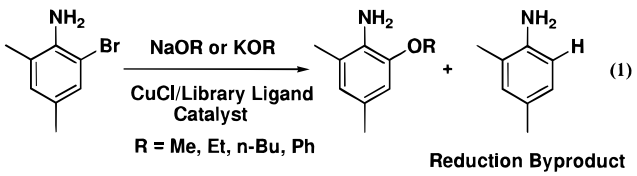
Table 1. Parent Ligand Library of Pyridine and Pyridine-like Ligands

no.	ligand	no.	ligand	no.	ligand
1	pyridine	33	nicotine	65	2,6-lutidine-α-2,3-diol
2	2-picoline	34	1-(2-pyridyl) piperazine	66	2,6-pyridinedimethanol
3	2-aminopyridine	35	ethyl 2-pyridyl acetate	67	2-quinolinol
4	2-hydroxypyridine	36	2-benzylpyridine	68	2-quinolinethiol
5	3-cyanopyridine	37	2-anilinopyridine	69	2,3-pyridine dicarboxylic acid
6	4-cyanopyridine	38	4-chloroquinaldine	70	2,6-pyridine dicarboxylic acid
7	2,4-lutidine	39	2-(2-diethylaminoethyl)pyridine	71	3,5-pyridine dicarboxylic acid
8	2,6-lutidine	40	4-(2-diethylaminoethyl)pyridine	72	quinoline−4-carboxylic acid
9	2-ethylpyridine	41	7,8-benzoquinoline	73	8-hydroxy-5-nitroquinoline
10	2-amino-6-methylpyridine	42	phenanthridine	74	isoquinoline−3-carboxylic acid hydrate
11	2-(aminomethyl)pyridine	43	acridine	75	9-aminoacridine
12	2-(hydroxymethyl)pyridine	44	1,10-phenanthroline	76	proflavine
13	2-hydroxy-6-methylpyridine	45	4-benzoylpyridine	77	4-(2-pyridylazo) resorcinol
14	2,4,6-collidine	46	di-2-pyridyl ketone	78	1,2-dihydro-1-(2-(2-pyridyl)-ethyl)-3,6-pyridazinedione
15	picolinamide	47	4,4′-dimethyl-2,2′-dipyridyl	79	5-nitroquinaldic acid
16	2-dimethylaminopyridine	48	6,6′-bi-2-picoline	80	5-nitro-1,10-phenanthroline
17	4-dimethylaminopyridine	49	8-acetoxyquinoline	81	9-hydroxy-4-methoxyacridine
18	2-(2-hydroxyethyl)pyridine	50	2-methyl-8-nitroquinoline	82	4-chloro-7-(trifluoromethyl) quinoline
19	quinoline	51	2,6-di-*tert*-butyl pyridine	83	8-hydroxyquinoline−5-sulfonic acid monohydrate
20	isoquinoline	52	1,3-di(4-pyridyl)propane	84	2,3-di-3-pyridyl-2,3-butanediol
21	1,4,5-triazanaphthalene	53	2-phenylquinoline	85	2-phenyl-4-quinoline carboxylic acid
22	4-tert-butylpyridine	54	neocuproine	86	acridine orange
23	3-acetoxypyridine	55	2,2′-pyridil	87	cinchonidine
24	3-pyridinepropanol	56	2,2′:6′,2″-terpyridine	88	quinine
25	quinaldine	57	(S,S)−2,6-bis(4-isopropyl-2-oxazolin-2-yl) pyridine	89	bathophenanthroline
26	8-hydroxyquinoline	58	3-hydroxypyridine	90	spiramycin
27	ethylpicolinate	59	2-mercaptopyridine	91	2,4-dihydroxy quinoline monosodium salt
28	ethylisonicotinate	60	isonicotinamide	92	8-ethoxyquinoline-5-sulfonic acid sodium salt
29	2-phenylpyridine	61	picolinic acid	93	bicinchonic acid sodium salt (bca)
30	4-phenylpyridine	62	2-(2-methylaminoethyl) pyridine	94	1-(4-pyridyl) pyridinium chloride
31	2,2′-dipyridyl	63	3-hydroxy picolinamide	95	2-pyridylacetic acid hydrochloride
32	2-(2-thienyl)pyridine	64	3-hydroxypicolinic acid	96	8-mercaptoquinoline hydrochloride

constitute a set of ligands that can be sterically and electronically varied. We thus set out to screen pyridine and pyridine-like compounds to find the best ligand for copper to produce the highest yield with the least amount of reduction byproduct. The particular reactions chosen for study were alkoxylations of 2-bromo-4,6-dimethylaniline because these were related to a problem of practical interest to Dupont. This substrate was also readily synthesized, and presented a somewhat challenging case being an electron-rich, unprotected aniline that might react sluggishly under typical Ullmann conditions (eq 1).



(1)

Experimental Section

All reactions were prepared and performed under an atmosphere of nitrogen. The compounds in the ligand libraries were obtained from commercial sources, and were purified by distillation, sublimation, or recrystallization; the compounds were stored under nitrogen before use. Solvents were distilled from drying agents under nitrogen using standard procedures: methanol from magnesium turnings; benzotrifluoride and acetonitrile from P_2O_5; tetrahydrofuran (THF), dimethoxyethane (DME), diglyme, and toluene from sodium benzophenone ketyl; dimethylformamide (DMF) from calcium hydride; and dimethylacetamide (DMAc) from barium oxide. Copper(I) chloride was purified according to the literature.[19] A slight modification of the literature procedure was used to synthesize 2-bromo-4,6-dimethylaniline:[20] it was further purified by vacuum distillation to remove dark impurities. The compound 3-(2-bromophenyl)-1-propanol was synthesized according to the literature.[21]

Solutions of the ligands were prepared with the aid of a Bohdan automated workstation with liquid handling capability and which was modified to operate under a dinitrogen atmosphere. The 96 ligands were prepared as either benzotrifluoride (ligands 1−57) or methanol (ligands 58−96) solutions (0.0200 M) and are listed in Table 1. These solutions were prepared in glass vials capped with Teflon-lined silicone septa to maintain inert atmosphere and prevent evaporation. Care was taken to replace the pierced septa after robotic runs to minimize the amount of evaporation; the vials were stored in a nitrogen atmosphere to ensure the integrity of the ligand solutions between runs.

Preparation of catalyst solutions was performed on the Bohdan automated work station. In a typical automated procedure, each sample was prepared by adding 150(±3) μL of a CuCl solution (0.0200 M in CH_3CN) and 150(±3) μL of a ligand solution (0.0200 M in benzotrifluoride or MeOH) to a septa sealed 2 mL glass vial in a rack. The solvents were then removed simultaneously from all vials in the rack by purging with nitrogen gas streams. After briefly drying the rack of vials in a vacuum chamber (ca. 5 min) the vials were mounted back on the Bohdan automated liquid handler for addition of the remaining reagents. First, 150(±3) μL of a solution of 2-bromo-4,6-dimethylaniline and biphenyl (0.400 and 0.00125 M in diglyme, respectively) were added in sequence into each vial. Finally, 150(±3) μL of potassium phenoxide (0.600 M in diglyme) or sodium methoxide (0.600 M in methanol) was added in sequence to each vial. Depending on the

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experiment, the septa on the 2 mL vials containing the reaction solutions were either replaced with fresh septa, or the pierced septa were left on to allow for faster evaporation if desirable as in the case of methanol. The vials were placed in an orbital shaker/metal block heater. The block had a sealing cover allowing the vials to be maintained under an inert dinitrogen atmosphere during the reaction run. The block was heated to the desired temperature (typically 100 °C), which was accurate to ±1 °C across the entire block. At the end of the run, each reaction solution was diluted with 0.8 mL of toluene and was analyzed by gas chromatography (HP6890 with auto sampler and a 5 m × 0.53 mm HP-1 capillary column). Response factors were calculated and yields were derived. Variations on this basic procedure were carried out to test the effects of ligand-to-copper ratio, solvent variation, etc.

Large-Scale Synthesis of 2-Phenoxy-4,6-Dimethylaniline. To a 100-mL sidearmed flask was charged under nitrogen in succession 6.0 g (30 mmol) of 2-bromo-4,6-dimethylaniline (distilled), 15 mL of diglyme (freshly opened bottle, anhydrous), 165 mg (1.68 mmol) of CuCl (freshly opened bottle), 210 mg (1.45 mmol) of 8-hydroxyquinoline, and 4.6 g (35 mmol) of freshly prepared potassium phenoxide (from KOt-Bu/phenol/MeOH, stripped at reduced pressure and dried in vacuo) and the mixture was heated at 90−95 °C for 16 h. The conversion by GC area % was 91.3%, with 82.7% product and 8.7% 2,4-dimethylaniline. Another 1.0 g (7.5 mmol) of KOPh was added and heating was continued for 8 h, at which time GC-analysis showed 88.9 area % product, 3.1% bromide, and 7.6% 2,4-dimethylaniline. The mixture was cooled to ambient temperature, 20 mL of 3% aqueous NH_4OH was added, and the mixture was extracted with 100 mL of hexanes. The organic layer was washed with 3% aqueous NH_4OH, then with water, decanted from tarry impurities, dried ($MgSO_4$), filtered, and concentrated to dryness to afford 5.6 g of crude product which was purified by chromatography on silica gel, eluting with hexanes to obtain 4.4 g (69%) of product which was >99 area % purity by GC-analysis, mp 55−56 °C. ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 6H), 3.60 (br s, 2H), 6.57 (d, 1H, J = 1 Hz), 6.70 (d, 1H, J = 1 Hz), 7.0 (m, 3 H), 7.3 (m, 2H). Elemental Anal. (Calcd) for $C_{14}H_{15}NO$: C, 78.59 (78.84); H, 7.48 (7.09); N, 6.56 (6.57).

Large-Scale Synthesis of 2-Methoxy-4,6-dimethylaniline. A 250-mL sidearmed flask containing 10.0 g (50.0 mmol) of distilled 2-bromo-4,6-dimethylaniline in 15 mL of diglyme was flushed with nitrogen and charged with 0.20 g (0.21 mmol) of 2-aminopyidine, 0.25 g (0.25 mmol) of cuprous chloride, and after 5 min, 16 mL (74 mmol) of 25% methanolic sodium methoxide. The mixture was heated under nitrogen for 24 h at reflux (85 °C), at which time GC-analysis indicated 94% conversion with about 2% hydrodebromination. The mixture was cooled to ambient temperature, diluted with water, and extracted with cyclohexane. The organic layer was concentrated on a rotary evaporator, diluted with hexanes, and washed with water to remove residual diglyme. The hexane was removed on the rotovap, and the crude air-sensitive product (6.9 g, 92%) was purified via the hydrochloride salt as follows. A solution of HCl in ether (50 mL of a 1 M solution) was added dropwise to a solution of the crude product in 20 mL of ether, and the precipitated salt (8.4 g, 94% pure by GC, corrected yield is 84%) was filtered. Tarry impurities were removed by recrystallization from 2-propanol to afford 4.9 g (52% yield) of 98%-pure product, sublimation at 243−246 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H), 2.34 (s, 3H), 3.85 (s, 3H), 6.64 (br s, 1H), 6.86 (br s, 1H), 9.9 (br s, 2H). Elemental Anal. (Calcd) for $C_9H_{14}ClNO$: C, 57.34 (57.60); H, 7.49 (7.52); N, 7.43 (7.46).

Synthesis of 2,3-dihydrobenzofuran. A 50-mL round-bottomed flask was charged sequentially with 18 mg of Cuprous chloride (0.18 mmol), 18 mg of 2-aminopyridine (0.19 mmol), 730 mg of 2-bromophenethyl alcohol (3.63 mmol), and diglyme (20 mL). Then sodium methoxide (300 mg, 5.55 mmol) was added as a solid. The solution was heated to 100 °C with stirring and kept there for 20 h. A sample was taken and GC indicated complete conversion. Once cooled to ambient temperature, the solution was quenched with 2 N HCl (40 mL) and the product was extracted with 3 × 20 mL hexane. The organic layer was washed with 3 × 20 mL of H_2O and the solvent removed. The product was further purified by preparative TLC (ethyl acetate/hexane, 5:95). The isolated yield is 184 mg (42%). The spectroscopic data fit with a sample obtained from Aldrich. ^{1}H NMR (300 MHz, 23 °C, $CDCl_3$): δ 7.4−6.7 (m, 4H, Ar), 4.57 (t, J = 9 Hz, 2H, CH_2O), 3.22 (t, J = 9 Hz, 2H, CH_2Ar). ^{13}C NMR (125 MHz, 23 °C, $CDCl_3$): δ 159.5 (s, quaternary C), 127.4 (s, ArCH), 126.3 (s, quaternary C), 124.3 (s, ArCH), 119.7 (s, ArCH), 108.8 (s, ArCH), 70.4 (s, CH_2O), 29.2 (CH_2Ar).

Synthesis of Chroman. A 50-mL round-bottomed flask was charged sequentially with 6 mg of Cuprous chloride (0.06 mmol), 8 mg of 2-aminopyridine (0.08 mmol), 268 mg of 3-(2-bromophenyl)-1-propanol (1.25 mmol), and diglyme (10 mL). Then sodium methoxide (100 mg, 1.85 mmol) was added as a solid. The solution was heated to 100 °C with stirring and kept there for 20 h. A sample was taken and GC indicated complete conversion. Once cooled to ambient temperature, the solution was quenched with 2 N HCl (40 mL) and the product was extracted with 3 × 20 mL of hexane. The organic layer was washed with 3 × 20 mL of H_2O and the solvent removed. The product was further purified by preparative TLC (ethyl acetate/hexane, 5:95). The isolated yield is 119 mg (71%). ^{1}H NMR (300 MHz, 23 °C, $CDCl_3$): δ 7.2−6.7 (m, 4H, Ar), 4.19 (t, J = 5 Hz, CH_2O), 2.80 (t, J = 6 Hz, 2H, CH_2Ar), 2.01 (m, J = 9 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, 23 °C, $CDCl_3$): δ 154.7 (s, quaternary C), 129.6 (s, ArCH), 127.0 (s, ArCH), 122.0 (s, quaternary C), 119.9 (s, ArCH), 116.5 (s, ArCH), 66.2 (s, CH_2O), 24.7 (s), 22.2 (s).

Results and Discussion

Phenoxylation of 2-Bromo-4,6-dimethylaniline: Parent Library. Under our standard conditions, we used 1.5 equiv of potassium phenoxide in diglyme and 5 mol % of copper(I) chloride and ligand relative to 2-bromo-4,6-dimethylaniline. We did not explore the use of different copper(I) salts since bromide ion builds up during the reaction. In one experiment, copper(I) bromide performed equivalently within experimental error to copper(I) chloride. Biphenyl was used as an internal gas chromatography (GC) standard. Diglyme was the preferred solvent for our initial experiments as this diminishes solvent loss during the long run times (90 °C, 20 h). Twenty hours was chosen as the run time to allow for comparison of the lowest and highest yielding ligands. (For the phenoxylation reaction, we were primarily interested in identifying the ligands giving the best yield.)

The results of screening our parent library of 96 ligands are presented in Figure 1. Because we were running a robotic protocol and reproducibility was a concern, the data in Figure 1 show two identical sets of experiments for each ligand. The reproducibility was good with the standard deviation being on average ±2% of the average value of the two experiments for the two highest values. The average standard deviation for the remaining ligands in the library was ±18% of the average value of the two measurements. The observation that the errors tend to be smaller for those ligands that give higher overall yield occurs in methoxylation data sets as well (see discussion on errors below). Two ligands which were the most active clearly stand out in both runs, i.e., 8-hydroxyquinoline and 8-acetoxyquinoline. It is likely that under the basic reaction conditions, 8-acetoxyquinoline is hydrolyzed to 8-hydroxyquinoline and this explains the observed structure−activity relationship.

We propose two methods to evaluate the performance of a ligand library. One measure is the Average Library Production (ALP), where j is the number of ligands in the library. For the

$$\mathrm{ALP} = [\sum_{i=1}^{j} (\text{Yield Product})_i]/j$$

experiment in Figure 1, the ALP is 13% yield per ligand (the average values of the two runs were used to calculate ALP). Alternatively, one can measure a Library "Hit Frequency" (LHF) above an arbitrarily chosen yield, that is the number of ligands

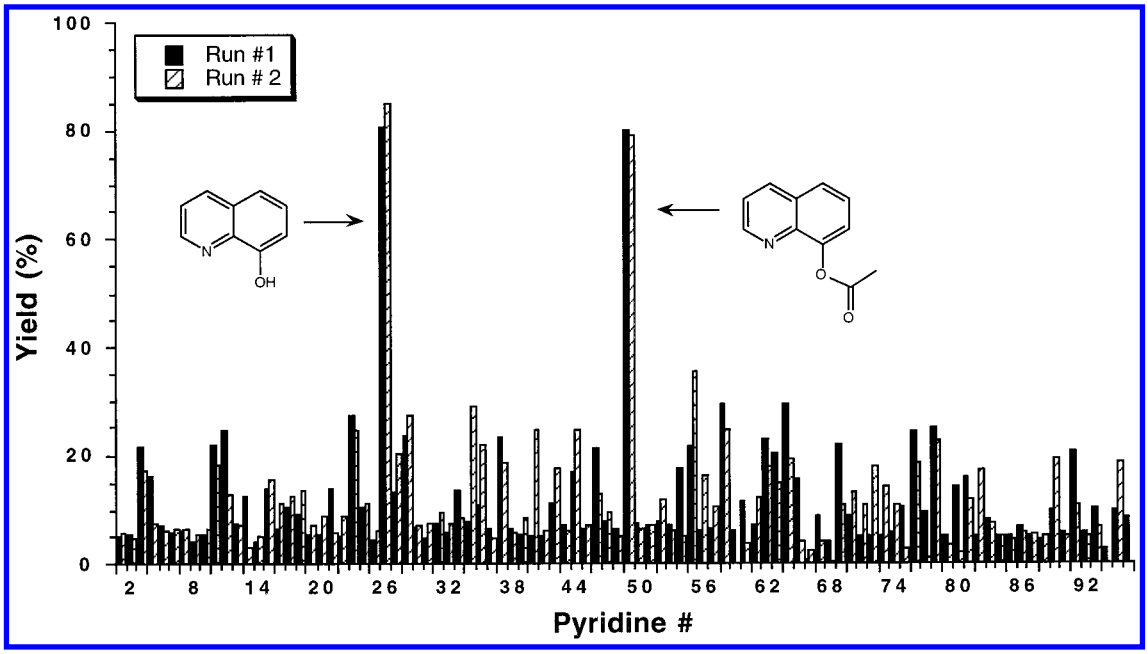


Figure 1. Yields of 2-phenoxy-4,6-dimethylaniline versus pyridine numbers. For the identity of the pyridine ligands refer to Table 1.

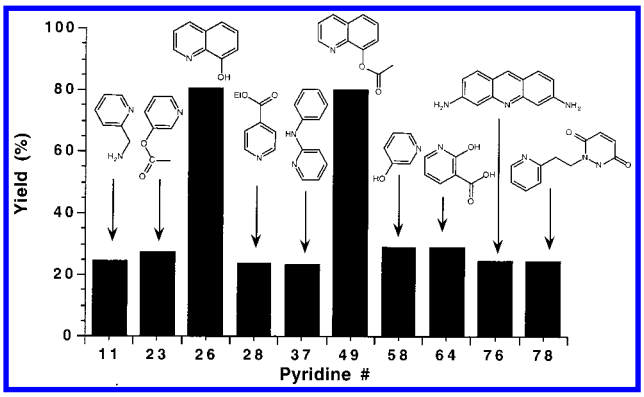


Figure 2. Yields of 2-phenoxy-4,6-dimethylaniline versus the best pyridine numbers.

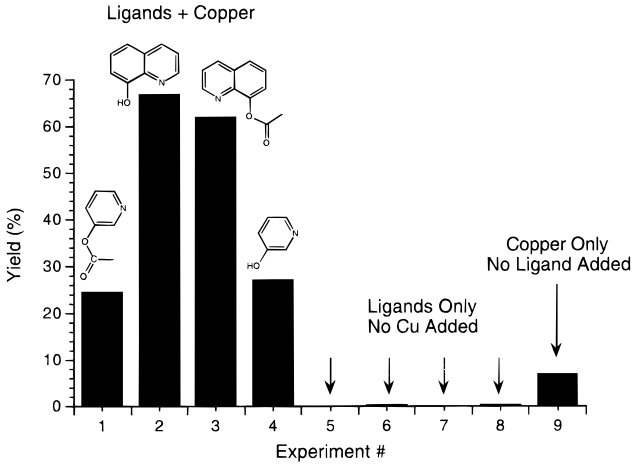


Figure 3. Control experiments. Yields of 2-phenoxy-4,6-dimethylaniline versus conditions. Experiments 1−4 are ligands plus copper, 5−8 are ligands alone, and 9 is with copper only.

above a certain threshold divided by the total number of ligands in the library. The LHF for the library in Figure 1 is (2/96) = 0.02 at 50% yield.

Several other ligands give yields greater than the arbitrarily chosen limit of 23% yield (Figure 2); the LHF is (10/96) = 0.10 at 23% yield. Most of these have structural motifs with a pyridine donor ligand that is connected to a second donating group. However, there are several exceptions to this such as 3-hydroxypyridine and 3-acetoxypyridine which are among the next highest yielding cases relative to 8-hydroxyquinoline.

Control experiments were performed to demonstrate the requirement for both ligand and copper in the catalysis reactions. Figure 3 shows the results of runs with ligand and copper added, ligands alone added, and copper alone added for four ligands (8-hydroxyquinoline, 8-acetoxyquinoline, 3-hydroxypyridine, 3-acetoxypyridine). A reaction of ca. 5% yield is seen by using Cu(I) alone as a catalyst, but clearly the combination of ligand and copper is required to obtain high yields.

The effect of a lower ligand-to-metal ratio was investigated (0.5:1 vs 1:1 ligand-to-copper:ligand mole ratio). For the best set of ligands, there was no obvious effect of varying this parameter, and within experimental error the experiments gave identical results.[22] The effect of having protic impurities was examined by performing experiments on solutions that contained 10 mol % phenol relative to the phenoxide present. Except for the best ligands that exhibited a ca. 10−20% decline in overall yield, the added phenol did not have a large effect.[22] (This was of interest because it was found that the presence of methanol affects the rate of methoxylation as discussed below).

Phenoxylation of 2-Bromo-4,6-dimethylaniline: Focused Libraries. The results of the above experiments led us to choose both 8-hydroxyquinoline and 3-hydroxyquinoline as the basis for the creation of two focused or daughter libraries. The goal was to see if an improved ALP or LHF could be obtained for each of these classes of ligand. Hydroxyquinoline and hydroxypyridine libraries were created incorporating a diverse range of electronic and steric features. The members of each library are listed in Tables 2 and 3, respectively.

The results of screening the hydroxyquinoline focused library are shown in Figure 4. In comparison to Figure 1, an increase in the number of ligands giving high yields is immediately apparent. The six most active ligands are shown in Figure 4. From the results, it is apparent that electron-withdrawing groups in the 4-quinoline position were detrimental, as well as steric

(22) See the Supporting Information for details.

Table 2. Focused 8-Quinolinol Library

no.	ligand	no.	ligand	no.	ligand
1	*N*-methyl-2,2′-imino bis(8-hydroxyquinoline)	11	tributyl(8-quinolyloxy)tin	21	8-quinolinyl trifluoromethanesulfonate
2	quinoline	12	4-hydroxyacridine	22	8-hydroxy-7-(4-sulfo-1-naphthylazo)-5-quinolinesulfonic acid, disodium salt
3	8-hydroxyquinaldine	13	quinoline-8-sulfonic acid sodium salt	23	5-nitroso-8-hydroxyquinoline
4	5-chloro-8-hydroxyquinoline	14	2-amino-8-quinolinol	24	8-hydroxyquinoline-7-sulfonic acid
5	8-hydroxy-5-nitroquinoline	15	8-hydroxyquinoline-2-carboxaldehyde	25	indooxime sodium salt
6	8-hydroxyquinoline	16	8-hydroxyquinoline-2-carboxylic acid	26	quinoline yellow
7	8-aminoquinoline	17	5,7-dimethyl-8-hydroxyquinoline	27	8-hydroxyquinoline-5-sulfonic acid monohydrate
8	5-amino-8-hydroxyquinoline dihydrochloride	18	5-octyloxymethyl-8-quinolinol	28	8-hydroxyquinoline-5-sulfonic acid dihydrate
9	5,7-dichloro-8-hydroxyquinaldine	19	8-hydroxyquinoline-2-carbonitrile	29	2,8-quinolinediol
10	8-aminoquinaldine	20	8-hydroxyquinoline-2-sulfonic acid monohydrate	30	8-hydroxy-7-quinolinecarboxylic acid

Table 3. Focused 3-Hydroxypyridine Library

no.	ligand	no.	ligand	no.	ligand
1	3-ethoxy-2-nitropyridine	9	2-amino-3-hydroxypyridine	17	2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one
2	3-hydroxy-2-nitropyridine	10	pyridoxine	18	pyridoxamine dihydrochloride
3	3-hydroxy-6-methyl-2-nitropyridine	11	3-hydroxy-6-methylpyridine	19	5-chloro-2,3-dihydroxypyridine
4	2,3-dihydroxypyridine	12	2-(dimethylaminomethyl)-3-hydroxypyridine	20	3-hydroxy-2-(hydroxymethyl)-pyridine hydrochloride
5	3-hydroxy-2-mercaptopyridine	13	2,6-lutidine-α-2,3-diol	21	3-hydroxy-2-methylpyridine
6	3-hydroxypicolinic acid	14	3-acetoxypyridine	22	5-hydroxynicotinic acid methyl ester
7	3-hydroxypicolinamide	15	3-hydroxypyridine	23	oxazolo[4,5-*b*]pyridin-2(3*H*)thione
8	2-amino-3-benzyloxypyridine	16	5-chloro-3-hydroxypyridine		

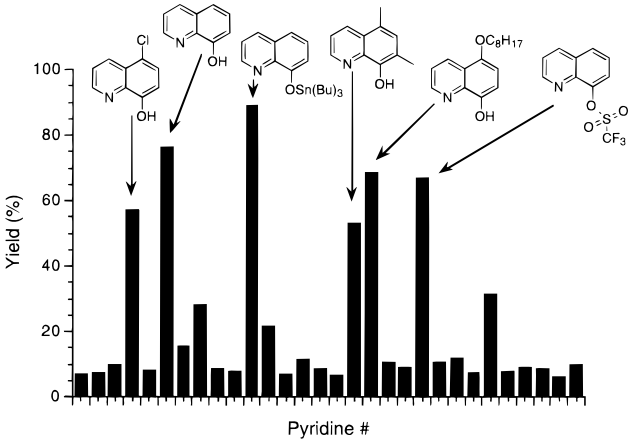


Figure 4. Yields of 2-phenoxy-4,6-dimethylaniline versus the 8-quinolinol focused library. For the identity of the ligands refer to Table 2.

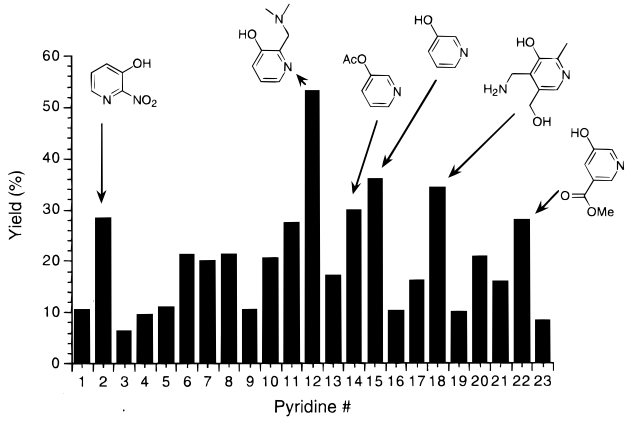


Figure 5. Yields of 2-phenoxy-4,6-dimethylaniline versus the 3-hydroxypyridine focused library. For the identity of the ligands refer to Table 3.

hindrance at the 2-position. One ligand, namely the tributyltin-derivatized 8-hydroxyquinoline, was apparently better than 8-hydroxyquinoline ligand in this experiment, although the basis for this difference is not understood and is within experimental error. For this library, the ALP of 23% yield per ligand and the LHF of 0.20 at 50% yield is higher than that observed for the parent library (ALP = 13%; LHF = 0.02 at 50% yield). From these metrics we conclude that the daughter library performed significantly better than the parent library.

The use of 8-hydroxyquinoline has been noted previously in the patent literature for other Ullmann coupling reactions.[14,23] Although by this study we have "rediscovered" this ligand, we could not have predicted ahead of time this would be the best ligand for these particular reaction conditions and substrate.

(23) For recent applications see: (a) Nagai, R.; Myaki, K. Preparation of fluoroalkoxybenzenes from bromofluorobenzenes. JP 1991-216630 19910802. (b) Gillet, J.-P. Process for the Preparation of Esters of Alkoxyphenoxybenzoic Acids and their Dealkylation to Hydroxyphenoxybenzoic Acids. EP 1992-401918. (c) Okizaki, A.; Yoshimitsu, M.; Kubo, M. Preparation of 4,4′-dialkoxybiphenyls. JP 1987-317365 19871217.

The results of screening the 3-hydroxypyridine library are presented in Figure 5. For this library, we observed an increase in ALP (20% yield per ligand) versus the parent library (13% yield per ligand), and the LHF (7/23 = 0.30 at 23% yield) was also larger compared to the parent library (0.10 at 23% yield). Of significance is that an improved ligand was identified over the initial 3-hydroxypyridine lead ligand found in the parent library, i.e., 2-dimethylaminomethyl-3-hydroxypyridine (53% yield). This particular ligand has not been mentioned before in the literature on Ullmann reactions.

Methoxylation of 2-Bromo-4,6-dimethylaniline: Parent Library. For standard conditions, we used 1.5 equiv of sodium methoxide in methanol, 5 mol % of both copper chloride, and ligand relative to 2-bromo-4,6-dimethylaniline. Biphenyl was used as an internal gas chromatography (GC) standard. Reactions were run at 100 °C for 20 h. In this case, we were interested in discovering catalytic systems giving both high yields and low amounts of reduction.

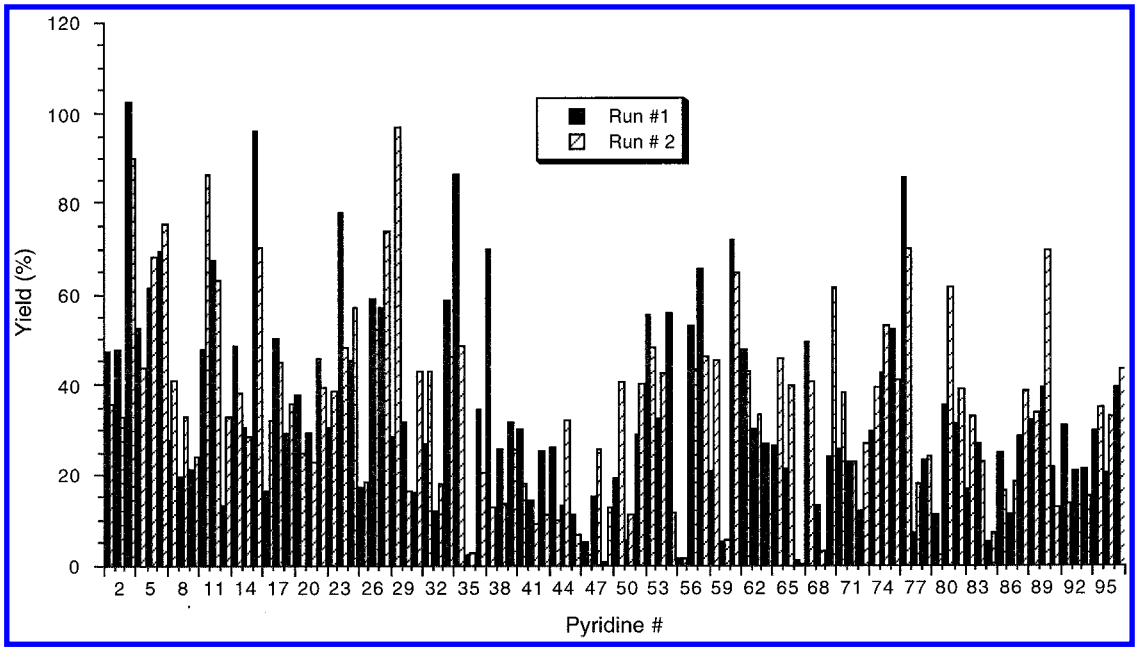


Figure 6. Yields of 2-methoxy-4,6-dimethylaniline versus pyridine numbers. For the identity of the pyridine ligands refer to Table 1.

It was observed that the yield was affected by whether the vials were capped with pierced septa or sealed septa during the runs. This suggested the rate of evaporation of methanol affected the rate of the reactions since runs with pierced septa tended to exhibit higher yields than those run with sealed septa. Careful study on large-scale reactions confirmed that the presence of methanol retarded the rate of the methoxylation reaction. Despite this effect, the same ligand trends were identified whether the vials were capped or not. We found that running the reactions at 90−100 °C was preferrable as this tended to evaporate the methanol fairly rapidly.

We found the reproducibility of the 96 experiments to be acceptable by rerunning the robotic protocol under the same conditions. The results of two identical runs using our 96-pyridine parent library are presented in Figure 6.

The reproducibility was good with the standard deviation being on average ±13% of the average value of the two experiments for the eight highest values. The average standard deviation for the remaining ligands in the library was ±23% of the average value of the two measurements. Two identical runs were also carried out at 90 °C and similar results were obtained, although total yields tended to be lower than the 100 °C run.[22]

The observation that the highest values tend to have less error associated with the measurement of activity is an important observation, and something that should be known when evaluating combinatorial catalysis results. The implication is that it would be relatively difficult to pick out lead compounds from a set of ligands that gave relatively low conversion. Knowing the errors involved at different levels of activity is critical to make judgments about the relative merit for choosing which focused library to prepare. We therefore would recommend duplicate runs at the minimum when establishing the validity of a robotic/screening protocol.

The observed ALP for the parent library in the case of methoxylation was 34% yield per ligand. The LHF was 0.19 at 50% yield. (The average values of the two runs for each ligand were used to determine ALP and LHF.) Figure 7 illustrates that among the best ligands for methoxylation in terms of yield and low reduction are pyridines bearing an amino group in the 2-position. As can be seen in Figure 7, other pyridines that do not possess this structural motif have a good overall yield of

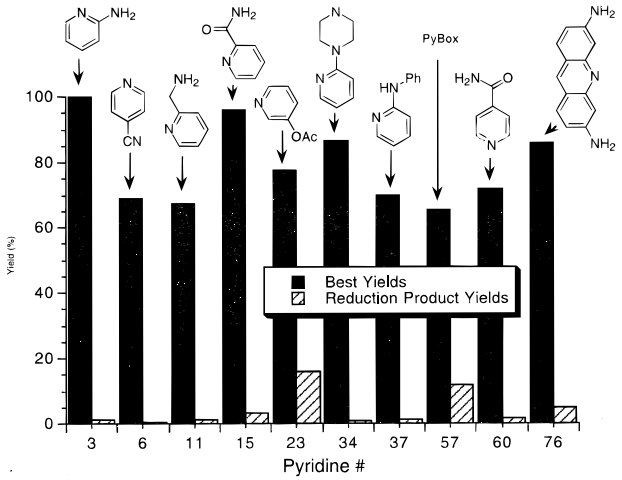


Figure 7. Yields of 2-methoxy-4,6-dimethylaniline versus the best pyridine numbers. For the identity of the pyridine ligands refer to Table 1.

product with a low amount of reduction byproduct. Some ligands gave relatively high yields but suffered from an increased yield of byproduct. The value of the combinatorial approach is shown by these experiments, since it was impossible to predict which ligands would give the best combination of yield and low reduction. By this approach, we have been able to identify several "lead" ligands for the development of focused libraries.

Intelligent Ligand Performance versus Random Ligand Performance in Methoxylation. Out of the 96 ligands used, 79 were intelligently chosen by the criteria previously discussed. Seventeen ligands were random selections since we either anticipated unwanted reactivity under the very basic reaction conditions or they had structural features that were considered to be outside the parameters taken into account in the intelligent set. Specifically, the "random" ligands were 5, 6, 21, 40, 45, 46, 52, 55, 76, 77, 78, 84, 86, 87, 88, 90, and 94 in Table 1. We can use the ALP and LHF measures to examine how the randomly chosen library members performed (ALP = 30%; LHF = 0.18 at 50% yield; LHF = 0.00 at 80% yield) compared to the intelligently chosen set (ALP = 44% and LHF = 0.16 at 50% yield; LHF = 0.04 at 80% yield). It would appear from

Table 4. Focused 2-Aminopyridine Library

no.	ligand	no.	ligand	no.	ligand
1	7-azaindole	15	2-amino-4-methylpyridine	29	2-amino-3-chloro-5-trifluoromethylpyridine
2	2,2′-dipyridylamine	16	2-amino-4,6-dimethylpyridine	30	2-(formylamino)pyridine
3	2-anilinopyridine	17	2-amino-5-chloropyridine	31	2-aminoquinolin-4-ol
4	2-hydrazinopyridine	18	2-amino-5-nitropyridine	32	2-benzylamino-6-methylpyridine
5	2-(methylamino)pyridine	19	2-amino-5-methylpyridine	33	10*H*−pyrido(3,2-*b*)(1,4)benzothiazine
6	2-benzylaminopyridine	20	2,6-diaminopyridine	34	2-amino-8-quinolinol
7	2-benzylamino-4-methylpyridine	21	2-amino-6-methylpyridine	35	2-methoxy-6-methylaminopyridine
8	2-aminopyridine	22	2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one	36	1′,3′-dihydrospiro(cyclohexane-1,2′-(2*H*)imidazo(4,5-*b*)pyridine)
9	2-amino-3,5-dichloropyridine	23	niflumic acid	37	2-pyridyldithiocarbamic acid ethyl ester
10	2-amino-3-nitropyridine	24	1-phenyl-3-(2-pyridyl)-2-thiourea	38	2-(2-aminoethylamino)-5-nitropyridine
11	2-amino-4-methyl-3-nitropyridine	25	5-nitro-2-benzylaminopyridine	39	2,3-diaminopyridine
12	2-amino-3-benzyloxypyridine	26	1-aminoisoquinoline	40	piroxicam
13	2-amino-3-hydroxypyridine	27	2-aminoquinoline	41	sulfapyridine
14	2-amino-3-methylpyridine	28	2,5-diaminopyridine dihydrochloride		

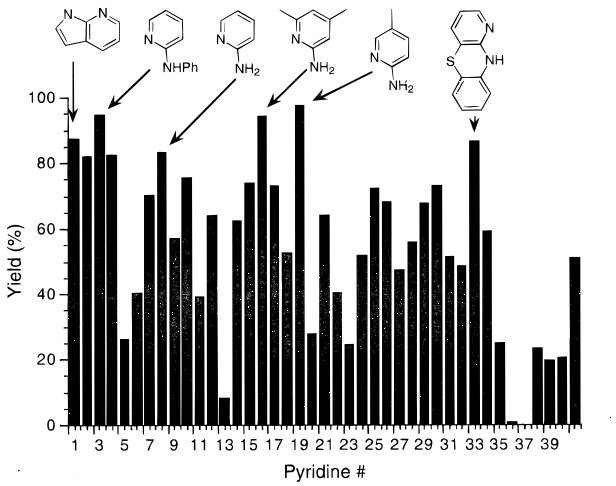


Figure 8. Yields of 2-methoxy-4,6-dimethylaniline versus the 2-aminopyridine focused library. For the identity of the ligands refer to Table 4.

these data that the intelligently chosen library performed better than the random set. The overall ALP was slightly higher, and the quality of hits (i.e., those that gave higher yields) was better in the intelligent set (see LHF's at 80% yield). One should be cautious not to overinterpret these results, since the exact line between randomly chosen versus intelligently chosen ligands is partially subjective. However, we did try to cover all of the important parameters (sterics, electronics, bite-angle, etc.) with the intelligently chosen library, and the higher quality of hits from the intelligent library members suggests some advantage to this approach.

Methoxylation of 2-Bromo-4,6-dimethylaniline: Focused Library. On the basis of the results described above, we prepared a daughter library of 2-aminopyridine type ligands which are listed in Table 4. This class of ligands was chosen because of the observed high yields with low levels of reduced side product. They were also readily available commercially, and offered some practical benefits if this chemistry was to be used in a commercial process. Results of screening this library are shown in Figure 8. We observed an increase in the ALP (55% yield per ligand) and LHF (0.68 at 50% yield) relative to the original library of ligands which had ALP at 34% per ligand and an LHF of 0.19 at 50% conversion. As in the phenoxylation reaction, the parent library again led us to a ligand class that functions in an improved manner by these metrics.

Scale-Up of Reactions. It was important to validate the findings of small-scale reactions to see if similar results could be obtained on a large scale. Both the phenoxylation with 8-quinolinol as a ligand and methoxylation with 2-aminopyridine as a ligand were scaled up. The product from phenoxylation was obtained in 69% isolated yield upon scale-up of the reaction. The isolated yield of product in the case of methoxylation was 52%, and very little reduction sideproduct was observed. The material was isolated in pure form as the hydrochloride salt (see the Experimental Section). The moderate isolated yields are due in part to the formation of tars which were difficult to work up and losses during crystallization. However, the conversions by GC area % (which we found closely related to the yields) for the phenoxylation and methoxylation reactions were 89% and 92%, respectively. These results were similar to what we found from small-scale screening experiments.

Alkoxide Generality. The parent library was also screened for ethoxylation, butoxylation, isopropoxylation, and *tert*-butoxylation activity. Promising results were found using NaOEt and NaOBu as alkoxides. The same class of ligands found for NaOMe operated efficiently.[22] However, in the case of the secondary and tertiary alkoxide (sodium isopropoxide and potassium *tert*-butoxide) reactions were sluggish for all ligands giving either very low conversions or no product at all under our standard reaction conditions.

Solvent Effects. We examined solvents effects and found that ether solvents (diglyme or DME) were best for the methoxylation reaction.[22] The use of DMAc or DMF reduces the yields of product considerably (less than half of the DME yield).[22] It is noteworthy that the most efficient ligands found for these solvents (8-hydroxyquinoline and phenanthrolines) are much different from the class found in DME.[22] These experiments point out how difficult it is to predict which ligands will function under a particular set of conditions, and again demonstrates the usefulness of the combinatorial catalysis approach in this case.

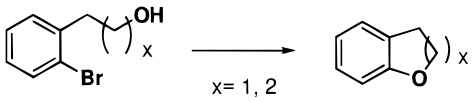
Substrate Generality. Having found that 2-aminopyridine was a good ligand for Ullmann reactions in ether solvents, we explored the generality of this ligand for use with other substrates. Table 5 summarizes these results for other substrates run under our standard conditions. Overall, the data suggest this ligand performs quite well for most of the substrates examined. We are depending solely on GC/mass spectral data to determine that the major observed product had the expected mass, but it should be noted we have not performed these reactions on a large scale. The low yield observed for β-bromostyrene is associated with the formation of the byproducts tentatively identified by GC/mass spectral analysis as 1,4-diphenylbutadiyne (ca. 59%) and 2-phenylnaphthalene (ca. 7%).

Intramolecular Ullmann Ether Formation. Reports of intramolecular Ullmann ether reactions are rare. There are

Table 5. Substrates and Observed Gas Chomatographic Yields of Product Using 2-Aminopyridine as Ligand

entry	name	GC yield (%)	entry	name	GC yield (%)
1	2-bromoanisole	98	11	4-bromobenzonitrile	100
2	2-bromothioanisole	99	12	1-bromonaphthalene	100
3	4-bromo-*m*-xylene	93	13	2-bromothiophenol	–
4	2-bromo-*m*-xylene	97	14	1-bromo-2-nitrobenzene	100
5	3-bromoanisole	93	15	1-bromo-4-nitrobenzene	100
6	4-bromoanisole	90	16	2-bromoaniline	89
7	4′-bromoacetophenone	90	17	3-bromoaniline	85
8	β-bromostyrene	34	18	4-bromoaniline	91
9	9-bromoanthracene	99	19	4-bromoveratrole	83
10	2-bromobenzonitrile	100	20	2-bromo-4,6-dimethylaniline	81

sporadic reports of copper-catalyzed reactions[17c,f,g] and a palladium route using secondary or tertiary alcohols was recently reported by Buchwald.[18g] The ligand 2-aminopyridine was shown to be effective for intramolecular Ullmann reactions as well. Reaction of 2-bromophenethyl alcohol and 3-(2-bromophenyl)-1-propyl alcohol proceed cleanly and in good yields forming 2,3-dihydrobenzofuran and chroman, respectively (eq 2).



Conclusion

In summary, using combinatorial chemistry methods, we have been able to scout a large array of catalyst solutions in a relatively short period of time. By starting with a ligand library that contained both intelligently chosen and random members, we were able to determine some initial lead ligands for both phenoxylation and methoxylation reactions for the substrate of interest. From the lead compounds, we created focused libraries that performed better than the parent library, and in some cases resulted in the discovery of new ligands.

The impetus to use combinatorial techniques in catalysis was the assumed analogy to drug discovery. In the pharmaceutical paradigm, screening for lead compounds for enzyme inhibition would lead to structure−activity relationships that could be expanded into more focused libraries for screening and eventual optimization of inhibition. No studies to our knowledge have clearly demonstrated that this approach can be successful for homogeneous catalysis. The data presented in this paper lead us to conclude that in certain instances, this paradigm can work in homogeneous catalysis discovery and optimization.

We believe part of the key to success in the current study was that our initial design of the parent library included an intelligent aspect, i.e., we took into account the typical parameters which affect homogeneous catalyst performance. Whether the Ullmann reaction is monometallic, bimetallic, or metal cluster mediated, the same ligand parameters we took into consideration are likely to be important in one sense or another.

Overall, there is the trend that bidentate chelators with a relatively small bite angle are favored to work well (2-aminopyridines, 8-hydroxyquinolinols, etc.). However, there are many exceptions to this general trend, and the appearance of ligands such as for example proflavine in some of the screens defies ready explanation. Because of the complexity of this reaction, it is likely our intelligently chosen parameters are not the sole important ones. This would argue for the need for "random" member selection in any library design aimed at a poorly understood reaction. The bottom line for this particular study is that this approach of intelligent/random library screening led us to the correct ligands for our particular needs.

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Supporting Information Available: Graphs of ligand ratio effects and additive effect for the phenoxylation reaction; graph of the methoxylation reaction at 90 °C; graphs and tables of data describing solvent effects (DME, DMAC, and DMF) for the methoxylation reaction; graphs and tables of data for the ethoxylation and *n*-butoxylation reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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