# A Fluorescence-Based Assay for High-Throughput Screening of Coupling Reactions. Application to Heck Chemistry

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**Abstract:** A new fluorescence-based assay for high-throughput screening of reactions that couple two organic molecules is described. The assay involves reaction of one substrate containing a tethered fluorophore with a second molecule that is attached to a solid support. A successful coupling process is signaled by fluorescence of the solid support, which can be isolated by either simple centrifugation or filtration. To evaluate this assay in the context of a catalytic process under intense current study, we searched for improved, readily available phosphines for Heck chemistry. An acrylate containing a tethered coumarin was reacted with an aryl halide supported on a cross-linked polystyrene resin. Comparison of the results from our fluorescence-based assay with results from serial GC analysis showed that the fluorescence-based assay accurately selected the most active ligands for the Heck coupling of aryl bromides and chlorides. Two ligands chosen by the assay, tri(*tert*-butyl)phosphine and di(*tert*-butylphosphino)ferrocene, were found to be the most active systems to date for the olefination of unactivated aryl bromides, and di(*tert*-butylphosphino)ferrocene is the most efficient ligand for olefination of unactivated aryl chlorides.

## Introduction

The design and selection of organometallic catalysts that are capable of efficient and selective transformations of organic substrates has been an important area of chemical research over the past decade. The search for such catalysts would benefit from efficient strategies to determine the activity of individual members of a large set of catalyst systems. High-throughput screening of small molecules that are potential drugs has driven the preparation of large libraries of organic molecules by combinatorial methods.[1,2] The rapid screening of potential drugs has been pursued because the necessary structural characteristics for the desired biological activity are often poorly understood. In catalysis, it is also difficult to predict a priori the optimal metal/ligand combination for a specific transformation, particularly when mechanistic data are unavailable. Thus, combinatorial chemistry in its various forms has been applied to the preparation of potential new catalysts.[3]

Several groups have applied combinatorial chemistry in its broad definition to the preparation of libraries of ligands for the enantioselective transformation of organic substrates by homogeneous catalysis.[4−10] In some cases, reaction parameters have been varied over a large number of parallel reactions in an effort to efficiently optimize reaction conditions.[11] In general, elegant ligand libraries have been prepared for use in homogeneous catalysis, but screening of the libraries for activity and selectivity has typically involved serial analysis by GC or HPLC.

Only recently have high-throughput screening methodologies been developed for determination of catalytic activity. IR thermography has been used to analyze catalytic activity of exothermic reactions in a high-throughput fashion.[12−14] The viability of simple colorimetric assays has been demonstrated in the analysis of fuel cell cathodes using a fluorescent indicator,[15] and recent studies have demonstrated the ability to visualize catalytic activity using specific, colored alkene substrates.[16]

Overall, the synthesis of libraries of potential catalysts has preceded the ability to conduct high-throughput screening, a sequence of events that contrasts the initial development of high-throughput assays for drug discovery. To rectify this problem, we have initiated studies to develop colorimetric assays for catalyst activity that could be applied to a wide variety of reactions, would be amenable to rapid screening processes, could ultimately be conducted with automated systems, and analyze for product formation. The success of combinatorial chemistry

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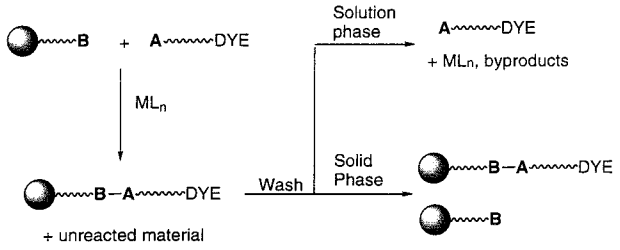
**Scheme 1.** Proposal for Visual Assay for Coupling Reactions

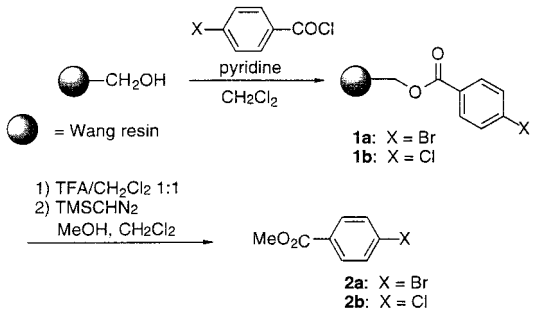



in drug design rests upon detecting small molecule−macromolecule binding events. The most common assays involve treating a resin-bound library of molecules with the appropriate receptor containing a dye or radiolabel.[17−26] Successful binding is signaled by a colored or radioactive bead.

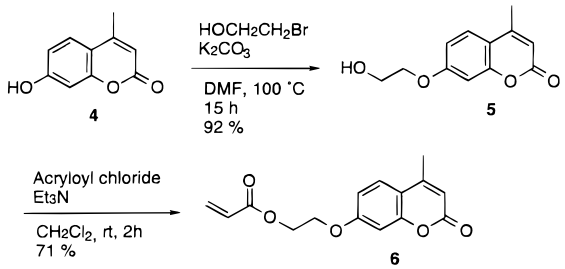
We felt that an analogous strategy could be applied to the visual screening of a large set of parallel chemical reactions that join two molecules by covalent, rather than noncovalent, interactions. In our study, one substrate (**A**) would be attached to a dye molecule, while a second substrate (**B**) would be attached to a solid support (Scheme 1). After a successful coupling reaction, substrate **A** would be bound to the solid support via substrate **B**. Filtering and washing of the beads, ultimately generated from reactions in microtiter plates with a fritted bottom, would reveal which wells contained reagents and/or catalysts that were suitable for the construction of a covalent bond between **A** and **B**. We have initially tethered to substrate **A** a fluorescent dye that can be observed with a hand-held UV lamp typically used to assay TLC plates. In turn, substrates with a fluorescent tag can be used for a number of additional assays that allow one to retrofit instrumentation used for macromolecule−small molecule interactions in biological studies. Nevertheless, the simple assay described in this paper should prove general enough to be applied to any reaction that can be conducted using a solid-supported substrate and a reagent with a tethered fluorescent tag.

We chose the Heck coupling process as an initial reaction to demonstrate this simple assay. The Heck reaction can be carried out using solid-supported aryl halides,[27−32] and many groups have been studying potential Heck catalysts that would be capable of very high ($>10^5$) turnovers with aryl bromides and/or high activity with aryl chlorides at moderate temperatures.[33−36] Improved ligand systems are needed to carry out the reaction at low temperatures, to conduct chemistry with aryl chlorides in the absence of bromide additives at mild temperatures,[33] and to conduct reactions with electron-rich aryl bromides. It was our initial goal to develop an assay for catalytic activity before construction of ligand libraries. Thus, we elected to use, for this study, the large pool of phosphine ligands which are either commercially available or have been prepared previously by our group. Remarkably, screening of this library with the assay described here led us to discover two ligand systems that show marked improvements over previous Heck catalyst systems for reactions of aryl chlorides and unactivated aryl bromides.

**Scheme 2.** Preparation and Cleavage of Supported Aryl Halides




**Scheme 3.** Preparation of Dye-Containing Substrate **6**




## Results

**1. Development of the Assay for Heck Couplings: Selection of Substrates and Reaction Conditions.** For our solid-supported and soluble tagged substrate, we chose aryl halides supported on Wang resin and acrylates tethered by an alkyl group to 4-methyl-7-hydroxycoumarin (**4**). Aryl halides supported on Wang resin have been used previously in solid-phase Heck chemistry.[27−32] Coumarin **4** is inexpensive, and alkylation of the phenolic oxygen does not decrease the fluorescence intensity.

Treatment of Wang resin with 4-halobenzoyl chloride and pyridine in methylene chloride resulted in complete conversion of the OH groups, as determined by FTIR analysis (Scheme 2). Cleavage of the resin-bound aryl bromide (**1a**) with trifluoroacetic acid (TFA) followed by treatment with trimethylsilyldiazomethane gave methyl 4-bromobenzoate (**2a**). The loading was found to be 0.57 mmol of ArBr/g of resin

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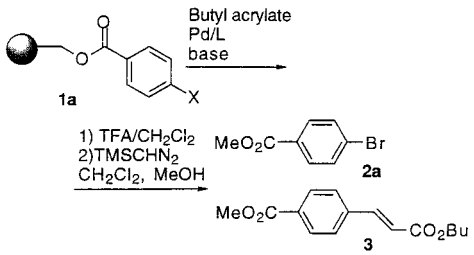
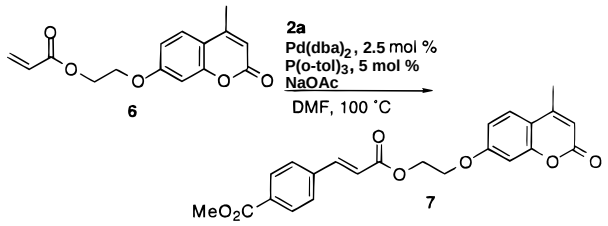
(theoretical maximum = 0.54 mmol/g) by GC analysis with an internal standard. The coumarin-containing acrylate (**6**) was prepared in two steps in 65% overall yield from **4**, as shown in Scheme 3.

We sought a benchmark system which would show high activity in both solution- and solid-phase reactions. The standard Heck coupling system utilizes P(*o*-tol)$_3$ and Pd(OAc)$_2$ as the catalyst precursor and NaOAc as base.[37] This system has also been used successfully in solid-phase Heck couplings.[27] Coupling of butyl acrylate and **1a** at 100 °C for 12 h using the P(*o*-tol)$_3$/Pd(OAc)$_2$/NaOAc system resulted in complete consumption of the aryl halide and a quantitative yield of the cinnamate product **3** (eq 1) after cleavage from the resin. In




(1)

comparison, solution-phase coupling of aryl halide **2a** and butyl acrylate by this system at 100 °C for 2 h resulted in 88% isolated yield of **3**. The tagged dye **6** gave nearly identical results in solution-phase coupling to butyl acrylate: coupling of **2a** and **6** using the P(*o*-tol)$_3$/Pd(dba)$_2$/NaOAc system gave the coupled product **7** in 92% isolated yield (eq 2).




(2)

With an acrylate suitably substituted with a dye and an aryl halide bound to a resin in hand, we carried out experiments using the solid-supported aryl halide to compare the reactivity of the dye substrate **6** to that of butyl acrylate. Couplings of butyl acrylate or **6** with supported aryl halide **1a** were carried out in a series of parallel reactions at 100 °C with the P(*o*-tol)$_3$/Pd(OAc)$_2$/NaOAc system over a range of reaction times. Upon completion of each reaction, the organic products were cleaved from the resin to give a mixture of unreacted halide **2a**, the simple cinnamate product **3**, or the coumarin-tagged cinnamate **7** (Scheme 2, eq 1). The conversion of **2a** to **3** was determined by GC, while the yield of **7** was determined from its UV absorbance at 288 nm. The results are shown in Table 1. The rate of formation of coupled products was similar for butyl acrylate and for coumarin-tagged acrylate **6**. After 2 h, both reactions gave approximately 50% yield, while after 4 h the reactions were nearly complete.

The resins obtained from the reactions in Table 1 were observed under UV light to compare the observed fluorescence with the degree of dye incorporation before the products were cleaved. The resin obtained after 2 h, which was 55% functionalized with dye, was only faintly fluorescent (Table 1, entry 2). The resin samples obtained from reactions lasting 4 h or longer, which were completely labeled with dye, were strongly fluorescent. In addition, resin-bound aryl halide was treated with dye substrate **6** in the absence of catalyst, and no fluorescence was observed. Thus, unreacted dye substrate is not trapped in the resin, an event that would generate fluorescent beads from reactions involving inactive catalysts.

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**Table 1.** Comparison of Butyl Acrylate and Fluorescent Acrylate **6** in the Solid-Phase Heck Coupling[a]

| entry | acrylate | time (h) | yield **3**[b]/**7**[c] *(%)* | fluorescence of resin[d] |
|---|---|---|---|---|
| 1 | BA[e] | 2 | 40 | |
| 2 | **6** | 2 | 55 | weak |
| 3 | BA | 4 | 86 | |
| 4 | **6** | 4 | 100 | strong |
| 5 | BA | 6 | 97 | |
| 6 | **6** | 6 | 100 | strong |

[a] Reactions were run with 55 mg of resin **1a** (0.03 mmol of ArBr), 3 equiv of acrylate and sodium acetate, 7.5 mol % Pd(dba)$_2$, and 30 mol % ligand at 100 °C in DMF for the indicated time. Isolation and cleavage were carried out as described for the preparation of **1a**. [b] Determined by GC. [c] Determined by measurement of UV absorbance at 288 nm. [d] Observed under UV lamp irradiation. [e] BA = butyl acrylate.

**Table 2.** Identity of Ligands in the First Screen

| Entry | Ligand Abbr. | Ligand Structure | Entry | Ligand Abbr. | Ligand Structure |
|---|---|---|---|---|---|
| 1 | $PPh_3$ | $PPh_3$ | 21 | DPPE | $Ph_2P(CH_2)_2PPh_2$ |
| 2 | $Ph_2P(o\text{-tol})$ | $Ph_2P(o\text{-tol})$ | 22 | DPPBz |  |
| 3 | di(2,4-xyl)PPh |  | 23 | DPPP | $Ph_2P(CH_2)_3PPh_2$ |
| 4 | $P(o\text{-tol})_3$ | $P(o\text{-tol})_3$ | 24 | DPPB | $Ph_2P(CH_2)_4PPh_2$ |
| 5 | $P(2,4\text{-xyl})_3$ |  | 25 | DPPF |  |
| 6 | $P(Np)_3$ |  | 26 | DTPF |  |
| 7 | $P(2,6\text{-xyl})_3$ |  | 27 | D*p*-MeOPPF |  |
| 8 | $P(o\text{-anis})_3$ |  | 28 | D*p*-$CF_3$PPF |  |
| 9 | (2-BTF)P(*o*-anis)$_2$ |  | 29 | D*t*-BPF |  |
| 10 | (2-BTF)$_2$P(*o*-anis) |  | 30 | DPPR |  |
| 11 | P(2-BTF)$_3$ |  | 31 | (DCPFc)DPPE |  |
| 12 | (DPPFc)EtOMe |  | 32 | (DPPFc)DCPE |  |
| 13 | (DPPFc)EtNMe$_2$ |  | 33 | (DCPFc)DCPE |  |
| 14 | (DPPPh)EtOMe |  | 34 | (D*t*-BPFc)DPPE |  |
| 15 | P(2-MOMPh)$_3$ |  | 35 | *rac*-BINAP |  |
| 16 | P(2-(1-MOE)Ph)$_3$ |  | 36 | DPPNp |  |
| 17 | P(*n*-Pr)$_3$ | P(*n*-Pr)$_3$ | 37 | DPPDPE |  |
| 18 | P(*i*-Pr)$_3$ | P(*i*-Pr)$_3$ | 38 | DTPDPE |  |
| 19 | P(cy)$_3$ | P(cy)$_3$ | 39 | DPPX |  |
| 20 | P(*t*-Bu)$_3$ | P(*t*-Bu)$_3$ | 40 | DTPX |  |

**2. Use of the Assay for High-Throughput Screening. A. Selection of Ligands.** Two ligand sets were tested for activity in the Heck reaction. The first ligand set (Table 2, entries 1−20) was comprised of monophosphines. A series of triarylphosphines with increasing steric bulk in the ortho position (entries 1−7) was included, along with phosphines whose electronic properties varied while the compounds maintained similar steric demands (entries 8−11). A series of phosphines with groups that could

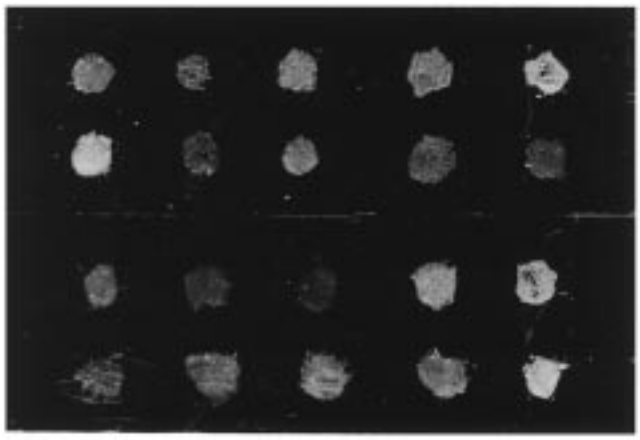


**Figure 1.** Beads obtained from the first screening study using monophosphine ligands 1−20. Beads are displayed on a black slide after isolation (top row, ligands 1−5 (left to right); second row, ligands 6−10; third row, ligands 11−20; bottom row, ligands 16−20).

coordinate weakly (entries 12−16) and a series of alkylphosphines with increasing bulk (entries 17−20) were also included in this first set. Diphosphine ligands comprised the second ligand set. A range of backbones (entries 21−25, 30, 35−37, and 39) was explored. The effects of different electronic and steric properties of diphosphines were explored using a constant ferrocene backbone (entries 25−29, 31−34). Sterically demanding versions of the different ligands were also included (entries 26, 38, and 40).

**B. Initial Round of Screening.** Reactions were carried out in sets of 20, which was the capacity of the available heating block used in these experiments. Clearly, the number of reactions can be expanded in future studies. In a drybox, glass vials were charged with sodium acetate (1.5 equiv based on ArBr) and the aryl bromide resin (0.54 mmol/g) **1a**. To each vial was added stock solutions in DMF of the dye substrate **6** (1.5 equiv), Pd(dba)$_2$ (5 mol % based on ArBr), and the appropriate ligand solution (3 equiv of P/Pd). The reaction vials were placed in an aluminum heating block preheated to 100 °C and stirred magnetically for 4 h. After this time, the vials were centrifuged, the solvent was decanted, and the resin was washed with DMF, methylene chloride, methanol, and ether. The resin was then dried under mild heating and viewed against a black background simply by using a hand-held UV lamp as an irradiation source. Figure 1 shows the resin isolated from run 2 of the monophosphine ligand assay (entries 1−20, Table 2). The picture was taken under a short-wave UV radiation source. Samples 4, 5, 6, 14, 15, and 20 appear much brighter than the other resin samples. The contrast is more significant when viewed in color. The bright blue of the coumarin fluorophore is easily distinguished from the pale blue fluorescence of the polymer beads.

The assays were run twice with each ligand set to determine the reproducibility of the procedure. The results from both the monophosphine and diphosphine sets showed that the assay is highly reproducible (Table 3). Only reactions with P(*o*-tol)$_3$ gave different levels of fluorescence during the two runs. Resin isolated from the first run was dark black, making it impossible to determine if there was any fluorescence. However, the resin isolated from the same system in the second run was light tan and was strongly fluorescent. The cause of this single discrepancy is unknown.

The ligands that showed moderate or high activity in the fluorescence assay appeared to be structurally similar. Di(2,4-xyl)PPh, P(*o*-tol)$_3$, P(2,4-xyl)$_3$, P(Np)$_3$, P(*o*-anis)$_3$, (DPPPh)EtOMe, and P(2-MOMPh)$_3$ are all sterically demanding ortho-substituted arylphosphines. P(*t*-Bu)$_3$ is also sterically demanding, but it is more electron-donating than the arylphosphines. The diphosphines selected by the assay also tended to contain sterically demanding di(*o*-tolyl)phosphine groups (DTPDPE and DTPX). Only two backbones (diphenyl ether and 9,9-dimethylxanthene) were found in the chelating ligands that gave positive results.

To determine the accuracy of the assay, each reaction was repeated using the soluble aryl halide **2a**. The reactions were carried out in a fashion similar to the solid-phase reactions, but with only 2.5 mol % Pd and for only 2 h. The reactions were analyzed by GC. The coupling reactions were run multiple times

**Table 3.** Comparison of Fluorescence Assay with GC Results

| | fluorescence[a] | | | | fluorescence[a] | | |
|---|---|---|---|---|---|---|---|
| ligand | run 1 | run 2 | GC yield[b] (%) | ligand | run 1 | run 2 | GC yield[b] (%) |
| $PPh_3$ | − | − | 12 | DPPE | − | − | 0 |
| $Ph_2P$(*o*-tol) | − | − | 9 | DPPBz | − | − | 0 |
| di(2,4-xyl)PPh | + | + | 82 | DPPP | − | − | 36 |
| P(*o*-tol)$_3$ | −[c] | ++ | 99 | DPPB | − | − | 0 |
| P(2,4-xyl)$_3$ | ++ | ++ | 97 | DPPF | − | − | 0 |
| P(Np)$_3$ | ++ | ++ | 96 | DTPF | − | − | 0 |
| P(2,6-xyl)$_3$ | − | − | 6 | D*p*-MeOPPF | − | − | 25 |
| P(*o*-anis)$_3$ | + | + | 7 (20)[d] | D*p*-$CF_3$PPF | − | − | 0 |
| (2-BTF)P(*o*-anis)$_2$ | − | − | 64 | D*t*-BPF | − | − | 6 |
| (2-BTF)$_2$P(*o*-anis) | − | − | 5 | DPPR | − | − | 6 |
| P(2-BTF)$_3$ | − | − | 23 | (DCPFc)DPPE | − | − | 0 |
| (DPPFc)EtOMe | − | − | 10 | (DPPFc)DCPE | − | − | 0 |
| (DPPFc)EtNMe$_2$ | − | − | 0 | (DCPFc)DCPE | − | − | 0 |
| (DPPPh)EtOMe | + | + | 25 (66)[d] | (D*t*-BPFc)DPPE | − | − | 1 |
| (2-MOMPh)$_3$P | ++ | ++ | 85 | *rac*-BINAP | − | − | 36 |
| (2-(1-MOE)Ph)$_3$P | − | − | 0 | DPPNp | − | − | 40 |
| P(*n*-Pr)$_3$ | − | − | 2 | DPPDPE | + | + | 35 (42)[d] |
| P(*i*-Pr)$_3$ | − | − | 0 | DTPDPE | ++ | ++ | 65 |
| P(cy)$_3$ | − | − | 0 | DPPX | − | − | 0 |
| P(*t*-Bu)$_3$ | ++ | ++ | 95 | DTPX | ++ | ++ | 100 |

[a] Reactions were run for 4 h at 100 °C as described in the Experimental Section. Visual observation of resin fluorescence: −, weak or no fluorescence; +, moderate fluorescence; and ++, strong fluorescence. [b] Average yield of **3** from at least two runs. Reactions were run with Pd(dba)$_2$ ($3.5 \times 10^{-4}$ mmol), ligand ($1.0 \times 10^{-3}$ mmol), methyl 4-bromobenzoate (0.015 mmol), butyl acrylate, and sodium acetate (0.022 mmol) in 150 μL of DMF for 2 h at 100 °C. [c] Resin was blackened during the reaction, making observation of fluorescence difficult. [d] Reactions were run for 4 h.

**Table 4.** Ligands Added for the Second Round of Screens

| Entry | Ligand Abbr. | Ligand Structure |
|---|---|---|
| 1 | Di(2-Me-4-FPh)PPh |  |
| 2 | P(2-Me-4-FPh)$_3$ |  |
| 3 | ($t$-Bu)$_2$PPh | ($t$-Bu)$_2$PPh |
| 4 | ($t$-Bu)$_2$P($o$-tol) |  |
| 5 | ($t$-Bu)$_2$PFc |  |

**Table 5.** Evaluation of the Active Ligand Subset under Various Conditions

| ligand | ArBr at 75 °C[a] | ArBr at 50 °C[a] | ArCl at 100 °C[b] |
|---|---|---|---|
| di(2,4-xyl)PPh | − | − | − |
| di(2-Me-4-FPh)PPh | ++ | ++ | − |
| P($o$-tol)$_3$ | ++ | − | − |
| P(2,4-xyl)$_3$ | ++ | ++ | − |
| P(2-Me-4-FPh)$_3$ | − | − | − |
| P(2,6-xyl)$_3$ | − | − | − |
| P($o$-anis)$_3$ | − | − | − |
| (DPPh)EtOMe | − | − | − |
| P(2-MOMPh)$_3$ | − | − | − |
| ($t$-Bu)$_2$PPh | ++ | − | ++ |
| ($t$-Bu)$_2$P($o$-tol) | − | − | − |
| ($t$-Bu)$_2$PFc | ++ | ++ | ++ |
| P($t$-Bu)$_3$ | ++ | ++ | ++ |
| DPPDPE | − | − | − |
| DTPDPE | − | − | − |
| DTPX | ++ | − | − |

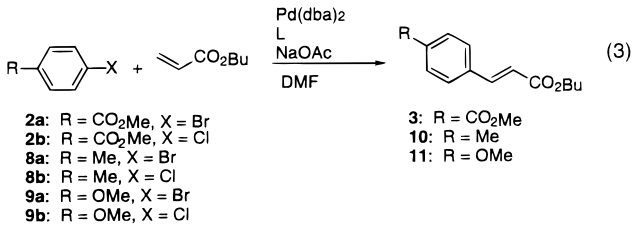
[a] Reactions were run at the indicated temperature for 4 h as described in the Experimental Section. −, weak or no observed fluorescence in isolated resin; ++, strong or moderate fluorescence in isolated resin. [b] Reaction was run with resin **1b** for 12 h.

for each ligand to generate reliable yield data. Comparison of the solution-phase reactions analyzed by GC with the reactions of solid-supported substrate analyzed by fluorescence shows a high level of agreement (Table 3). All of the ligands that gave GC yields higher than 80% showed strong fluorescence in the rapid assay. Only P($o$-anis)$_3$, (DPPPh)EtOMe, and DPPDPE were judged active by the fluorescence assay while giving low (<35%) yields of **3** by GC analysis. Increasing the reaction time in the solution-phase reactions of these three ligands showed that (DPPPh)EtOMe was, indeed, modestly active (66% yield after 4 h), but the others were not. Thus, the weaker fluorescence of the beads from reactions using P($o$-anis)$_3$ and DPPDPE does correspond to lower activity in solution. Importantly, all of the ligands that gave negative results in the fluorescence assay provided yields of **3** that were less than 65% when analyzed in solution by GC; in other words, the assay gave no false negatives.

**C. Second Round of Screening.** Since we were able to use the assay to select the best ligands for the coupling reaction, we used the same procedure to select active ligands under more demanding reaction conditions. In this round of screening, the 11 active ligands from Table 3 were combined with five new ligands. The new ligands were chosen because they shared structural characteristics with those that showed activity in the initial assay. The new ligands are listed in Table 4. *p*-Fluorinated versions of ligands di(2,4-xyl)PPh and P(2,4-xyl)$_3$ were selected, along with a series of di(*tert*-butyl)phosphinoarenes (($t$-Bu)$_2$PPh, ($t$-Bu)$_2$P($o$-tol), and ($t$-Bu)$_2$PFc). This set of 16 ligands was evaluated using the aryl bromide resin at successively lower temperatures until only a few ligands showed activity. The ligand set was also evaluated with an aryl chloride resin, **1b**.

Reactions using resin **1a** at 75 °C for 4 h resulted in only half of the ligand set showing activity (Table 5). Reactions at 50 °C for 4 h revealed only four active ligands. Di(2-Me-4-FPh)PPh and P(2,4-xyl)$_3$, which both contain bulky *o*-tolyl substituents, were selected, along with the hindered alkylphosphine ligands ($t$-Bu)$_2$PFc and P($t$-Bu)$_3$. The commonly used P($o$-tol)$_3$ was not selected. Reactions using aryl chloride resin **1b** at 110 °C for 12 h revealed ($t$-Bu)$_2$PPh, ($t$-Bu)$_2$PFc, and P($t$-Bu)$_3$ as active ligands for Heck reactions using chloroarenes.

**D. More Detailed Solution-Phase Studies Employing the Ligands Selected by the Fluorescence Assay.** A series of small-scale (0.2 mmol) reactions were conducted in the solution phase using ligands selected by the assay for Heck reactions with a variety of aryl halides. P($o$-tol)$_3$ was also tested as a benchmark for comparison because it is a commonly used ligand that showed poor activity by our assay for reactions of aryl chlorides and aryl bromides at lower temperatures.[38] The ligands di(2-Me-4-FPh)PPh, P(2,4-xyl)$_3$, ($t$-Bu)$_2$PFc, and P($t$-Bu)$_3$, which showed activity for reaction of aryl bromides at 50 °C, were used in the Heck coupling of a series of aryl halides ranging from electron-deficient **2a** to electron-rich **9a** (eq 3).



(3)

Diphosphine ligand DTPX, which gave a positive result at 75 °C, but not at 50 °C, was also tested to determine if the assay correctly determined that this ligand produces a catalyst that is less active than those shown to be active at 50 °C.

The Heck couplings were carried out with 2.5 mol % of catalyst at 75 °C and were analyzed by GC after 2 h. Reactions involving the electron-deficient aryl halide **2a** and P($o$-tol)$_3$, P(2,4-xyl)$_3$, ($t$-Bu)$_2$PFc, or P($t$-Bu)$_3$ as ligand gave >90% yield of the cinnamate product **3** (Table 6). Reactions involving **2a** and di(2-Me-4-FPh)PPh as ligand, however, gave low yields (9−27%) of the cinnamate product. As predicted by the assay, DTPX generated a less efficient catalyst than those, except di(2-Me-4-FPh)PPh, chosen by the assay. Reactions using DTPX produced **3** in only 53% yield. When the reaction was repeated at 65 °C using only 1 mol % catalyst, P($o$-tol)$_3$ and the structurally similar P(2,4-xyl)$_3$ were the only ligands that led to significant yields of the coupled product (81 and 85%, respectively). The *tert*-butyl ligands ($t$-Bu)$_2$PFc and P($t$-Bu)$_3$ gave little or no conversion at this lower temperature (0 and 22% yield, respectively).

However, reactions using the *tert*-butyl ligands ($t$-Bu)$_2$PFc and P($t$-Bu)$_3$ gave nearly quantitative yields for electron-neutral *p*-tolyl bromide or electron-rich 4-bromoanisole using 2.5 mol % catalyst at 75 °C, while use of P(2,4-xyl)$_3$ (51% yield of **10**) and P($o$-tol)$_3$ (31% yield of **10**) produced less active catalysts. The low yield observed with P($o$-tol)$_3$ is consistent with the results from the fluorescence assay, which showed that complexes of P($o$-tol)$_3$ were less active than those of the two *tert*-butyl ligands or P(2,4-xyl)$_3$. Interestingly, reactions involving di(2-Me-4-FPh)PPh also gave good yields of **10** (67−87%), while DTPX produced a catalyst with very low activity for the formation of **10** (4% yield). Results with the electron-rich bromoanisole were similar to those observed with *p*-tolylbromide. Use of the *tert*-butyl ligands ($t$-Bu)$_2$PFc and P($t$-Bu)$_3$ again

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**Table 6.** Solution-Phase Heck Couplings with Ligands Selected by Fluorescence Assay[a]

| ligand | R = $CO_2$Me,[b] X = Br, 2 h, 75 °C | R = Me,[b] X = Br, 2 h, 75 °C | R = OMe,[b] X = Br, 2 h, 75 °C | R = $CO_2$Me,[a] X = Cl, 4 h, 110 °C | R = Me,[b] X = Cl, 22 h, 110 °C | R = OMe,[b,c] X = Cl, 24 h, 110 °C |
|---|---|---|---|---|---|---|
| P(*o*-tol)$_3$ | 97% (81%)[c] | 31% | 31% | 0% | 0% | 0% |
| di(2-Me-4-FPh)PPh | 5% (30%)[d] (2%)[e] | 67% (87%)[d] | 41% (47%)[d] | | | |
| P(2,4-xyl)$_3$ | 88% (85%)[e] | 51% | 38% | | | |
| (*t*-Bu)$_2$PPh | | | | 77% | 16% | 20% |
| (*t*-Bu)$_2$PFc | 92% (0%)[e] | 100% | 91% | 97% | 67% | 63% (80%)[f] |
| P(*t*-Bu)$_3$ | 94% (22%)[e] | 100% | 95% | 96% | 51% | 48% (44%)[f] |
| DTPX | 53% | 4% | | | | |

[a] GC yields of two runs. ArBr conversion was within 10% of the yield for all runs. Reactions were carried out with 0.2 mmol of aryl halide, 2.5 mol % Pd(dba)$_2$, 5.0 mol % L, 1.5 equiv of butyl acrylate, and 1.5 equiv of NaOAc in 2 mL of DMF. [b] See eq 3 for substrates' structures. [c] 5 mol % Pd and 10 mol % ligand used. [d] 5 mol % Pd(dba)$_2$ and 10 mol % ligand used. [e] Reactions were carried out at 65 °C using 1 mol % Pd(dba)$_2$ and 2 mol % ligand. [f] Reactions under conditions optimized by Fu et al. (ref 54): 3 mol % Pd(dba)$_2$, 6% ligand, 1 mmol of ArCl, 2.1 mmol of butyl acrylate, 1.1 mmol of $Cs_2CO_3$, 1 mL of dioxane, 110 °C, 24 h.

**Table 7.** Comparison of Ligand Activity to That of [Pd(OAc)P(*o*-tol)$_2$($C_6H_4CH_2$)]$_2$

| Catalyst | TON (× $10^{-3}$ mmol prod/mmol Pd)[a] 16 h | 90 h |
|---|---|---|
|  | 144 | 256 |
| Pd(dba)$_2$/(*t*-Bu)$_2$PFc | 113 | 151 |
| Pd(dba)$_2$/P(*t*-Bu)$_3$ | 54 | 53 |

[a] Reactions were run with 20 mmol of **2a**, 30 mmol of butyl acrylate, 30 mmol of sodium acetate, and 2 × $10^{-5}$ mmol of Pd at 100 °C. P/Pd = 2 except for palladacycle. TON is the average of two runs.

gave over 90% yield of cinnamate **11**. P(*o*-tol)$_3$ gave a much lower yield (31%), as did P(2,4-xyl)$_3$ and di(2-Me-4-FPh)PPh (38 and 41%, respectively).

The ligands shown by the assay to be active for Heck reactions with aryl chlorides, along with P(*o*-tol)$_3$, were examined in these reactions with a series of aryl chlorides at 110 °C. Reactions using P(*o*-tol)$_3$ as ligand gave no coupling product with aryl chlorides. Typically, a bromide source and higher temperatures (>140 °C) are required in order to give moderate coupling yields with aryl chlorides using the P(*o*-tol)$_3$ as ligand.[33] When using the activated aryl chloride **2b**, reactions involving the ligands (*t*-Bu)$_2$PFc and P(*t*-Bu)$_3$ gave high yields of **3** (93 and 90%, respectively) at 110 °C after 4 h, while (*t*-Bu)$_2$PPh gave a lower yield (67%). For reactions of chlorotoluene, significantly longer times were required in order to achieve moderate to high levels of conversion. Heating the reaction for 22 h at 110 °C using (*t*-Bu)$_2$PFc and P(*t*-Bu)$_3$ as ligand gave moderate yields of **10** (67 and 51%, respectively). Reactions involving (*t*-Bu)$_2$PPh gave a much lower yield (16%). Nearly identical results were obtained in the Heck coupling of the electron-rich chloroanisole. Use of 5 mol % Pd(dba)$_2$ and 10 mol % (*t*-Bu)$_2$PFc or P(*t*-Bu)$_3$ again gave moderate yields of **11** (63 and 48%, respectively) after 24 h. Thus, the activity of the *tert*-butyl ligands was superior to that of Pd(OAc)$_2$/P(*o*-tol)$_3$ mixtures for the reactions of unactivated aryl bromides and chlorides.[33,34]

We also compared the activity of these ligands with that of the dimeric palladacycle studied by Beller and co-workers[34] for coupling of activated aryl bromides with activated olefins at low catalyst loads. The coupling of 4-bromobenzonitrile and butyl acrylate was conducted using 1 × $10^{-4}$ mol % Pd at 100 °C in DMF. The reaction was monitored over time, and the results after 16 and 90 h are shown in Table 7. Although reactions involving P(*t*-Bu)$_3$ gave high yields of product for these substrates under standard catalysts loads (2.5 mol %), this ligand was significantly less active than either (*t*-Bu)$_2$PFc or the palladacycle at low catalyst loads. P(*t*-Bu)$_3$ appeared to generate a relatively short-lived catalyst with no activity observed after 16 h. However, a mixture of Pd(dba)$_2$ and (*t*-Bu)$_2$PFc showed total turnover numbers in the same range as those for the dimeric palladacycle studied by Beller and co-workers.[34] Thus, the activity of this system with reactive substrates at high temperatures is similar to those reported previously, and the activity with unreactive substrates is significantly higher.

## Discussion

**1. Evaluation of the Fluorescence Assay. A. Demonstrated Strengths.** The fluorescence-based assay described here accurately and reproducibly indicates the success of the Heck coupling reactions >95% of the time. Most importantly, the procedure selected all of the ligands that produced the most effective catalysts for Heck reactions conducted in the solution phase and analyzed by GC. Although two ligands showed modest activity by the fluorescence assay but low activity in solution, the inclusion of these ligands in subsequent experiments did not affect selection of the most active catalyst systems. They did prove to be less active ligands when reactions were analyzed by the fluorescence assay under more demanding conditions, such as lower temperature. The assay provides qualitative yield data, but subtle differences in activities between ligands were, in fact, detected. For example, DTPX, which showed activity by the assay at 75 °C but not at 50 °C, was shown to be less active by standard analytical methods than the ligand set that was selected by the assay at 50 °C. Similarly, P(*o*-tol)$_3$ was not selected by the assay at 50 °C and was shown to be significantly less active by standard methods for reaction with electron-neutral and electron-rich aryl bromides **8a** and **9a**. Thus, di(2-Me-4-FPh)PPh was the only ligand for which fluorescence analysis showed good activity at 50 °C but GC analysis of solution-phase reactions showed poor activity.

In addition to accuracy, the ability to conduct a colorimetric assay in a high-throughput fashion is crucial to the ultimate utility. We have not optimized our method for efficiency, but the procedure is significantly faster than analysis by GC or HPLC even in its crudest form. Utilizing manual, serial isolation of the resin, we were able to analyze the resin from 40 reactions in 2−3 h. By comparison, analysis of these same 40 reactions by GC required approximately 16 h of GC time. With much larger libraries, the difference in time would be even more significant. Clearly, the time required for analysis of reactions by GC increases linearly with the number of reactions, but the time required to analyze a library of reactions by fluorescence does not. Most importantly, workup of these reactions is analogous to that of standard solid-phase processes that are the core of robotics-based library synthesis. The use of microtiter

plates comprised of wells with fritted bottoms[39] should allow for rapid manual analysis of large sets of reactions, and the technique should be amenable to rapid automated analysis.

Assets of standard GC analysis are the wide range of reactions that can be evaluated by this method and the ability to obtain activity and selectivity data simultaneously. Concerning the issue of generality, the fluorescence assay should be amenable to many standard reactions for which appropriate dye-labeled and solid-supported substrates can be constructed. Solid-phase organic chemistry has been applied to a wide variety of structures,[40] making it possible to find an appropriate solid-supported substrate for the study of many different types of transformations. Similarly, the hydroxyethyl-substituted dye **5** should allow preparation of a wide variety of reactants that would bear a fluorescent tag. With the exception of some reactions modifying small molecules such as CO, $H_2$, $O_2$, and $CO_2$ that cannot be tagged, this assay should be applicable to many types of reactions.

Concerning the issue of analyzing for activity and selectivity, any assay for activity will allow one to analyze a subset of reactions in a more conventional manner for selectivity. Clearly, one would analyze for selectivity only a subset of the many systems determined to be highly reactive in an assay for activity such as our colorimetric one. Should selectivity have been an issue in our study, only a small set of the initial 40 ligands, perhaps five, would have been chosen for individual reactions to be analyzed by GC for selectivity. In addition, there are certain types of selectivity that would be evaluated along with activity by the assay for coupling of two molecules. In some cases, a catalyst may have high activity for a reaction that consumes one or both substrates but may not provide a coupled product. For example, a catalytic cycle that involves $\beta$-hydrogen elimination rather than reductive elimination often consumes two substrates in palladium-catalyzed coupling chemistry but does not generate a coupled product.[41,42] In the case of a catalyst that is highly active for addition of aryl halide but selects $\beta$-hydrogen elimination rather than reductive elimination, the solid-supported substrate would not become fluorescent. A catalyst for aryl halide reduction would, therefore, not be selected by our assay.

**B. Potential Limitations.** While the fluorescence assay has been very successful in its application to the Heck reaction, there are some potential limitations that should be explicitly stated. First, the reaction relies on parallel reactivity between reactions of solid-supported substrates and dissolved substrates. Similar reactivity is usually observed in solution- and solid-phase reactions and was clearly observed in the Heck reaction. However, significant differences in reactivity may be observed for certain catalytic systems, and a preliminary screen to determine the similarity or difference in reactivity between soluble and solid-supported substrates is advised before screening a large number of systems. For example, a reagent that may lead to stable dimeric versions of the catalyst in solution may show significantly different reactivity with substrates spacially isolated on a bead and those in solution.

The fluorescence of dyes bound to resins can also be complicated by fluorescence quenching due to interactions with the resin, other dye molecules,[43] or other species that become trapped in the resin. Given the strong correlation between the observed fluorescence and solution-phase yield data, quenching of the fluorescent dye did not appear to interfere with identification of the most active catalyst systems in the Heck reaction. Again, one should conduct a preliminary set of experiments to show that increasing conversion does lead to an increase in the intensity of fluorescence. We are currently exploring solution-based fluorescence methodologies such as measurements of fluorescence resonance energy transfer (FRET) and fluorescence anisotropy that are used to assay binding phenomena in biological systems and can be adapted to assay for covalent bond formation. These solution-phase assays may ultimately be used in cases of distinct reactivity with solid-supported and dissolved reagent. The solution-phase fluorescence measurements may also increase the speed of the assay by allowing direct measurement in solution.

**2. Improved Ligands for Heck Chemistry.** By using the assay described in this paper, five ligands for Heck couplings with aryl bromides and three ligands for Heck couplings with aryl chlorides were selected from a small library of 45 structurally varied phosphines. Of the ligands selected by our assay for activity in reactions of aryl bromides, four out of five were also highly active in standard solution-phase reactions with aryl bromide **2a** that were analyzed by GC. Two of these ligands, $(t\text{-Bu})_2$PFc and P($t$-Bu)$_3$, retained high activity with less reactive substrates such as bromotoluene and bromoanisole, while P(2,4-xyl)$_3$ gave lower yields when reactions were conducted with more electron-rich aryl bromides. Both ($t$-Bu)$_2$PFc and P($t$-Bu)$_3$ produced catalysts generating product in high turnover numbers ($10^4-10^5$), although $(t\text{-Bu})_2$PFc gave a longer lived, more active catalyst than did P($t$-Bu)$_3$. $(t\text{-Bu})_2$PFc in combination with Pd(dba)$_2$ showed turnover numbers for reactions of activated aryl bromides and activated olefins similar to those for the dimeric palladacycle studied by Beller and coworkers.[34] Moreover, $(t\text{-Bu})_2$PFc and P($t$-Bu)$_3$ generated catalysts that produced Heck products in excellent yields using 4-bromotoluene or 4-bromoanisole, substrates that give lower yields of product when the dimeric palladacycle is used.[34] Finally, the use of $(t\text{-Bu})_2$PFc gave good yields of coupled product after 1 day at 110 °C, even from reactions of butyl acrylate with chlorotoluene and chloroanisole. The dimeric palladacycle shows very low activity with these substrates, even at high temperatures.

Thus, $(t\text{-Bu})_2$PFc appears to generate the most active catalyst for the Heck coupling reaction. *tert*-Butylphosphines have recently been reported to be efficient ligands for the Suzuki coupling[44−46] of aryl chlorides as well as the coupling of aryl halides, including chlorides, with amines.[47−51] Previous reports of the use of *tert*-butylphosphines in Heck couplings have involved cyclometalated complexes.[52,53] Independent studies in Fu's laboratory[54] have corroborated our finding that tri(*tert*-

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butyl)phosphine palladium complexes are unusually active catalysts for Heck coupling of aryl chlorides, and Littke and Fu[55] have demonstrated high activity in Susuki−Miyaura reactions[56] with aryl chlorides. The high activity of the *tert*-butyl-substituted bis-phosphines has been ascribed to their strongly electron donating character, which accelerates oxidative addition.[47] However, the steric demand of the *tert*-butyl ligands should also generate higher concentrations of three-coordinated palladium complexes that would undergo olefin insertion. Mechanistic studies to determine the important features of the (*t*-Bu)$_2$PFc ligand are in progress.

## Conclusion

An assay allowing rapid visual analysis of large numbers of parallel reactions has been described. Using this assay, we were able to screen 45 ligands for their ability to form an active catalyst with palladium for the Heck coupling reaction in a short period of time. To provide a detailed account of the accuracy of this assay, each of the reactions conducted using our fluorescence assay was subsequently analyzed by GC. Although time-consuming, this set of experiments conclusively showed the assay to be accurate and reproducible. Using the leads obtained from our assay, two highly effective ligands for the Heck coupling of both aryl halides and aryl chlorides were revealed: di(*tert*-butylphosphino)ferrocene and tri(*tert*-butyl)-phosphine. Di(*tert*-butylphosphino)ferrocene is the most efficient ligand yet reported for olefination of unactivated aryl chlorides.

## Experimental Section

**General Considerations.** All reagents were commercially available and used without further purification unless noted below. DMF for Heck couplings was anhydrous grade from Aldrich and was stored and dispensed in a drybox. Wang resin 100−200 mesh with a loading of 0.60 mmol/g was purchased from Nova Biochem. Pd(dba)$_2$[57] and the palladacycle[33] were prepared according to literature procedures. The following ligands were prepared according to literature methods: P(2,4-xyl)$_3$,[58] P(2-BTF)$_3$,[59] P(2-MOMPh)$_3$,[60] DPPBz,[61] DTPF,[62] D*p*-MeOP-PF,[63] D*p*-CF$_3$PPF,[64] D*t*-BPF,[65] DPPR,[66] DPPNp,[67,68] DPPDPE,[69] DTPDPE,[62] DPPX,[69] DTPX,[62] P(2-Me-4-FPh)$_3$,[70] (*t*-Bu)$_2$PPh,[71] and (*t*-Bu)$_2$P(*o*-tol).[72] Synthesis of new ligands is described below.

All Heck reactions were carried out in sealed vials prepared in a drybox under a nitrogen atmosphere. Reaction vials were heated in an aluminum block placed on top of a heater/stirrer and surrounded by glass beads for insulation. Reported reaction temperatures are for the heating block or oil bath and are ±3 °C. GC yields were determined by comparison of product peaks to an internal standard (naphthalene) using response factors determined with authentic materials. Spectral data for Heck coupling products **10** and **11** were consistent with those reported previously.[73]

**Preparation of [Di(2,4-dimethylphenyl)phosphino]benzene (Di-(2,4-xyl)PPh).** 2,4-Dimethylbromobenzene (10.0 g, 54.1 mmol) was dissolved in 30 mL of THF and added dropwise to Mg (1.50 g, 61.7 mmol). The reaction was refluxed for 5 h and then cooled to room temperature. The Grignard solution was added dropwise to a solution of dichlorophenylphosphine (3.87 g, 27 mmol). The reaction was refluxed for 4 h and then hydrolyzed with saturated $NH_4Cl$. The mixture was extracted with ether. After the mixture was dried over $MgSO_4$, the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to give white crystals (1.54 g, 18%), mp = 139 °C. $^1$H NMR (500 MHz, $C_6D_6$): 7.02 (dd, $J$ = 4.37, 8.21 Hz, 3H), 6.89 (d, $J$ = 5.50 Hz, 3H), 6.79 (d, $J$ = 7.50 Hz, 3H), 2.48 (s, 9H), 2.07 (s, 9H) ppm. $^{31}$P{$^1$H} NMR (202 MHz, $C_6D_6$): −21.9 (s) ppm. Anal. Calcd for $C_{22}H_{23}P$: C, 82.99; H, 7.28. Found: C, 83.08; H, 7.25.

**Preparation of 2-[Di(2-trifluoromethylphenyl)phosphino]anisole ((2-BTF)$_2$P(*o*-anis)).** A solution of 0.667 g (1.67 mmol) of bis[2-(trifluoromethyl)phenyl]monochlorophosphine[74] in dry THF was chilled to −78 °C under nitrogen in a 50-mL Schlenk flask. A Grignard solution prepared from 0.411 g (2.20 mmol) of 2-bromoanisole and 58.8 mg (2.40 mmol) of Mg was added dropwise via cannula. The flask was allowed to warm to room temperature and then fitted with a reflux condenser. The reaction was then refluxed overnight, resulting in a deep reddish-brown solution. The solvent was removed in vacuo, and the residue was taken up in ether and rinsed with brine. After the organic phase was dried ($MgSO_4$), the solvent was removed with a rotary evaporator. The residue was then chromatographed on silica with 5% EtOAc in hexanes. The crude product was then taken into the drybox and recrystallized from THF/pentane, resulting in the isolation of 0.255 g (0.596 mmol, 35.7%) of **2** as a white solid. $^1$H NMR (500 MHz, $C_6D_6$): 7.47 (m, 2H), 7.15 (br, 2H), 7.05 (br, 1H), 6.86 (m, 4H), 6.68 (m, 2H), 6.40 (m, 1H), 3.05 (s, 3H) ppm. $^{31}$P NMR (202 MHz, $C_6D_6$) −28.2 (complex heptet) ppm. Anal. Calcd for $C_{21}H_{15}F_6OP$: C, 58.89; H, 3.53. Found: C, 58.78; H, 3.54.

**Preparation of 2-[Di(2-methoxyphenyl)phosphino]trifluoromethylbenzene ((2-BTF)P(*o*-anis)$_2$).** A 100-mL Schlenk flask charged with 2.02 g (14.7 mmol) of $PCl_3$, 30 mL of dry THF, and a stir bar was chilled to −78 °C under nitrogen. A Grignard solution made from 3.30 g (14.7 mmol) of 2-bromobenzotrifluoride and 0.388 g (1.1 equiv) of Mg was added dropwise via addition funnel. The reaction was warmed to room temperature and allowed to stir for 5 h. The solvent was removed in vacuo, and 50 mL of fresh THF was added. The solution was then chilled to −78 °C, and a second Grignard reagent synthesized from 5.50 g (29.4 mmol) of 2-bromoanisole and 0.846 g (35.3 mmol) of Mg was added dropwise via cannula. The reaction was allowed to warm to room temperature, and the flask was fitted with a reflux condenser. After the solution was heated at reflux overnight, the reaction was quenched with 2 mL of methanol, and the solvent was removed in vacuo. The residue was dissolved in ethyl acetate, rinsed with brine, and dried over $MgSO_4$. After removal of the solvent, the crude product was suspended in cold ether and filtered. It was then recrystallized from degassed ethanol/ethyl acetate until colorless to yield 2.25 g (5.76 mmol,

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39.2%) of **3** as a white solid. $^1$H NMR (500 MHz, $C_6D_6$): 7.54 (m, 1H), 7.34 (m, 1H), 7.09 (t, $J$ = 7.5 Hz, 2H), 6.94 (br, 2H), 6.86 (m, 2H), 6.74 (t, $J$ = 7.2 Hz, 2H), 6.46 (dd, $J_d$ = 7.8 Hz, $J_d$ = 6.0 Hz, 2H), 3.14 (s, 6H) ppm. $^{31}$P NMR ($C_6D_6$) −29.1 (q, $J$ = 95.3 Hz) ppm. Anal. Calcd for $C_{21}H_{18}F_3OP$: C, 64.62; H, 4.65. Found: C, 64.52; H, 4.60.

**Preparation of Tri(2-methoxymethyl)phosphine (P(2-MOMPh)$_3$).** Methyl (2-bromobenzyl) ether (2.21 g, 11.0 mmol) was added to a suspension of Mg (294 mg, 12.3 mmol) in 10 mL of THF. A solution of $PCl_3$ (457.7 mg, 3.33 mmol) in 50 mL of THF was prepared under $N_2$ and cooled to −78 °C. To this solution was added the Grignard reagent via cannula. The reaction was allowed to warm to room temperature and was refluxed overnight. The reaction was quenched by addition of an $NH_4Cl$ solution. The aqueous layer was washed with ether, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave a white solid, which was recrystallized from degassed ethanol to give 798 mg (61%) of a colorless solid. $^1$H NMR (500 MHz, $C_6D_6$): 7.72−7.69 (m, 3 H), 7.22−7.19 (m, 3H), 7.14−7.11 (m, 3H), 6.99−6.96 (m, 3H), 4.80 (s, 6H), 3.09 (s, 9H) ppm. $^{31}$P{$^1$H} NMR (202 MHz, $C_6D_6$): −36.0 (s) ppm. Anal. Calcd for $C_{24}H_{33}O_3P$: C, 73.08; H, 6.90. Found: C, 72.79; H, 6.90.

**Preparation of Tri[2-(1-methoxyethyl)phenyl]phosphine (P(2-MOEPh)$_3$).** This ligand was prepared in an identical fashion to P(2-MOMPh)$_3$ using 1-(2-bromophenyl)ethyl methyl ether (749 mg, 3.50 mmol), magnesium (89.0 mg, 3.70 mmol), and $PCl_3$ (137.3 mg, 1.00 mmol). A greasy, white solid was obtained (240 mg, 55%). This product is presumably a mixture of four diastereomers. The NMR spectra of this compound gave very broad resonances. $^1$H NMR (500 MHz, $C_6D_6$): 7.64−7.61 (m, 3H), 7.14−7.10 (m, 3H), 7.09−7.06 (m, 1H), 7.01−6.98 (m, 2H), 6.87−6.84 (m, 3H), 5.38−5.19 (br m, 3H), 3.11−2.94 (br m, 9H), 1.53−1.36 (br m, 9H) ppm. $^{31}$P{$^1$H} NMR (202 MHz, $C_6D_6$): −40.5 (br m) ppm.

**Preparation of [Di(4-fluoro-2-methylphenyl)phosphino]benzene (Di(2-Me-4-FPh)PPh).** This ligand was prepared as described for di-(2,4-xyl)PPh. The Grignard reagent formed from 10 g of 2-bromo-5-fluorotoluene (90.1 mmol) and Mg (2.22 g, 91.7 mmol) was added to 2.80 mL of dichlorophenylphosphine (90 mmol) in 10 mL of THF. The crude product was recrystallized from methanol to give 2.1 g (10%) of colorless plates, mp = 86 °C. $^1$H NMR (500 MHz, $C_6D_6$): 7.25−7.21 (m, 2H), 7.07−7.05 (m, 3H), 6.75−6.72 (m, 2H), 6.69 (dt, $J$ = 3.33, 9.41 Hz, 2H), 6.57 (td, $J$ = 2.64, 8.50 Hz, 2H) ppm. $^{31}$P{$^1$H} NMR (202 MHz, $C_6D_6$): −23.1 (s) ppm. Anal. Calcd for $C_{20}H_{17}F_2P$: C, 73.61; H, 5.25. Found: C, 73.58; H, 5.26.

**Preparation of [Di(*tert*-butyl)phosphino]ferrocene ((*t*-Bu)$_2$PFc).** Ferrocene (9.311 g, 50.00 mmol) was deprotonated by addition of a 2.6 M solution of *t*-BuLi (38 mL, 98.8 mmol) by the method of Guillaneux and Kagan.[75] The lithioferrocene was quenched with di-(*tert*-butyl)chlorophosphine (25.0 g, 138 mmol). The crude product was sublimed twice (85 °C, 0.01 mmHg) to generate material that was used in these studies, but it was contaminated with roughly 5% of ferrocene (4.46 g, 27% yield). A third sublimation gave analytically pure material. $^1$H NMR (300 MHz, $C_6D_6$): 4.17 (m, 2H), 4.08 (m, 2H), 4.04 (s, 5H), 1.23 (s, 18H). $^{31}$P{$^1$H} NMR (202 MHz, $C_6D_6$): 27.5 (s) ppm. Anal. Calcd for $C_{18}H_{27}FeP$: C, 65.47; H, 8.24. Found: C, 65.51; H, 8.34.

**Preparation of Methyl 4-(3-Butoxy-3-oxo-1-propenyl)benzoate (3).** In a drybox, $Pd(OAc)_2$ (12.2 mg, 0.05 mmol), P(*o*-tol)$_3$ (68.5 mg, 0.23 mmol), sodium acetate (182 mg, 2.22 mmol), and **2a** (430 mg, 2.00 mmol) were combined in a small, round-bottom flask and were dissolved in 10 mL of DMF. To this solution was added butyl acrylate (0.32 mL, 2.23 mmol). The reaction was placed in an oil bath at 100 °C and stirred for 6 h. The reaction mixture was cooled and poured into saturated $NH_4Cl$ solution. The aqueous layer was extracted with ether. The ether layers were washed with brine and dried over $MgSO_4$. Removal of solvent gave a yellow oil that was purified by flash chromatography, eluting with 5% ethyl acetate in hexanes. The product was recovered as a yellow solid (462.3 mg, 88%). $^1$H NMR (300 MHz, $CDCl_3$): 8.05 (dd, $J$ = 1.65, 7.17 Hz, 2H), 7.68 (d, $J$ = 16.04 Hz, 1H), 7.58 (d, $J$ = 8.33 Hz, 2H), 6.53 (d, $J$ = 15.89 Hz, 1H), 4.22 (t, $J$ = 6.64 Hz, 2H), 0.3.93 (s, 3H), 1.72−1.65 (m, 2H), 1.48−1.41 (m, 2H), 0.97 (t, $J$ = 7.35 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): 166.5, 166.3, 143.0, 138.7, 131.3, 130.0, 127.8, 120.6, 64.5, 52.1 30.7, 19.1, 13.6 ppm. FTIR (KBr pellet): 2949, 1724, 1640, 1280, 1196 cm$^{-1}$. Anal. Calcd for $C_{15}H_{20}O_5$: C, 68.68; H, 6.92. Found: C, 68.64; H, 6.75.

**Preparation of Aryl Halide-Functionalized Resin.** Wang resin (3.023 g, 1.814 mmol) was suspended in 50 mL of dry methylene chloride and stirred for 10 min to allow the beads to swell. Pyridine (1.46 mL, 18.1 mmol) was added, followed by 4-bromobenzoyl chloride (1.833 g, 8.960 mmol). The reaction was stirred for 12 h and then filtered. The resin was then suspended in DMF and stirred for 10 min before being filtered. This process was repeated once more with DMF and then with methylene chloride, methanol (2×), and ether. The resin was then dried in vacuo for several hours until a free-flowing solid was obtained. FTIR (KBr pellet) showed no residual OH peak and a strong C=O stretch at 1721 cm$^{-1}$. To quantify the loading, the aryl halide was cleaved from the resin by treatment of 100 mg of the resin with 2 mL of 1:1 TFA/methylene chloride. After being stirred for 1 h, the mixture was filtered and the resin washed with methylene chloride and methanol. The solvent was removed from the filtrate, and the residue was dissolved in 3 mL of 3:1 methylene chloride/methanol and cooled to 0 °C. A solution of TMS-diazomethane in hexanes was added until the yellow color persisted. After the solution was stirred for 3 h, the solvent was removed, the residue was dissolved in methylene chloride, and acetophenone (8.2 mg) was added. The solution was then analyzed by GC. Resin **1a** was found to have a loading of 0.57 mmol/g (theoretical maximum = 0.54 mmol/g), while resin **1b** had a loading of 0.59 mmol/g (theoretical maximum = 0.55 mmol/g).

**Synthesis of 2-[(4-Methyl-2-oxo-2*H*-7-chromenyl)oxy]ethyl Acrylate (6). (i) Preparation of 2[(4-Methyl-2-oxo-2*H*-7-chromenyl)oxy]-ethanol (5).** Coumarin **4** (5.300 g, 30.08 mmol) and potassium carbonate (8.376 g, 59.92 mmol) were dissolved in 100 mL of DMF. To this suspension was added 2-bromoethanol (3.20 mL, 45.1 mmol). The reaction was heated at 100 °C and stirred overnight. TLC (20% ethyl acetate/$CH_2Cl_2$) showed complete conversion of **4** to a single new product with lower $R_f$. The reaction was allowed to cool and was then poured into 10% HCl and shaken to give a white suspension. The mixture was extracted with $CH_2Cl_2$. The combined organic extracts were washed with water and brine and then dried over magnesium sulfate. Removal of solvent gave a pale yellow solid (6.066 g, 92% yield), which was judged pure by $^1$H NMR spectroscopy and was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$): 7.65 (d, $J$ = 9.44 Hz, 1H), 6.94 (m, 2H), 6.18 (s, 1H), 4.95 (t, $J$ = 4.32 Hz, 1H), 4.08 (t, $J$ = 4.42 Hz), 3.76−3.71 (m, 2H), 2.37 (s, 3H) ppm.

**(ii) Acryloylation of 5.** Alcohol **5** (6.066 g, 27.55 mmol) was suspended in 150 mL of $CH_2Cl_2$ and cooled to 0 °C. To the suspension was added triethylamine (5.80 mL, 41.5 mmol), followed by acryloyl chloride (2.40 mL, 29.5 mmol). The solid was slowly consumed, giving a yellow solution. After the solution was stirred for 4 h, the reaction was extracted with water. The resulting aqueous solution was extracted with methylene chloride, and combined organic extracts were washed with saturated sodium bicarbonate solution and brine. After the organic solutions were dried over magnesium sulfate, the solvent was removed under reduced pressure. The resulting yellow oil was purified by flash chromatography ($SiO_2$), eluting with a gradient of 0−10% ethyl acetate in methylene chloride to give 5.385 g (71%) of a pale yellow solid, which was judged to be pure by $^1$H NMR spectroscopy. Recrystallization from ethanol gave an off-white solid that was analytically pure. $^1$H NMR (500 MHz, $CDCl_3$): 7.50 (d, $J$ = 8.9 Hz, 1H), 6.88 (dd, $J$ = 2.17, 8.82 Hz, 1H), 6.83 (d, $J$ = 2.49 Hz, 1H), 6.45 (d, $J$ = 17.30 Hz, 1H), 6.17 (m, 1H), 6.14 (s, 1H), 5.87 (d, $J$ = 10.26 Hz, 1H), 4.54 (t, $J$ = 4.64 Hz, 2H), 4.28 (t, $J$ = 4.62 Hz, 2H), 2.39 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): 165.9, 161.4, 161.1, 155.2, 152.4, 131.6, 127.9, 125.6, 114.0, 112.5, 112.2, 101.6, 66.3, 62.4, 18.7 ppm. FTIR (KBr pellet): 2956, 1704, 1613, 1395, 1195 cm$^{-1}$. Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.40; H, 5.23.

**Heck Coupling of Methyl 4-Bromobenzoate (2a) and 6.** In a drybox, $Pd(dba)_2$ (14.4 mg, 0.025 mmol), P(*o*-tol)$_3$ (15.1 mg, 0.050 mmol), sodium acetate (90.2 mg, 1.10 mmol), **2a** (213.8 mg, 0.994 mmol), **6** (301.2 mg, 1.098 mmol), and DMF (10 mL) were placed into a small, round-bottom flask which was then sealed with a septum. The flask was heated in an oil bath at 100 °C for 2 h and then allowed

(75) Guillaneux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502−2505.

to cool to room temperature. The reaction mixture was diluted with methylene chloride, and the resulting solution was washed with saturated ammonium chloride. The aqueous layer was extracted with methylene chloride. The combined organic layers were then washed with water and dried over magnesium sulfate. Evaporation of solvent under vacuum gave a yellow solid, which was purified by flash chromatography, eluting with methylene chloride followed by 5% ethyl acetate in methylene chloride. The product (**7**) was recovered as a white solid (375.0 mg, 92%). $^1$H NMR (300 MHz, $CDCl_3$): 8.05 (d, $J$ = 8.3 Hz, 2H), 7.75 (d, $J$ = 16.06 Hz, 1H), 7.59 (d, $J$ = 8.31 Hz, 2H), 7.52 (d, $J$ = 8.73 Hz, 1H), 6.93−6.86 (m, 2H), 6.57 (d, $J$ = 15.98 Hz, 1H), 6.16 (s, 1H), 4.62 (m, 2H), 4.32 (m, 2H), 3,93 (s, 3H), 2.40 (d, $J$ = 1.04 Hz, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): 166.3, 166.2, 161.4, 161.1, 155.2, 152.4, 144.1, 138.4, 131.6, 130.1, 128.0, 125.7, 119.8, 114.0, 112.5, 112.3, 101.7, 66.4, 62.7, 52.3, 18.6 ppm. FTIR (KBr pellet): 2960, 1715, 1620, 1267, 1176 cm$^{-1}$. UV ($CH_2Cl_2$) $\lambda_{max}$ = 288 ($\epsilon$ = 24 500), 320 ($\epsilon$ = 16 600) nm. Anal. Calcd for $C_{23}H_{20}O_7$: C, 67.64; H, 4.94. Found: C, 67.61; H, 4.98.

**General Method for Fluorescence Assay.** In a drybox, each of 20 vials was charged with sodium acetate (1.8 mg, 0.02 mmol) and resin **1a** or **1b** (25 ± 2 mg, 0.014 mmol). To each vial was added 100 $\mu$L of a 0.20 M DMF solution of **6**, 25 $\mu$L of a 0.027 M DMF suspension of $Pd(dba)_2$, and 40.5 $\mu$L of a toluene solution of ligand that was 0.05 M in monophosphine ligand or 0.025 M in bis-phosphine ligand. The vials were sealed and removed from the drybox. The vials were placed in a preheated aluminum block at the appropriate temperature and stirred for 4 h. After the reactions were allowed to cool, the resin was transferred to a microcentrifuge tube using DMF. The resin was spun down and the supernatant poured off. This process was repeated twice more with DMF, and the beads were suspended in a small amount of methylene chloride and allowed to stand for 5 min to extract the DMF from the beads. Methanol was added to sink the beads. The sample was centrifuged, and the liquid was decanted. The washing/centrifuging cycle was repeated once more with methanol and then with ether. The resin was then dried at 40 °C for 1 h. At this point, the fluorescence was observed by shining a hand-held UV lamp over the resin. To observe the resin from all reactions simultaneously, the resins were attached to a blackened microscope slide by using silicone grease. No change in the fluorescence of the samples was observed over the period of several months.

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