

Screening of Homogeneous Catalysts by Fluorescence Resonance Energy Transfer. Identification of Catalysts for Room-Temperature Heck Reactions

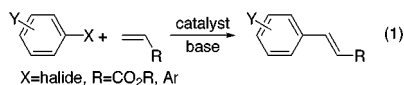
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Methods to screen catalyst activity rapidly are being developed to address the challenge of pinpointing the optimal catalyst for a particular reaction or of generating a lead catalyst structures for a new process.¹ Previous high-throughput screening methods have utilized HPLC,² mass spectrometric,³ colorimetric,⁴ IR thermographic,⁵ capillary electrophoretic,⁶ and fluorescence^{7,8} methods. None of these methods apply to all problems. Many of them are relatively slow, are equipment intensive, are specific to a particular reaction, or analyze activity for formation of any product and not necessarily the one desired.

We envisioned an assay that could provide a more general, rapid approach to screen for product formation that would use inexpensive, currently available equipment and that would be highly sensitive, noninvasive, and time resolved. To develop this assay, we decided to build upon our qualitative fluorescent method that used substrates conveniently tagged with a fluorophore.⁷ We report a method to screen for transition metal-catalyzed reactions based on Fluorescence Resonance Energy Transfer (FRET) and the use of this assay to identify catalysts for room-temperature Heck reactions (eq 1)⁹ of aryl bromides. FRET has been exploited as a highly sensitive assay for biological systems. We have adapted this assay for homogeneous catalysis.



(1) Crabtree, R. H. *Chem. Commun.* **1999**, 1611–1616. Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, 3, 313–319. Jandeleit, B.; Weinberg, W. H. *Chem. Ind.* **1998**, 19, 795–798. Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, 38, 2494–2532. Bein, T. *Angew. Chem., Int. Ed.* **1999**, 38, 323–326.

(2) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **1996**, 35, 220–222. Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, 120, 9180–9187.

(3) Senkan, S.; Krantz, K.; Ozturk, S.; Zengin, V.; Onal, I. *Angew. Chem., Int. Ed.* **1999**, 38, 2794–2799. Hinderling, C.; Chen, P. *Angew. Chem., Int. Ed.* **1999**, 38, 2253–2256. Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, 38, 1758–1761. Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, 38, 1755–1758.

(4) Lavastre, O.; Morken, J. P. *Angew. Chem., Int. Ed.* **1999**, 38, 3163–3165. Cooper, A. C.; McAlexander, L. H.; Lee, D.-H.; Torres, M. T.; Crabtree, R. H. *J. Am. Chem. Soc.* **1998**, 120, 9971–9972.

(5) Reetz, M. T.; Becker, M. H.; Liebl, M.; Furstner, A. *Angew. Chem., Int. Ed.* **2000**, 39, 1236–1239. Taylor, S. J.; Morken, J. P. *Science* **1998**, 280, 267–270. Holzwarth, A.; Schmidt, H.-W.; Maier, W. F. *Angew. Chem., Int. Ed.* **1998**, 37, 2644–2650.

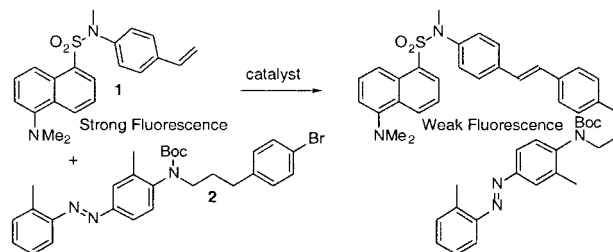
(6) Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem., Int. Ed.* **2000**, 39, 3891–3893. Zhang, Y.; Gong, X.; Zhang, H.; Larock, R. C.; Yeung, E. S. *J. Comb. Chem.* **2000**, 2, 450–452.

(7) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, 121, 2123–2132.

(8) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, 121, 4306–4307. Harris, R. F.; Nation, A. J.; Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2000**, 122, 11270–11271.

(9) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 100, 3009–3066. For a room temperature process with tetraalkylammonium promoters and vinyltrimethylsilane as olefin see: Jeffery, T. *Tetrahedron Lett.* **1999**, 40, 13–1676.

Scheme 1



For many years, FRET has been used to measure binding constants and enzyme activity.¹⁰ FRET occurs when the emission band of one molecule overlaps with an excitation band of a second molecule, and when the two chromophores are located within 20–80 Å of each other. Upon excitation of the fluorophore that absorbs at the higher energy (the FRET donor), quenching of its emission occurs by the FRET acceptor. At an appropriate constant total concentration of free and associated FRET pairs, the emission of the FRET donor is inversely related to the mole fraction of associated molecules. Thus, the product yields for a reaction that forms a covalent bond can be determined fluorimetrically by using an inexpensive, automated fluorescence plate reader when using one reagent containing a fluorophore and a second containing a quencher.

Scheme 1 shows the two reagents we have chosen for our first study, in which we evaluated catalysts for low-temperature Heck reactions. A dansyl fluorophore was tethered covalently to a styrenyl group, and an azodyne quencher was tethered to an aryl bromide. Compounds **1** and **2** (Scheme 1) were synthesized by conventional methods (see Supporting Information). A fluorophore and quencher were chosen that contained functionality that is compatible with most cross-coupling processes, including Heck reactions. The dansyl group has an emission wavelength that overlaps with an absorption band of the diazo compound. Upon covalent linking of the two molecules by the Heck coupling, the emission of the dansyl group was quenched by the diazo compound. The emission intensity was then converted to reaction yield by using a linear plot correlating emission intensity to mole fraction of coupled product. We generated this standard curve by preparing 10⁻⁵ M solutions in *m*-xylene containing various mole fractions of the two reagents and isolated product. Correlation coefficients obtained for such plots were typically 0.99.

With appropriate substrates in hand, we conducted a set of Heck reactions in a 96-well format, delivering reagents from stock solutions using a multichannel pipet. Each well contained a different phosphine, some of which were commercially available and some of which we prepared by solution-phase methods. The structures and synthetic procedures for the 96 phosphines evaluated in this assay are provided as Supporting Information.

All reactions contained a 1:1 ratio of compounds **1** and **2**, 2.5 equiv of Et₃N, 37.2 μL of DMF solvent, 5.0 mol % of CpPd(allyl), and 5.0 mol % of ligand. The reactions were conducted using an aluminum reaction block containing a 96-well glass plate. The plate was sealed with a single Teflon sheet and Viton gasket. The glass plate was then heated with an agitating aluminum block at 70 °C for 15 h. After this time, a 3.3 μL aliquot was removed from each well, diluted in *m*-xylene to 1.0 × 10⁻² mM, and analyzed (1 s/well) on an automated fluorescent plate reader. This assay was run in duplicate. Of the 80 ligands which showed moderate activity (greater than 50% yield), only four showed a difference between the average yield and the yields for

(10) Stryer, L.; Haugland, R. P. *Proc. Natl. Acad. Sci.* **1967**, 58, 719–726. Wu, P.; Brand, L. *Anal. Biochem.* **1994**, 218, 1–13.

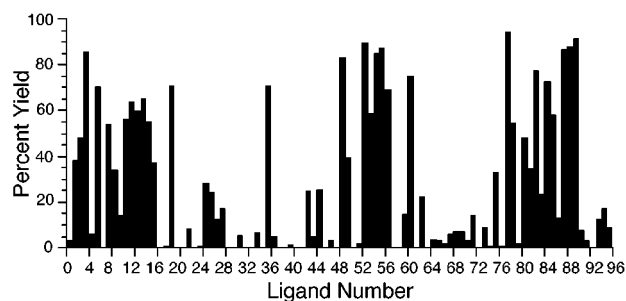


Figure 1. Yields by FRET for 96 reactions with different ligands.

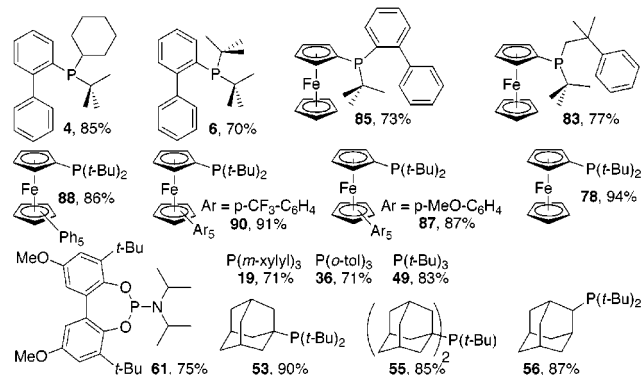


Figure 2. Ligands that gave $\geq 70\%$ yield of Heck product (Ligand #, Yield).

the individual runs that was greater than 8%. The results of this screen are shown in Figure 1. Of the 95 ligands used, 15 provided reaction yields greater than or equal to 70% (Figure 2).

The 15 ligands that generated the most active catalysts were then used in a second screen to determine if the optimal solvent for each catalyst system varied with structure. With the structures of the ligands contained in the most active catalysts of the first screen in mind, we synthesized 1-adamantyl-*tert*-butyl ferrocenyl phosphine (FcP(*t*-Bu)Ad) and included it in the second screen. An aluminum block containing 96 7 × 40 mm glass vials was assembled containing the 15 ligands in Figure 2 and FcP(*t*-Bu)-Ad. Six different solvents were used: toluene, dioxane, 1,2-dichloroethane, butyronitrile, propyl methyl ketone, and a 1:1 mixture of butyronitrile with propyl methyl ketone. Considering that Heck reactions are almost always run in polar solvents such as DMF, it was remarkable that these highly active catalysts showed little solvent effect when using a base, such as NEt₃, that is miscible with all the solvents (see Supporting Information for details). Because this method for determining product yield is unusual, we evaluated the yields of several reactions by HPLC using an internal standard. Only 1 of 10 cases showed a yield by HPLC that was more than 10% different from the yield determined by FRET, and this discrepancy was readily identified by the duplicate experiment analyzed by FRET. The ligand in this experiment, P(*t*-Bu)₃, showed a high yield in its reaction conducted in the second plate analyzed by FRET.

In general, Heck reactions are conducted at elevated temperatures. Reports of catalyst systems labeled “highly active” involve temperatures in the range of 115–140 °C.¹¹ Although a number of these systems produce high turnover numbers, they do not operate at low temperatures. Low-temperature processes are important for reactions of substrates that are less stable than the common model substrates, and room-temperature reactions are useful for parallel synthesis.

Table 1. Room-Temperature Heck Reactions of Aryl Bromides^a

ArBr + $\text{CH}_2=\text{CH}-\text{R}$		$\xrightarrow[1.2 \text{ eq. NEt}_3, \text{ DMF, RT}]{2.5 \text{ mol\% Pd(dba)}_2, 5.0 \text{ mol\% L}}$		Ar-CH=CH-R		
Entry	Ar	Yield(%)	Entry	Ar	Yield(%)	
	R = $\text{CH}_2=\text{CH}-\text{C}(=\text{O})\text{OMe}$		L = Ph ₅ FcP(<i>t</i> -Bu) ₂	6		94
			L = 1-AdP(<i>t</i> -Bu) ₂			
1		91	7		93	
2		91	8		99	
3		95	9		94	
4		88				
5		89				

^a Reactions conducted on a 1 mM scale in DMF for 20 h with 1.0 equiv of aryl halide, 1.1 equiv of vinyl substrate, 2.5 mol % of Pd(dba)₂, 5.0 mol % of L, and 1.1 equiv of NEt₃. Isolated yields are an average of two runs.

Of the ligands in Figure 2, two of the most active members, 1-adamantyl-di-*tert*-butyl phosphine and Ph₅FcP(*t*-Bu)₂, were used as candidates for room-temperature Heck reactions. 1-Adamantyl-*tert*-butyl phosphine is new, and Ph₅FcP(*t*-Bu)₂ was recently used for efficient C–O bond formations.¹² Indeed, palladium complexes comprised of these ligands catalyzed the Heck reaction of aryl bromides at room temperature.

Table 1 summarizes room-temperature reactivity of catalysts generated from two of the ligands identified as highly active by our screening method. Both ligands catalyzed Heck reactions involving activated substrates at room temperature, as well as deactivated substrates such as bromoanisole. For reactions of acrylate substrates, the ferrocenyl ligand provided a more active catalyst system than AdP(*t*-Bu)₂. However, a reaction of 2-bromoanisole with methyl acrylate did not go to completion after 33 h at room temperature with the ferrocenyl ligand, while 2-bromoanisole was coupled in high yield to styrene by the adamantyl ligand.

Because of the large number of FRET pairs, this method may prove suitable for screening of catalysts for many different reactions and, perhaps, for high-throughput kinetic analysis. However, the FRET pair used here should, alone, serve as suitable tags for reagents in many reactions such as aryl halide amination, aryl halide etherification, carbonyl α -arylation, Suzuki coupling, and Hiyama coupling with silanes. Future studies will focus on these reactions, as well as determining the full scope of the catalyst systems for low-temperature Heck reactions, using aryl chloride variants of **2** to identify systems for room-temperature Heck reactions of aryl chlorides, and conducting mechanistic studies to determine the origin of the high activity of the systems uncovered here.

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Supporting Information Available: Structures and synthetic methods for preparation of ligands used in the screening assay and experimental procedures for catalyst screening and for room temperature Heck reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Hermann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Ofele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357–1364. Ohff, M.; Ohff, A.; Milstein, D. *Chem. Commun.* **1999**, 357–358. Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361–1362. Reetz, M.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, 8449–8452.

(12) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.