Reactive Dyes as a Method for Rapid Screening of Homogeneous Catalysts

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Received May 26, 1998

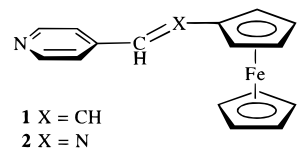
The advent of combinatorial chemistry[1] has raised the question of how to apply these methods to homogeneous catalyst discovery[1b,c] where a wide variety of rapid parallel assays will be needed. Recent reports have proposed IR thermography[1b] or laser photoionization[1d] to select active catalysts. The formation of colored products has long been used[2] for monitoring enzyme reactions, and here we discuss reactive dyes that change color upon undergoing a catalytic reaction. Visual selection of the most active candidate catalysts should then be possible by noting which catalysts cause the most rapid color change. Further studies will always be required to confirm that the "hits" indeed correspond to active homogeneous catalysts and to determine the other properties of each catalyst. In this paper we describe the screening of conventional catalyst candidates for alkene and imine hydrosilation with reactive dye−substrates. We have chosen a well-known reaction[3] with well-established characteristics to test the method but will extend this approach to other reactions in the future.

The new dyes contain an electron donor (*D*) and an acceptor (*A*) group linked by the appropriate reactive functionality (*RF*), a C═C or a N═C bond in this case: *D*-CH═CH-*A* and *D*-N═CH-*A*. When the reactive functionality is saturated upon undergoing the catalytic reaction of interest, the electronic connection between the *D* and the *A* groups is severed, and the intensity of color is strongly diminished; the result is an apparent bleaching of the dye color.

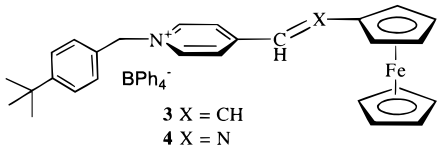
We have avoided the commercially preferred[4] *A* and *D* groups which have undesired functionality, such as -NR_2, -NO_2 or -OR, that could bind to, oxidize, or otherwise inhibit the catalysts under study. Instead, we have used a ferrocenyl (Fc) *D* group and a pyridinium *A* group, so that the *RF* group is the only part of the dye expected to show significant affinity for the catalyst.

We have synthesized the known compound *trans*-**1**[5] and the new compound **2**[6] in acceptable yields by conventional routes. Pro-dyes **1** and **2** are strongly colored, being violet-red (**1**) or dark red (**2**) in THF or EtOAc; the UV−vis spectral data are shown in Table 1.

Quaternization proceeds readily (DMF, 25−80 °C) with a variety of benzyl halides, but 4-(*tert*-butyl)benzyl bromide gave the most soluble derivatives. Anion exchange (excess $NaBPh_4$, acetone) to give[6b] the BPh_4^- salts **3** and **4** avoids the presence of potentially ligating halide counterions. Conversion of pyridines **1** and **2** to the more strongly electron-accepting pyridinium salts **3** and **4** led to a significant intensification and red shift of the absorption maxima (Table 1); **3** was deep purple and **4** was dark blue in THF or EtOAc. The dyes are somewhat solvatochromic.[6c] The ^3J(H,H′) ^{1}H NMR coupling constant[7] for the CH═CH group of **3** was 15.9 Hz, consistent with a *trans* geometry. N-substituted imines such as **4** are not expected[8] to be rigid but tend to adopt a *trans* geometry. Each product showed a useful IR signature from the *RF* group (**3**, ν(CC) = 1675 cm^{-1}{m}; **4**, ν(NC) = 1636 cm^{-1}{ms}).



1 X = CH
2 X = N



3 X = CH
4 X = N

With the dyes **3** and **4** in hand, we were able to implement the rapid screening protocol. Twelve hydrosilation catalysts[9a−c] were assayed (Table 2). Some were known to be active (e.g., entries 4 and 6), some were not previously studied for alkene hydrosilation (entries 8 and 10[9d]), and one was an entirely new compound (entry 11). Assays were run in a homemade 60-well plate machined from $^3/_4$-in Teflon (well capacity, 1 mL) in a glovebox under N_2 and Ar.[10] Stock solutions of Ph_2SiH_2 (5.0×10^{-2}M),[9e] dye (alkene, 3.3×10^{-4}M; imine, 6.6×10^{-4}M),[9f] and catalysts (3.3×10^{-4}M) were prepared in degassed anhydrous THF. Fixed volumes (silane, 0.100 mL; dye, catalyst 0.200 mL each) of the

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(6) (a) A mixture of ferrocenylamine (1.41 g, 7.0 mmol) and 4-pyridinecarboxaldehyde (0.75 g, 7.0 mmol) in benzene (50 mL) was refluxed with $MgSO_4$ (0.5 g) for 2 h. The reaction mixture was cooled to room temperature and the $MgSO_4$ filtered off. The filtrate, concentrated under reduced pressure, gave a dark red solid, which was purified by chromatography on alumina with 10/90 (v/v) ethyl acetate/hexane. The dye was obtained as a red solid (1.9 g, 94% yield). ^{1}H NMR ($CDCl_3$, 25 °C) 8.66 (d, J = 7.5 Hz, 2H), 8.56 (s, 1H), 7.63 (d, J = 7.5 Hz, 2H), 4.62 (t, J = 2.1 Hz, 2H), 4.36 (t, J = 2.1 Hz, 2H), 4.21 (s, 5H). Anal. Calcd for $C_{16}H_{14}FeN_2$: C, 66.20; H, 4.86; N, 9.65. Found: C, 66.62; H, 4.88; N, 9.38. (b) The pro-dyes **1** and **2** (3.46 mmol) were treated with 4-(*tert*-butyl)benzyl bromide (0.96 mL, 5.2 mmol) in DMF (50 mL) at 80 °C for 15 min. The cooled solution was poured into 1:1 (v/v) Et_2O/hexanes (100 mL) to precipitate a dark-colored solid, which was filtered, washed with Et_2O (3 × 30 mL), and dissolved in acetone (50 mL). Addition of $NaBPh_4$ (1.2 g, 3.5 mmol), stirring for 12 h, and removal of the acetone in vacuo gave a solid which was extracted with CH_2Cl_2 (2 × 20 mL). Evaporation of the combined extracts and recrystallization from 5:1 (v/v) MeOH/THF gave crystals of the products **3** (78%) and **4** (86%). (c) For an example, in DMSO, λ_{max} (ϵ) for **3** is 554 nm (62 000). This means that control wells need to be run in the same solvent during any catalyst assays.

(7) ^{1}H NMR ($CDCl_3$, 25 °C) of **3**: 7.55 (br s, 8H), 7.32 (d, J = 7.5 Hz, 2H), 7.12 (d, J = 15.9 Hz, 1H), 6.95 (m, 8H), 6.78 (d, J = 7.5 Hz, 2H), 6.77 (m, 4H), 6.25 (d, J = 5.4 Hz, 2H), 6.18 (d, J = 15.9 Hz, 1H), 6.08 (d, J = 5.4 Hz, 2H), 4.54 (br s, 4H), 4.18 (br s, 5H), 4.10 (s, 2H), 1.29 (s, 9H). Anal. Calcd. for $C_{52}H_{50}BFeN$: C, 82.69; H, 6.69; N, 1.85. Found: C, 82.40; H, 6.92; N, 1.78. ^{1}H NMR ($CDCl_3$, 25 °C) of **4**: 8.42 (s, 1H), 7.41 (m, 13H), 6.87 (m, 9H), 6.84 (m, 7H), 4.65 (t, J = 2.1 Hz, 2H), 4.57 (t, J = 1.8 Hz, 2H), 4.43 (s, 2H), 4.18 (s, 5H), 1.29 (s, 9H). Anal. Calcd for $C_{51}H_{49}BFeN_2$: C, 81.0; H, 6.53; N, 3.70. Found: C, 80.68; H, 6.39; N, 3.70.

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(9) (a) Some of these compounds had shown homogeneous catalytic activity in prior work.[3,9b,c] (b) Chaloner, P. A. *Handbook of Coordination Catalysis in Organic Chemistry*; Butterworths: London, 1986. (c) Barber, D. E.; Lu, Z,; Richardson, T.; Crabtree, R. H. *Inorg. Chem.* **1992**, *31*, 4709. (d) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Ofele, K.; Beller, M., *Chem. Eur. J.* **1997**, *3*, 1357. (e) Et_2SiH_2 and Ph_2SiH_2 were found to be the most reactive silanes tried in a preliminary assay, and Ph_2SiH_2 was therefore used subsequently. (f) More of the less intensely colored imine dye was required per well than of the more intense alkene. (g) Digital images for a sample screen are available on the Web at http://ursula.chem.yale.edu/~crabtree/ under "Research".

S0002-7863(98)01860-5 CCC: $15.00 © 1998 American Chemical Society
Published on Web 09/11/1998

Table 1. The New Dyes

dye	formula[a]	color (native)[b]	λ_{max} (ϵ)[c]	color (reduced)[d]
1	FcCH═CH(4-py)	violet-red	460 (1900)	lt yellow
3	[FcCH═CH(4-pyBz)]BPh_4	deep purple	607 (12600)	lt yellow
2	FcN═CH(4-py)	dark red	496 (2000)	lt yellow
4	[FcN═CH(4-pyBz)]BPh_4	dark blue	686 (5200)	lt yellow

[a] Fc = ferrocenyl; py = pyridyl; Bz = *p*-(*tert*-butyl)benzyl. [b] In EtOAc or THF. [c] In ethyl acetate solution. λ_{max} in nm; ϵ in M^{-1} cm^{-1}. [d] In THF.

Table 2. Results of Hydrosilation Catalyst Screens Using Dyes **3**−**4**

		time for dye bleaching[a] (min)					
		dye **3** (alkene)			dye **4** (imine)		
	compd	t_i	t_f	$t_f - t_i$	t_i	t_f	$t_f - t_i$
1	$[Ir(cod)(PPh_3)_2]BF_4$	0:05	>45[c]	>45[c]	0:05	>45[c]	>45[c]
2	$[Rh(cod)(PPh_3)_2]PF_6$	0:03	0:35	0:32	0:02	9	9
3	$[Rh(nbd)(PPh_3)_2]PF_6$	0:04	1	0:56	0:15	1:45	1:30
4	$RhCl(PPh_3)_3$	0:03	2	1:57	0:03	3	2:57
5	$[Rh(octanoate)_2]_2$	NR[b]	NR		NR[b]	NR	
6	$RuCl_2(PPh_3)_3$	0:10	>45[c]	>45[c]	0:10	>45[c]	>45[c]
7	$NiCl_2(PPh_3)_2$	NR[b]	NR		NR[b]	NR	
8	$[Ni(tss)]_2$	NR[b]	NR		NR[b]	NR	
9	Cp_2ZrClH	NR	NR		NR[b]	NR	
10	$[Pd(Ar_2PC_6H_4CH_2)OAc]_2$	0:01	1:15	1:14	0:01	1:15	1.14
11	$[(nbd)Rh(triphos)]SbF_6$	NR	NR		NR	NR	
12	$PtCl_2(NH_3)_2$	*d*			*d*		

[a] cod = 1,5-cyclooctadiene; nbd = norbornadiene; tss = salicylaldehyde thiosemicarbazonate (2-) (*o*-O−C_6H_4CH═N−N−C(S)NH); triphos = $Ph_2PC_2H_4PPhC_2H_4PPh_2$; Ar = *o*-tolyl. t_i, initial bleaching time; t_f, final bleaching time; NR, no discernible initial loss of color over 45 min. Times in min or min:s. [b] Very weak activity evident for these catalysts only at much higher (0.2−1.0 μmol/well) catalyst loadings; these were considered too slow to be useful. [c] Cases in which catalyst color tends to mask dye color and somewhat obscures final bleaching. [d] Compound insufficiently soluble in THF (or any common organic solvent) for meaningful assay.

stock solutions, added to the appropriate wells with an adjustable microliter pipet, delivered the following molar amounts to each well: catalyst, 66 nmol; alkene dye, 66 nmol; imine dye, 130 nmol; silane, 5.0 μmol. The amounts were chosen so that the dye masks the catalyst color. The fastest catalysts (entries 1−4, 6 and 10) were also successfully run at a dye/catalyst mole ratio of 5 to show that a stoichiometric reaction of catalyst with dye is not responsible for bleaching. The silane is involatile, and the solvent is sufficiently involatile for room temperature use. Manual recording of color changes was supplemented by recording images on a digital camera.[9g] Catalyst + dye controls were always run, and dye + silane and catalyst + silane controls were run once.

Two color change events, initial and final, were recorded, corresponding to the first sign of bleaching and full bleaching, respectively. The latter is somewhat less reliable when the catalyst color interferes, but the times were reproducible (initial ±5%; final ±15%). The order of initial times does not always correlate with the order of final times for different catalysts. The initial time is likely to be most influenced by any lag time due to slow catalyst activation and the difference between initial and final times to the rate of the activated catalyst. For the concentrations used in the screens, the earliest visually detectable bleaching corresponds to ca. 40% conversion and complete visual bleaching to ca. 95% dye conversion.

The bleaching times for the catalysts (Table 2) show that Wilkinson's catalyst is, as expected, among the most highly active. The most active for initial bleaching, however, is the new palladacyclic Heck reaction catalyst (entry 10) of Herrmann[9d] et al., a compound not previously considered for hydrosilation. Even in so small a group of catalysts, we therefore have a significant new hit.

The bleaching process indicates a change has taken place, such as loss of conjugation between *A* and *D* groups, but does not prove that hydrosilation is the cause. In the case of one of the best catalysts, $RhCl(PPh_3)_3$, we therefore confirmed that the color change was indeed a result of catalytic hydrosilation of the *RF* group of the dye by running a conventional reaction with Et_2SiH_2 on dyes **3** and **4** in an NMR tube. The identity of the hydrosilated dyes was verified by NMR spectroscopy.[11]

Because of the substantially different ϵ values of alkene and imine dyes, a higher substrate/catalyst ratio was required to mask the catalyst color for the imine versus alkene dye, making the comparison of rates for alkene and imine unreliable. In future work, we plan to make a more intense imine dye to allow direct comparisons. Catalyst solubility can also be a limitation (entry 12).

To see if the dye substrates have reactivity comparable to that of a conventional substrate, we looked at a conventional reaction of the best catalysts for Ph_2SiH_2 hydrosilation of cyclooctene. Because of the high dilution in the assay, good NMR data could only be obtained in more concentrated solutions. This and the presence of initial lag times for some catalysts made direct quantitative comparison of NMR and assay data difficult, but the qualitative rate patterns were maintained between assay and NMR data; for example, in the case of dye **3**, the catalysts of entries 4 and 10 were clearly the fastest catalysts, followed by entries 1−3. The dyes are activated substrates, however, and react much faster than standard alkenes such as cyclooctene, a feature which is helpful for rapid screening because many hydrosilation reactions normally require elevated temperature and long reaction times.

We conclude that the use of dyes containing suitable reactive functionalities is a useful, inexpensive method for the rapid visual screening of potential homogeneous catalysts and that the data obtained are relevant to the reactions of standard substrates containing the same functionality. In future work, we will report on the application of related soluble dyes to assay polymer-bound catalysts obtained from a combinatorial phosphine library.[12]

Acknowledgment. We thank the U.S. Department of Energy for funding, Roy Periana, John Hartwig, and Istvan Horvath for helpful discussions, Hye Kwon and James Kuo for experimental assistance, and Jennifer Loch and Christopher Beck for providing catalysts.

Supporting Information Available: General procedures for the assay and synthesis of reactive dyes (1 page, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA9818607

(10) A glovebag, used in initial runs, was satisfactory for the more air-stable catalysts.

(11) The hydrosilation of the dyes was verified by ^1H NMR and IR spectroscopy. Hydrosilation of **3**: characteristic product resonances grow in at δ 4.58 (m, 1H, C-$SiHEt_2$), δ 4.08 (br s, 1H, CH-$SiHEt_2$), and δ 2.38 (s, 2H, CH_2) while the olefinic resonances at δ 7.12 and δ 6.18 disappear. The ν(C═C) band of **3** at 1675 cm^{-1} disappears and the ν(Si−H) band of the hydrosilated product appears at 2110 cm^{-1}. Hydrosilation of **4**: characteristic[3c] product resonances grow in at δ 4.47 (m, 1H, N-$SiHEt_2$) and δ 4.58 (br s, 2H, N-CH_2-py), while the imine proton resonance at δ 8.42 disappears. The ν(C═N) band of **4** at 1636 cm^{-1} disappears and the ν(C−N) and ν(Si−H) bands of the hydrosilated product at 1312 and 2112 cm^{-1}, respectively, both appear.

(12) (a) Initial data[12b] suggest that other related soluble dyes can be useful for screening combinatorial libraries on polymer beads. (b) Cooper, A.; Loch, J.; Crabtree, R. H. *J. Am. Chem. Soc.*, in preparation.