Palladium-Catalyzed Arylation of Ethyl Cyanoacetate. Fluorescence Resonance Energy Transfer as a Tool for Reaction Discovery

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Rapid, parallel methods to evaluate catalyst activity provide the potential to accelerate the discovery of new reactions.[1] Recently, we developed an efficient screen based on fluorescence resonance energy transfer (FRET), and we demonstrated the utility of this assay by identifying catalysts for room temperature Heck reactions of aryl bromides.[2,3] The FRET assay provides product yields in roughly 1 s per sample. Although it requires an initial synthetic investment, our assay can be more general and less instrument-intensive than methods based on serial chromatography,[4,5] substrates with special electronic properties,[6] IR thermography,[7−9] or mass spectrometry.[10−12] We describe our experiments using the FRET-based method to uncover catalysts and reaction conditions for the arylation of cyanoacetates. This work constitutes an unusual example of high-throughput screening used during the discovery of a new method of bond-construction.[13,14]

α-Aryl cyanoacetates are useful intermediates in the preparation of amino alcohols,[15] β-amino acids,[16,17] and arylacetic acids,[18] all of which are common synthetic building blocks. Previous methods for the direct coupling of cyanoacetates with aryl halides used stoichiometric amounts or high catalyst loadings of copper and required iodide substrates and high temperatures.[13,19,20] The mild arylation of cyanoesters reported here displays broad reaction scope and the ability to construct materials with highly hindered quaternary carbons.

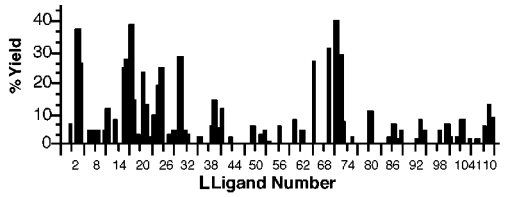
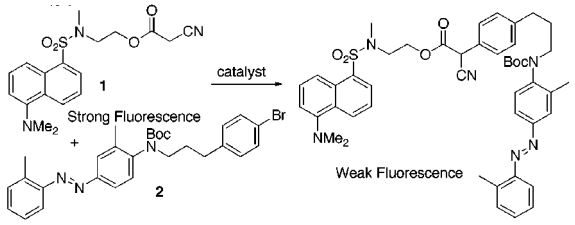


Figure 1. Yields by FRET for 113 reactions using different ligands.

Scheme 1



FRET occurs when the fluorescence emission band of one molecule (donor) overlaps with an excitation band of a second (acceptor) that is proximal to the donor (20−80 Å).[21,22] 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, or reaction yield in our case. A commercial, inexpensive fluorescence plate reader provides the fluorescence measurements.

Scheme 1 shows the two reagents we used to evaluate catalysts for cyanoester arylation. A dansyl fluorophore was tethered to a cyanoester (**1**), and an azodye quencher was tethered to an aryl bromide (**2**). Compounds **1** and **2** were synthesized by conventional methods (see Supporting Information). The emission of dansyl **1** overlaps with an absorption band of diazo dye **2**. Upon coupling of **1** with **2**, the emission of the dansyl group was quenched by the diazo compound. The emission intensity was converted to reaction yield using a linear plot that correlated emission intensity with mole fraction of coupled product.

With substrates **1** and **2** in hand, we conducted reactions in a 96-well format, delivering reagents from stock solutions using a multichannel pipet. For the first experiment, each well contained a different ligand from a 113-membered library, 39 of which were commercially available and 38 of which are new materials. The structures of the library components and synthetic procedures for new ligands are provided as Supporting Information.

All reactions were conducted using a 1:1 ratio of **1** and **2**, 5.0 mol % CpPd(allyl), 10.0 mol % ligand (5.0 mol % for bidentate ligands), and 2.0 equiv of K_3PO_4. The final solutions contained a 0.15 M concentration of substrate (7.5 μmoles) in a 10% H_2O/*m*-xylene solvent system. The plate was sealed and heated while agitating at 80 °C for 8 h. After this time, an aliquot was removed from each well, diluted with *m*-xylene to 10^{-5} M, and analyzed with a fluorescent plate reader. This assay was run in duplicate. The results of this screen are presented in Figure 1 as average yields. Of the 23 ligands that showed measurable activity (>10% yield) in at least one of the two experiments, only eight ligands showed a coefficient of variation greater than 0.30. Reactions using these eight ligands were conducted a third time. Using these data, the overall 12 most effective ligands (Figure 2) were selected for further optimization. The yields from this screen were low in part due to the inherent hydrolysis of **1**; however, the relative amounts of hydrolysis product were similar enough to have no bearing on the relative activities of the different catalysts.

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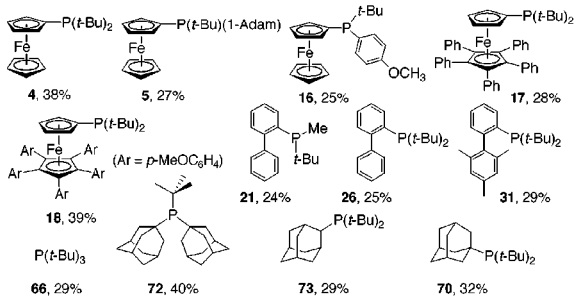


Figure 2. Ligands that gave >20% arylcyanoester (ligand #, yield).

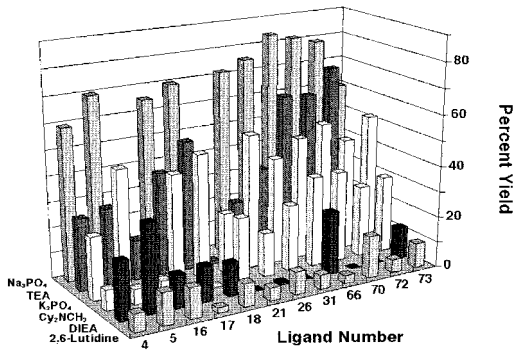


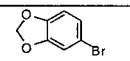
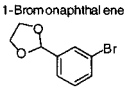
Figure 3. Evaluation of different bases using the FRET assay.

The 12 ligands were examined in a second screen to determine if the optimal precatalyst varied with ligand structure. Precatalysts for this screen included CpPd(allyl), $Pd(OAc)_2$, and $[(allyl)PdCl]_2$. We also included $Ni(COD)_2$ in this assay. The most effective precatalyst did not vary with ligand; catalysts formed from $[(allyl)PdCl]_2$ or CpPd(allyl) gave similar activity, while those formed from $Pd(OAc)_2$ showed lower activity. Those formed from $Ni(COD)_2$ showed no activity. A third screen conducted at 70 °C evaluated four tertiary amines in addition to K_3PO_4 and Na_3PO_4 as base (Figure 3). For 10 out of the 12 ligands screened, the use of Na_3PO_4 greatly improved reaction yields, while Et_3N was shown to be effective when the bulky alkyl phosphines **66**, **70**, and **72** were used. Use of this base would allow for reactions of solid-supported substrates.

Nine of the ligands that generated the most active catalysts from this screen, **4**, **5**, **17**, **26**, **31**, **66**, **70**, **72**, and **73**, were chosen to compare activity for anhydrous reactions on a 1 mmol scale using phenyl bromide and ethyl cyanoacetate. Di(1-adamantyl)-ferrocenyl phosphine was also included because of the somewhat higher activity observed when using ligand **5** relative to **4** (see Figure 3). At 70 °C in toluene solvent, using 3 equiv of Na_3PO_4 as base and 1 mol % $[(allyl)PdCl]_2$ as catalyst precursor, reactions containing the trialkyl phosphines **66**, **70**, **72**, and **73** and the pentaphenyl ferrocenyl **17** gave quantitative conversion of product after 2 h, while reactions employing **4**, **5**, or di(1-adamantyl)-ferrocenyl phosphine required 3−5 h for full conversion. Reactions employing **26** and **31** were complete after 10 h.

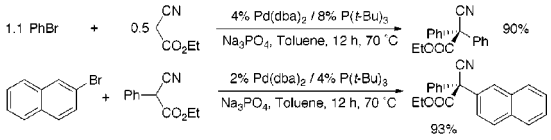
As a final step, we fine-tuned the reaction conditions using these most active ligands **66**, **70**, **72**, and **73**. Catalysts containing the 1-adamantyl ligands **70** and **72** were similar in activity and slightly more reactive than those containing $P(t\text{-}Bu)_3$ **66**, which were more active than those with the 2-adamantyl ligand **73**. Reactions in toluene solvent were the fastest, followed closely by those in dioxane. Acetonitrile and 1,2-dichloroethane were also suitable solvents, but reaction times were a factor of 2 to 3 longer. In contrast to other coupling processes with ligand **66**, no difference in reaction rate was observed when using a 0.8:1.0; 1.0:1.0, or 2.0:1.0 ratio of ligand to metal.[23,24]

Table 1. Preparative Scale Arylation of Ethyl Cyanoacetate[a]

Entry	Ar	L	Yield(%)	Entry	Ar	L	Yield(%)[a]
1	C_6H_5Br	$P(t\text{-}Bu)_3$	87	9		$P(t\text{-}Bu)_3$	84
2		$P(t\text{-}Bu)_3$	88[b]				
3		1-Ad$P(t\text{-}Bu)_2$	86, 87[c]	10	1-Bromonaphthalene	$P(t\text{-}Bu)_3$	83
4		$P(t\text{-}Bu)_3$	89[d]	11		$P(t\text{-}Bu)_3$	81
5	4-$MeOC_6H_4Br$	$P(t\text{-}Bu)_3$	89[b]				
6		1-Ad$P(t\text{-}Bu)_2$	85	12	C_6H_5Cl	$P(t\text{-}Bu)_3$	86[f]
7	2-$MeOC_6H_4Br$	$P(t\text{-}Bu)_3$	83[e]	13	4-$MeOC_6H_4Cl$	$P(t\text{-}Bu)_3$	90[f]
8	4-FC_6H_4Br	$P(t\text{-}Bu)_3$	91	14	2,5-$Me_2C_6H_3Cl$	$P(t\text{-}Bu)_3$	87[f]

[a] Reactions conducted on a 1 mmol scale in toluene using 1.1 equiv of cyanoacetate, 1.0 equiv of aryl halide, and 3 equiv of Na_3PO_4. Yields are for isolated material and are an average of two runs. [b] 1.0% $[(allyl)PdCl]_2$ used. [c] Room temperature, 96 h. [d] 0.050% $[(allyl)PdCl]_2$ used, 7 h at 100 °C. [e] 1.0% $[(allyl)PdCl]_2$ used, 8 h at 100 °C. [f] 1.0% $[(allyl)PdCl]_2$ used, 12 h at 100 °C.

Scheme 2



Using the reaction conditions that were optimal for rate, we evaluated the scope of the process. $Pd(dba)_2$[25] was not soluble enough to prepare stock solutions for the above screens, but it was an equally effective precatalyst as $[(allyl)PdCl]_2$ for preparative reactions. Table 1 shows results of synthetic studies using ligands **66** and **72** and demonstrates the broad scope of the process. Reactions of aryl bromides that are activated or deactivated all occurred in high yields, as did reactions of ortho-substituted aryl bromides. Even reactions of deactivated and ortho-substituted aryl chlorides occurred in good yields.[23,24] Generally, 2 mol % of catalyst was used, but the coupling of ethyl cyanoacetate with bromobenzene occurred in 88% yield when using 0.1 mol % catalyst at 100 °C. Furthermore, reactions could be conducted at low temperatures when using adamantyl ligand **72**. Ethyl cyanoacetate reacted with bromobenzene using 2.0 mol % catalyst in 87% yield after 96 h at room temperature.

The process can be used to produce diarylcyanoacetates (Scheme 2), as well as monoarylcyanoacetates. Using the standard procedure, the addition of 2 equiv of bromobenzene generated ethyl diphenylcyanoacetate in good yield. Alternatively, reaction of a phenylcyanoacetate with a substituted aryl bromide gave the unsymmetrical diaryl cyanoacetate efficiently. Thus, this methodology is suitable for the formation of highly hindered quaternary carbons. Alkyl-substituted ethyl cyanoacetates have not yet served as suitable substrates.

In summary, we have demonstrated a rare example of the discovery and optimization of a new method for bond construction using high-throughput screening. The coupling process is general and should serve as a useful method for forming β-arylamines, alcohols, and diarylacetic acids. Formation and reaction of these products in an enantioselective fashion and an understanding of the reaction mechanism will be the subject of future studies.

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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 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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