Discovery of Novel Catalysts for Allylic Alkylation with a Visual Colorimetric Assay**

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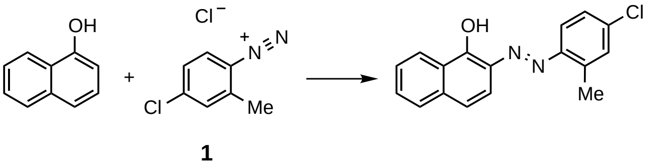
Transition metal catalyzed reactions are useful tools for the construction of complex organic molecules.[1] In this regard, catalytic allylic alkylation represents a particularly powerful method for the formation of carbon–carbon bonds.[2] While most investigations have focused on the catalytic efficacy of palladium complexes,[2,3] complexes involving nickel,[4] rhodium,[5] iron,[6] molybdenum,[7] ruthenium,[8] tungsten,[9] and iridium[10] have also shown promise. Current challenges to this field center on issues of regioselectivity and stereoselectivity, and thereby motivate the development of new catalytic systems. Recently, a number of groups have reported the application of combinatorial chemistry techniques to the development of catalytic processes.[11] In an effort to develop parallel assays for solution-phase catalysis, recent studies have demonstrated the visual detection of active catalysts by noting the modification of temperature,[12] color,[13] or fluorescence[14] induced by a catalytic reaction. Herein, we report a novel catalyst for allylic alkylation in neutral medium discovered with the aid of a fast, parallel colorimetric screening method.[15]

Our strategy for detection of allylic alkylation catalysts is described in Scheme 1 and relies on the fact that colorless 1-naphthol will undergo electrophilic aromatic substitution with Fast Red diazonium salt[16] (**1**) to give a bright orange azo product [Eq. (1)]. We envisioned that effective catalysts for allylic alkylation would ionize 1-naphthyl allyl carbonate (**2**) and, after release of CO_2, would furnish the naphthoxide along with the derived π-allyl metal complex (Scheme 1). For allylic alkylation to occur, the naphthoxide would deprotonate a β-dicarbonyl, which in turn would react with the π-allyl metal complex. Since the naphthol carbonate starting material is less active than 1-naphthol towards aromatic substitution, it does not generate color when treated with Fast Red. Critically, under the reaction conditions naphthyl allyl ether also does not generate color when treated with Fast Red. Thus if naphthoxide directly intercepts the π-allyl complex, no signal will be generated in the assay. Color formation on introduction of Fast Red is indicative only of the presence of 1-naphthol and therefore may be used as an indicator of the extent of allylic alkylation.



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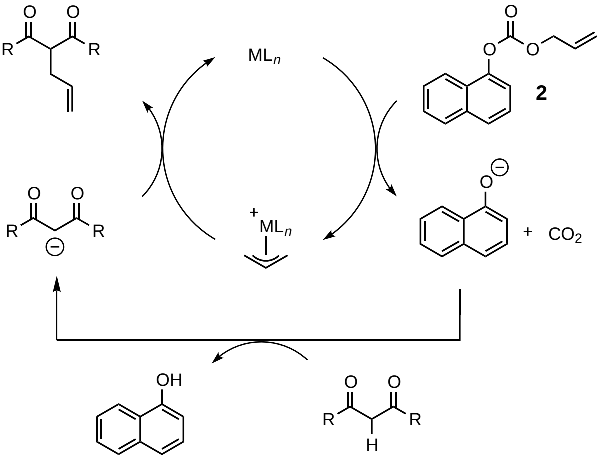

Scheme 1. Schematic representation of the strategy for detection of allylic alkylation catalysts (see text for details).

Using the colorigenic azo coupling assay we have screened several metal–ligand combinations using a 96-well plate format. In an inert atmosphere glovebox, eight ligands were introduced in rows 1 to 8 of the plate as indicated in Figure 1. Eleven different metal salts were then dispatched into columns 1 to 11 (ligand:metal = 3:1). Metal salt was not added to column 12 in order to ascertain that ligand alone does not generate color on treatment with Fast Red. Subsequently, a solution of diethyl malonate and **2** (substrates:catalyst = 100:1) was added to each well. After two hours a solution of Fast Red in wet THF was added. As can be

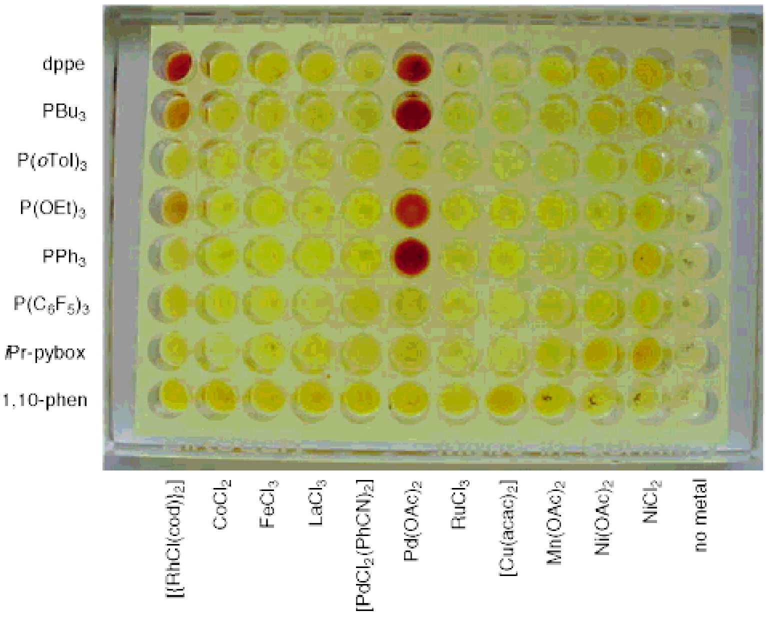

Figure 1. View of the 96-well plate after addition of Fast Red. acac = acetylacetone, *o*Tol = o-tolyl.

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seen in Figure 1, red color is generated in several wells and is indicative of allylic alkylation.

While simple visual analysis of the 96-well plate is sufficient to differentiate efficient from inactive catalysts, parallel UV analysis may be used to differentiate catalysts of similar activity and provides a means to subtract background color due to ligand or metal salt. This operation provided the data depicted in Figure 2a which correlates well with that obtained by visual inspection.

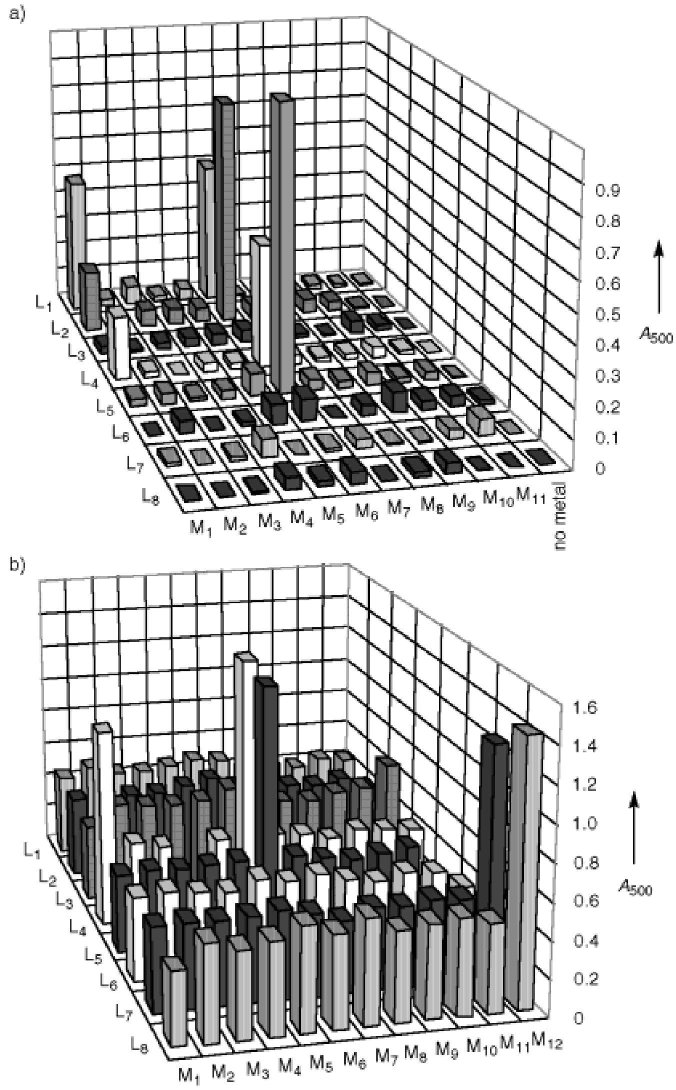
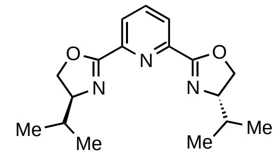


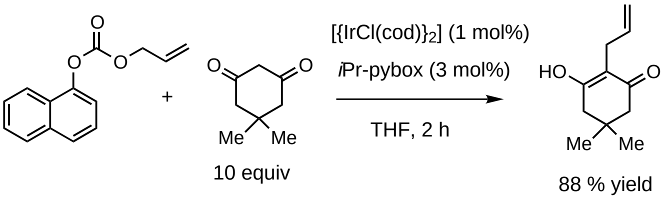
Figure 2. Relative absorbance of each well in the 96-well plate: a) with dimethyl malonate, b) with dimedone. M_1: [{RhCl(cod)}$_2$], M_2: $CoCl_2$, M_3: $FeCl_3$, M_4: $LaCl_3$, M_5: [$PdCl_2(PhCN)_2$], M_6: $Pd(OAc)_2$, M_7: $RuCl_3$, M_8: [Cu(acac)$_2$], M_9: $Mn(OAc)_2$, M_{10}: $Ni(OAc)_2$, M_{11}: $NiCl_2$, M_{12}: [{IrCl(cod)}$_2$], L_1: dppe, L_2: PBu_3, L_3: P(*o*Tol)$_3$, L_4: $P(OEt)_3$, L_5: PPh_3, L_6: $P(C_6F_5)_3$, L_7: *i*Pr-pybox, L_8: 1,10-phen.

The information in Figures 1 and 2a indicates that $Pd(OAc)_2$ when combined with diphenylphosphanylethane (dppe), PBu_3, $P(OEt)_3$, or PPh_3 provides an effective catalyst system. Also apparent is that [{RhCl(cod)}$_2$] (cod = 1,5-cyclooctadiene) with either dppe, PBu_3, or $P(OEt)_3$ as ligand serves as an active catalyst for allylic alkylation. In light of extensive studies with π-allyl palladium complexes,[2, 3] the results with $Pd(OAc)_2$ are not surprising. However, rhodium-catalyzed allylic alkylations in neutral medium are less well developed,[5a, c] and it is encouraging that this initial proof-of-concept revealed the effectiveness of these rhodium–ligand complexes.

To evaluate the impact of substrate structure on catalyst activity, we examined the use of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) as nucleophile. In this case, we used the experimental procedure as described above and employed the iridium salt [{IrCl(cod)}$_2$] in column 12. The results of this assay are depicted in Figure 2b. While it was found that unchanged dimedone generates a yellow color, it is still possible to identify the most active catalysts. In contrast to reactions involving malonate as nucleophile (Figure 2a), dppe and PBu_3 ligands are not effective with the Rh and Pd complexes for the allylation of the dimedone. In the case of [{IrCl(cod)}$_2$] it is clear that addition of either *i*Pr-pybox or 1,10-phenanthroline (1,10-phen) generates an active catalyst. Additional experiments (data not shown) showed that under the same assay conditions with either malonate or dimedone, none of the metal complexes, in the absence of ligand, generate red color.


*i*Pr-pybox

The relative activity of the new iridium catalysts for base-free allylation of dimedone was investigated in detail by ^{1}H NMR spectroscopy. In accord with the colorigenic assay, when PPh_3 is employed as the ligand, no catalytic reaction occurred and the starting materials were recovered. In contrast, when *i*Pr-pybox is employed as the ligand with ten equivalents of dimedone,[17] ^{1}H NMR analysis shows quantitative conversion is achieved in two hours. Moreover, the reaction product may be isolated in 88 % yield and in purity sufficient to obtain accurate elemental analysis [Eq. (2), see Experimental Section].[18]



(2)

In summary, we have reported an efficient colorimetric strategy for parallel analysis of catalysts for allylic alkylation. The colorigenic assay is simple and inexpensive, and should be applicable to other reactions of interest. While few examples of iridium-catalyzed allylic alkylation are known,[10] by noting formation of color, the assay revealed the first non-phosphane iridium catalysts for allylic alkylation.

Experimental Section

In THF (6 mL), **2** (91 mg, 0.4 mmol) and dimedone (0.57 g, 4 mmol) were allowed to react in the presence of [{IrCl(cod)}$_2$] (1 mol %) and *i*Pr-pybox (3 mol %) for 2 h. After evaporation of THF the solid residue was purified by silica gel chromatography with ethyl acetate/hexane (1/1) as eluant.

After evaporation of solvent, a white crystalline solid was isolated (63 mg) in 88% yield. Elemental analysis calcd for $C_{11}H_{16}O_2$: C 73.33, H 8.88; found: C 73.56, H 8.81; m.p. 143 °C (lit.[19] 143 °C). Spectroscopic data are in accordance with previous reports.[19]

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[17] With only one equivalent of dimedone, both monoallylation and bisallylation products were formed. With ten equivalents of dimedone only the monoallylation adduct was produced.

[18] Reaction of diethyl malonate with 1-naphthyl allyl carbonate catalyzed by the Ir/*i*Pr-Pybox catalyst proceeds with 100% conversion into 1-naphthyl allyl ether.

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Solid-State Coordination Chemistry: The Self-Assembly of Microporous Organic–Inorganic Hybrid Frameworks Constructed from Tetrapyridylporphyrin and Bimetallic Oxide Chains or Oxide Clusters[**]

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Jon Zubieta[*]

Oxygen is not only the most abundant terrestrial element but it is also highly reactive; consequently, oxides exist for all of the elements with the exceptions of radon and the lighter noble gases.[1] Inorganic oxides constitute a vast family of materials ubiquitous as both naturally occurring and synthetic materials.[2–4] The significant contemporary interest in solid-state oxides reflects a structural and compositional diversity that endows these materials with a range of physical properties that yield applications to heavy construction, sorption, catalysis, biomineralization, microelectronics, and solar energy conversion.[5] However, despite the practical and fundamental importance of inorganic oxides, the designed synthesis of such materials remains an elusive goal.

The synthetic challenge reflects the fact that binary metal oxides, for example, typically possess only one or a few thermodynamically stable modifications, which provides a limited range for design. While such simple oxides possess undeniably useful properties, there is, in general, a correlation between the complexity of the structure of a material and the functionality that it displays. Two general observations provide an insight into the synthesis of structurally complex oxides: a) if the formation of the oxide is carried out at low temperatures, and thus under kinetic control, it is possible to prepare metastable modifications and to influence the reaction process,[6] and b) organic molecules can dramatically influence the inorganic oxide microstructure, thus offering a powerful tool for the design of novel materials.[7]

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