Thin Layer Chromatography for the Detection of Unexpected Reactions in Organometallic Combinatorial Catalysis

Olivier Lavastre,* Rachid Touzani, Stefania Garbacia

Institut de Chimie, UMR 6509 CNRS-Université de Rennes 1, Campus de Beaulieu 35042 Rennes Cedex France
Fax: (+33)-223-236-939, e-mail: Olivier.Lavastre@univ-rennes1.fr

Received: March 20, 2003; Accepted: May 14, 2003

Abstract: Thin layer chromatography (TLC) represents a fast and inexpensive alternative to NMR spectroscopy or analytical methods based on chromatography for the detection of unexpected products in organometallic combinatorial catalysis. This screening test led to the detection of the catalytic system $[Ir(COD)Cl]_2/PPh_3$ for isomerisation of diolefinic substrates instead the expected ring closing metathesis (RCM) reaction.

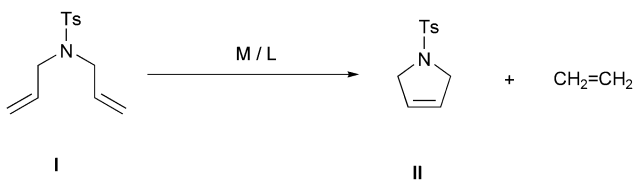
Keywords: catalysis; combinatorial chemistry; olefin; screening test; TLC

Combinatorial approaches are now involved in such diverse area as pharmaceutical research,[1] material[2] and polymer[3] sciences or heterogeneous[4] and homogeneous catalysis.[5] Innovative concepts in catalysis were recently reported to evaluate in one-shot large libraries, such as colourimetric[6] and fluorescence[7] based tests, infra-red thermography[8] or mass spectrometry labelled methods.[9] It should be noted that the presence of strongly coloured organometallic complexes able to interact with chromophores or fluorophores could be a limiting factor for the former methods. Moreover, all these high throughput screening (HTS) approaches are based on screening tests designed for a specific target, i.e., the expected product. This specificity excludes the detection of different and unexpected compounds, even if it represents the major product, if a complete analysis of the solution is not performed. This is a strong limitation because new and interesting catalytic reactions could be missed. This motivates the design of HTS tests able to give the real composition of a catalytic mixture. Thin layer chromatography represents an inexpensive and fast separation method able to generate a visual overview of composition of mixtures and was involved for antibody catalysis.[10]

To date, the combination of TLC and HTS as a general method for detection of unexpected products was not reported in combinatorial organometallic catalysis. We report here i) a combinatorial catalysis approach for the activation of diolefinic derivative **I** (Scheme 1) and ii) the impact of the TLC screening test for detection of unexpected catalytic activity.

Combinatorial catalysis: The catalyst diversity was obtained by different metal-ligand combinations using a 96-well plate format as indicated in Figure 1. Seven ligands and six metal-containing reagents were involved to generate a diversity of coordination complexes. Ligands were selectively introduced into row A to G of the plate (except tubes of column 11). The allenyl complex $[(1\text{-Me-4-}i\text{-Pr-}C_6H_4)RuCl(PCy)_3(=C=C=CPh_2)]PF_6$, already described for ring closing metathesis catalysis to generate compound **II**,[11] was put in each tube of column 11. This reference catalyst allowed a direct comparison for each row. The selective dispatching of other metal salts in columns 1 to 5 was duplicated in the columns 6 to 10 to generate two identical sets of catalysts. No ligands and no metal salts were added to row H and column 12, respectively. All tubes were closed and the 96-tube plate was heated at 45 °C in toluene for 2 hours. After cooling at room temperature a solution of the bis-allyltosylamide substrate **I** was added in all tubes for RCM. In addition to metal/ligand combinations M/L, all tubes of columns 6 to 10 also received the diazoalkane $N_2CHSiMe_3$. This additive has been shown to make an important contribution for the *in-situ* generation of active catalysts.[12] This led to the differentiation of sets 1–5 and 6–10. All tubes were closed and were heated at 70 °C for 16 hours. All these operations were performed in a glove box to prevent any interactions with oxygen or moisture.

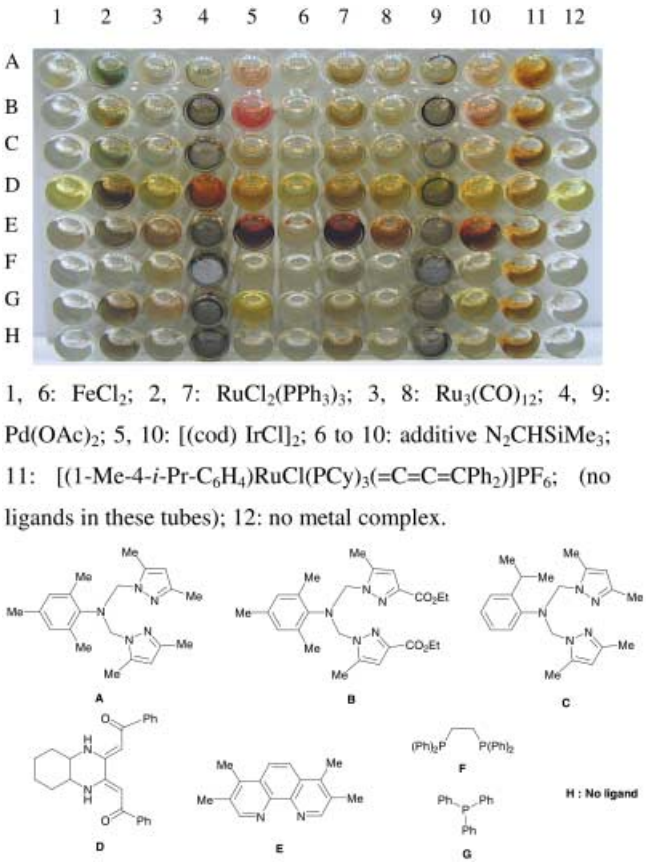
Several points merit mention in regards to the picture of the plate at the end of the reaction (Figure 1). The diversity of colour of individual tubes, even if it is not a direct proof of reaction, clearly illustrates significantly



I II

Scheme 1. Catalytic diolefin ring closing metathesis.

  DOI: 10.1002/adsc.200303056



1, 6: $FeCl_2$; 2, 7: $RuCl_2(PPh_3)_3$; 3, 8: $Ru_3(CO)_{12}$; 4, 9: $Pd(OAc)_2$; 5, 10: $[(cod)\ IrCl]_2$; 6 to 10: additive $N_2CHSiMe_3$; 11: $[(1\text{-Me-4-}i\text{-Pr-}C_6H_4)RuCl(PCy)_3(=C=C=CPh_2)]PF_6$; (no ligands in these tubes); 12: no metal complex.

Figure 1. 96 metal/ligand combinations.

different behaviours, according to the diversity of mixture composition. For instance, row B (influence of metal salts), column 5 (influence of ligands) and comparison between columns 2 and 7 (influence of $N_2CHSiMe_3$ additive) are representative examples of this diversity.

Detection of unexpected catalytic activity by TLC: One μL of each tube were directly transferred to a TLC silica plate by means of a 12-channel pipette. After elution (heptane:ethyl acetate, 8/2 v/v) of the 8 TLC plates (rows A to H) a visual evaluation of the region of interest (ROI), corresponding to starting product **I** (R_f: 0.63) and expected product **II** (R_f: 0.5), is possible under UV irradiation at 254 nm. By playing with eluant composition, $i-e$ eluants with low, medium and strong eluting power, the probability to have co-eluted spots is strongly reduced. As a representative example, the picture **a)** in Figure 2 shows the 12 results corresponding to row G. The presence of expected product was effectively detected for the reference catalyst (G11), indicating the efficiency of this TLC test for the quick detection of active catalysts.

None of the other 35 different M/L combinations (7 L × 5 M) gave the spot corresponding to expected product **II**. This indicated no catalytic activity or no formation of complexes ML, i.e., no interaction between

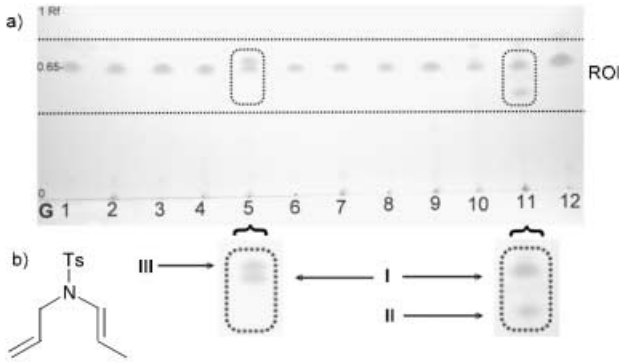


Figure 2. a) TLC of row G under UV (irradiation 254 nm); **b)** Expanded areas for G5 and G11.

M and L, in these specific experimental conditions. However a completely different situation was observed for G5 (picture **b**) in Figure 2. No spot related to expected product **II** was present but a new spot appeared (R_f: 0.68). This indicated the formation of a different product, thus the occurrence of an unexpected reaction in the tube G5. In order to confirm this result, the reaction with the catalytic system $[Ir(COD)Cl]_2$/PPh_3 was reproduced in a Schlenk tube at a 5-mL level. ^1H NMR spectroscopy showed that this different product was the derivative **III**, resulting from isomerisation of one double bond of compound **I**. A conversion of 48% was measured. The structure of product **III** was confirmed by a comparison with an authentic sample of **III**. The high selectivity for the isomerisation reaction was also confirmed as no trace of product **II** was visible in the ^1H NMR spectrum. It should be noted that the presence of this isomerisation product was reported as a side product for the RCM reaction, with some Ru catalysts for instance.[12] Interestingly, iridium cationic species were previously reported as efficient catalysts for isomerisation of oxygen containing allyl systems such as diallyl ether[13] or allyl silyl ether.[14] However, to date, no neutral Ir catalyst showing this very high selectivity was reported for the synthesis of vinylamine derivatives. This result was completely unpredictable, illustrating the impact of combinatorial approaches when no reliable theories are able to predict a result. If NMR spectroscopy and HPLC or gas chromatography are able to give information about the composition of a mixture, they also require specific equipment and, when applied to large numbers of samples, are really demanding in terms of consumables. In addition, a purification process is necessary in most cases to remove derivatives interfering with analysis, i.e., paramagnetic metal species for NMR or salts and insolubles for HPLC or GC columns. This represents a time-consuming process and when very small volumes are involved, as in combinatorial approaches, significant errors can occur during filtration or extraction steps.

As no analytical equipment and no purification steps are involved, the method reported here could be used as the simplest primary screening test in organometallic combinatorial catalysis able to detect both expected products and totally unexpected catalytic reactions. Notably this method can be directly applied to any type of catalytic reaction as TLC is a universal separation technique. Practically all types of molecule could be detected, directly in the case of coloured products, under UV excitation for colourless compounds, or after spraying with revealing solutions. This process could be adapted to large libraries of catalytic systems by use of robotic liquid handling and parallel elution equipment. Future studies from our laboratory will address the discovery of new reaction pathways, by the visual evaluation of number and relative position of spots on TLC plates.

Experimental Section

Catalysts Library Synthesis

In an inert atmosphere glovebox, we prepared 7 individual solutions (0.002 M) of ligands A to G and 6 individual solutions of metal complexes (0.001 M) 1 to 5 and 11 in toluene. The 96-tube plate (1 mL) was filled as follows: 100 μL of solution A were added to tubes 1 to 10 and 12 of the row A. The same procedure was operated for solutions of ligands B to G. Then, 100 μL of metal salt 1 using a multi-channel pipette were introduced to the tubes A to H of the columns 1 and 6. The same procedure was used for the four other solutions of metal complexes 2 – 5 by adding them to the rows 2 to 5, and to the rows 7 to 10, respectively. The reference catalyst was added to the row 11. As a result, each vial contained 200 μL of solution of a specific metal/ligand combination. All tubes were tightly closed and the plate was heated at 45 °C for 2 hours. Then, the tubes were allowed to cool to room temperature. Two substrate solutions were prepared: 0.1 M of diallyltosylamide in toluene and 0.3 M of diallyltosylamide containing of trimethylsilyldiazomethane (0.00 6 M) in toluene. Then, 100 μL of first solution were added to the columns 1 to 5, 11 and 12. 100 μL from the second solution were added to the columns 6 to 10. The total volume of each vial was 300 μL, final concentration of substrate was 0.03 M, metal salt 1% and ligand 2%. All tubes were tightly closed and the plate was heated at 70 °C for 16 hours. Aliquots of solution were deposited on TLC silica plates (TLC aluminium sheets, Silica Gel 60 F_{254}, Merck).

Metal salts 1 – 5 are commercially available and used as received. Ru reference catalyst[11] and ligand D[15] were prepared according to literature. The ligands A to C were prepared by the condensation of disubstituted 1-hydroxymethylpyrazole (2 equiv.) with primary amines (1 equiv.) in CH_3CN for 4 h at 40 °C. Then, the solution was dried with anhydrous $MgSO_4$. After filtration the solvent was removed under vacuum and the crude products were washed with ether and hexane then dried. The compounds A to C are white solids. ^1H NMR, ^{13}C NMR chemical shifts, IR and elemental analyses are in good agreement with the proposed structures.

Acknowledgements

The authors are grateful to the CNRS, to the MENRT, to the Région Bretagne and to the company TotalFinaElf for their support for the project Organometallic Combinatorial Chemistry.

References

[1] *Combinatorial Chemistry: Synthesis and application*, (Eds.: S. R. Wilson, A. W. Czarnik), Wiley, New York, **1997**.
[2] X.-D. Xiang, X. Sun, G. Briceño, Y. Lou, K.-A. Wang, H. Chang, W. G. Wallace-Freedman, S.-W. Chen, P. G. Schultz, *Science* **1995**, *268*, 1738 – 1740.
[3] a) S. Brocchini, K. Jamas, V. Tangpasuthadol, J. Kohn, *J. Am. Chem. Soc*. **1997**, *119*, 4553 – 4554; b) O. Lavastre, I. Ilitchev, G. Jegou, P. H. Dixneuf, *J. Am. Chem. Soc.* **2002**, *124*, 5278 – 5279.
[4] S. M. Senkan, *Nature* **1998**, *394*, 350 – 353.
[5] a) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem. Int. Ed.* **1999**, *38*, 2494 – 2532; b) O. Lavastre, J. P. Morken, *New. J. Chem.* **2002**, *26*, 745 – 749; c) K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220 – 222; d) S. Senkan, K. Krantz, S. Ozturk, V. Zengin, I. Onal, *Angew. Chem. Int. Ed.* **1999**, *38*, 2794 – 2799; e) S. Senkan, *Angew. Chem. Int. Ed.* **2001**, *40*, 312 – 329; f) M. B. Francis, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **1999**, *38*, 937 – 941; g) X. Gao, H. B. Kagan, *Chirality* **1998**, *10*, 120 – 124; h) K. Ding, A. Ishii, K. Mikami, *Angew. Chem. Int. Ed.* **1999**, *38*, 497 – 500; i) F. Taran, C. Gauchet, B. Mohar, S. Meunier, A. Valleix, P. Y. Renard, C. Créminon, J. Grassi, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 124 – 127.
[6] a) A. C. Cooper, L. H. McAlexander, D.-H. Lee, M. T. Torres, R. H. Crabtree, *J. Am. Chem. Soc*. **1998**, *120*, 9971 – 9972; b) O. Lavastre, J. P. Morken, *Angew. Chem. Int. Ed.* **1999**, *38*, 3163 – 3165.
[7] a) J. P. Stambuli, S. R. Stauffer, K. H. Shaughnessy, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 2677 – 2678; b) R. F. Harris, A. J. Nation, G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2000**, *122*, 11270 – 11271.
[8] a) S. J. Taylor, J. P. Morken, *Science* **1998**, *280*, 267 – 270; b) M. T. Reetz, M. H. Becker, M. Liebl, A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 1236 – 1239.
[9] J. W. Szewczyk, R. L. Zuckermann, R. G. Bergman, J. A. Ellman, *Angew. Chem. Int. Ed.* **2001**, *40*, 216 – 219.
[10] J.-L. Raymond, T. Koch, J. Schröer, E. Tierney, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 4251 – 4256.
[11] A. Fürstner, M. Lieble, C. W. Lehmann, M. Picquet, R. Kunz, C. Bruneau, D. Touchard, P. H. Dixneuf, *Chem. Eur. J.* **2000**, *6*, 1847 – 1857.
[12] a) J. Le Paih, S. Dérien, I. Özdemir, P. H. Dixneuf, *J. Am. Chem. Soc.* **2000**, *122*, 7400 – 7401; b) A. Demonceau, A. W. Stumpf, E. Saive , A. F. Noels, *Macromolecules* **1997**, *30*, 3127 – 3136; c) B. De Clercq, F. Lefebvre, F. Verpoort, *New J. Chem.* **2002**, 1201 – 1208.

[13] T. Higashino, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2000**, *2*, 4193–4195.
[14] D. Baudy, M. Ephritikhine, H. Felkin, *J. Chem. Soc. Chem. Commun.* **1978**, 694.
[15] R. Touzani, T. Ben-Hadda, S. El Kadiri, A. Ramdani, O. Maury, H. Le Bozec, L. Toupet, P. H. Dixneuf, *New. J. Chem*. **2001**, *3*, 391.

