TLC plates as a convenient platform for solvent-free reactions

Jonathan M. Stoddard,* Lien Nguyen, Hector Mata-Chavez and Kelly Nguyen

Received (in Austin, TX, USA) 10th November 2006, Accepted 30th November 2006
First published as an Advance Article on the web 4th January 2007
DOI: 10.1039/b616311d

Solvent-free oxidative couplings of naphthols have been optimized by co-spotting catalysts and substrates directly on silica TLC plates and heating, followed by chromatography, staining, and qualitative visualization.

Environmentally-friendly methods of solvent-free synthesis involve reactions in the solid state, melt or vapor phases and reduce the amount of waste from solvent.[1] Inorganic materials such as alumina and silica are common supports for reagents or catalysts in heterogeneous reactions that effectively replace the solvent. Silica, for example, can be a support for two reactants that undergo reaction upon microwave irradiation or heating and the resultant silica–product mixture directly subjected to chromatography without extractive work-up procedures. The development of these reactions involves mixing the two components with silica gel, providing the necessary heat, washing the product mixture from the silica gel with solvent, and analyzing the product mixture with thin-layer chromatography (TLC).

It has occurred to us, as well as others,[2] that TLC plates contain silica that, in principle, may act as a medium for solvent-free reactions. Although TLC plates are commonly treated with staining reagents and heat to assist with the visualization of absorbed components, the extension of this platform for developing solvent-free organic reactions has rarely been explored. We have devised a method for developing solvent-free reactions on silica TLC plates. The use of TLC plates as a medium for solvent-free organic synthesis enables the application of catalysts, reagents, and heat. Without further manipulations, the results of the reaction may be directly analyzed by chromatography, staining, and visualization. This methodology allows the reaction development process to take place completely on a disposable TLC plate, thereby further reducing waste and time during the development phase.

Herein, we report the use of TLC plates for the development of oxidative couplings of naphthols. The oxidative coupling of 2-naphthols is the first step in the synthesis of 2,2′-binaphthol (BINOL)-based asymmetric ligands. The solid-phase synthesis of BINOL has been accomplished in the solid state by co-grinding 2-naphthol with $FeCl_3 \cdot 6H_2O$ and heating at 50 °C for 2 h.[3] This protocol results in a 95% yield that we have found convenient on larger scales (10–100 g). We sought to reverse engineer this reaction on silica TLC plates before extending the methodology to other oxidative coupling reactions.

The presence of added silica on the solid-phase oxidative coupling of 2-naphthol by $FeCl_3$ had no effect. Different $FeCl_3 \cdot 6H_2O$–silica gel mixtures (50, 33, and 25 w/w%) were prepared by co-grinding the two components. 2-Naphthol was then co-ground with the mixture, placed in an oven at 50 °C, eluted with chloroform, and analyzed with TLC. In all cases, the 2-naphthol–BINOL reaction ratios were similar and it was concluded that added silica does not hinder the oxidative coupling reaction.

We found it necessary to optimize the application of $FeCl_3$ and 2-naphthol onto TLC plates so that there is adequate mixing of the two components and consistent results are obtained after heating the TLC plates. We found two methods that worked equally well. In the first method, $FeCl_3 \cdot 6H_2O$ (0.1 M in water) was spotted onto the baseline of a TLC plate. 2-Naphthol (0.1 M in acetone) was immediately spotted on the same location of the TLC plate. In the second method, the aqueous $FeCl_3 \cdot 6H_2O$ was spotted onto the TLC plate, heated at 100 °C for 5 minutes to evaporate most of the water, and allowed to cool before 2-naphthol was co-spotted. The key parameter affecting the efficiency of co-spotting, was to ensure that the $FeCl_3$ spot had a larger diameter than the 2-naphthol spot so that there was adequate interaction of 2-naphthol with the metal. It has been found that the Fe(III) is catalytically regenerated by oxygen in a solvent-free reaction[3] and thus it is not critical that the two spots perfectly overlap or are applied in equimolar amounts on the silica TLC plate.

We started by screening different metals in parallel on the same TLC plate and found $FeCl_3$, $FeCl_2$, and $CuCl_2$ catalysts to provide product. A TLC plate was spotted with 0.1 M aqueous solutions of $CuCl_2$, $FeCl_2$, $FeCl_3$, $NiCl_2$, and $CoCl_2$, dried, then co-spotted with a smaller diameter of 0.1 M 2-naphthol in acetone. The TLC plate was placed on a hotplate at 50 °C for 2 hours, cooled, chromatographed with 80 : 20 hexanes–ethyl acetate and stained with ceric ammonium molybdate. The $FeCl_3$, $FeCl_2$, and $CuCl_2$ catalysts indicated some product formation and were further investigated.

The TLC-supported oxidative coupling reactions were further optimized by placing TLC plates on hotplates at various temperatures (50, 100, 150, and 200 °C) for different reaction times (15, 30, 45, and 60 min). The TLC-based oxidative coupling of 2-naphthol with $CuCl_2$ produced more side products while $FeCl_3$ and $FeCl_2$ formed equal amounts of BINOL. Thus $FeCl_3$ was selected for further optimization at different temperatures and times (Table 1). The critical parameter affecting the relative amounts of BINOL and 2-naphthol is the temperature, 100 °C being optimal (Fig. 1). This is in contrast with the preparative solid-phase reaction between $FeCl_3$ and 2-naphthol where the ideal temperature is 50 °C.[3] The relative amount of BINOL produced with longer reaction times remained constant, with the exception of reactions at 150 °C where a less polar side product becomes prevalent with increasing reaction time. Furthermore, higher temperatures cause decomposition of 2-naphthol that occurs in the absence of $FeCl_3$ (Fig. 1).

Dept. of Chemistry and Biochemistry, California State University, Fullerton, CA 92834-6866, USA. E-mail: jstoddard@fullerton.edu; Fax: +1 714 5316; Tel: +1 714 278 5316

Table 1 Qualitative results of $FeCl_3$ oxidative coupling of 2-naphthol on silica TLC plates

		Relative amounts (%)[b]		
Temperature[a] °C	Time/min	2-Naphthol	BINOL	Impurity
50	15	60	40	—
50	30	60	40	—
50	45	60	40	—
50	60	60	40	—
100	5	10	90	—
100	15	2	98	—
100	30	2	98	—
100	45	2	98	—
100	60	2	98	—
150	15	45	45	10
150	30	40	40	20
150	45	35	35	30
150	60	30	30	40

[a] Measured using an IR-thermometer. [b] Chromatographed using 80 : 20 hexanes–ethyl acetate and stained using ceric ammonium molybdate; 2-naphthol (R_f = 0.34), BINOL (R_f = 0.16), impurity (R_f = 0.58).

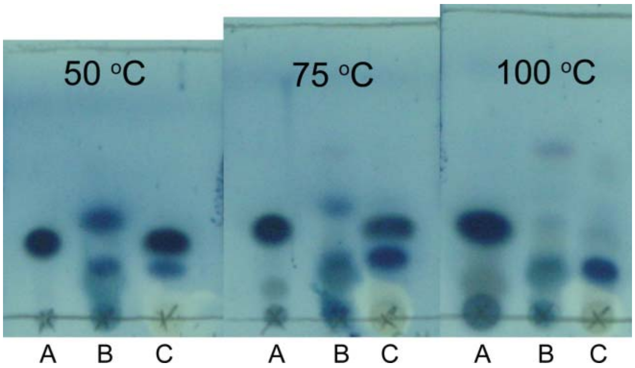

Fig. 1 All TLC plates heated 15 min, developed with 80 : 20 hexanes–ethyl acetate, and stained using ceric ammonium molybdate. Lanes: (A) 2-naphthol; (B) $CuCl_2$–2-naphthol; (C) $FeCl_3$–2-naphthol.

We next screened a number of different naphthols in parallel for their ability to undergo the oxidative coupling reaction on SiO_2 TLC plates where 2,3-naphthalene diol serves as a representative example. $CuCl_2$ and $FeCl_3$ catalysts were screened for the TLC-supported oxidative coupling of 2,3-naphthalene diol. $FeCl_3$ was found to provide more product conversion compared with $CuCl_2$ and was further optimized. The $FeCl_3{\cdot}6H_2O$ and 2,3-naphthalene diol were co-spotted onto silica TLC plates and heated at 50, 75, 100 °C for 15 min. It was found that the reaction was complete at 100 °C and 15 min. Higher temperatures or longer reaction times did not appear to produce more coupled product. With these results in hand, we undertook the preparative scale oxidative coupling reaction by co-grinding 2,3-naphthalene diol (10 g) with 2 equivalents of $FeCl_3{\cdot}6H_2O$ at 100 °C for 15 min to produce analytically pure tetraol in 66% yield.†

The oxidative coupling of 2-aminonaphthalene has been carried out with $CuCl_2$ and $PhCH_2NH_2$ or tBuNH$_2$ catalysts to afford 2,2′-diaminobinaphthyl (BINAM) in 45% yield,[4] but a solvent-free reaction has not yet been developed. We have prepared 2-aminonaphthalene *via* the Bucherer reaction[5] of 2-naphthol and investigated its TLC-supported oxidative coupling reactions. The BINAM (R_f = 0.24) product coordinates strongly to $CuCl_2$ and $FeCl_3$, which does not allow the product to be analyzed by TLC (R_f = 0) 80 : 20 hexanes–ethyl acetate. Instead we optimized the disappearance of 2-aminonaphthalene (R_f = 0.24). Our initial TLC-supported screens again indicated that $FeCl_3$ was a better catalyst than $CuCl_2$, which produced more side products. Upon co-spotting 2-aminonaphthalene onto the silica-supported $FeCl_3$, there was immediate dark coloration which indicated a reaction had taken place. Reactions using these two metals were carried out at 25, 35, and 45 °C for 5 minutes.

Reactions at longer reaction times did not show improvement. In addition, higher reaction temperatures showed increasing amounts of side products, especially in the case of $CuCl_2$. Interestingly, TLC reactions at 25 and 35 °C showed a small amount of less-polar material (R_f = 0.35), which may be an intermediate in the oxidative coupling reaction. At 45 °C this component was not detected after staining with ceric ammonium molybdate. Preparative scale oxidative couplings of 2-aminonaphthalene (1 equiv.) and $FeCl_3{\cdot}6H_2O$ (2 equiv.) were carried out by co-grinding the two in a mortar and pestle, placing in capped vials, and heating in a thermostated oven. After work-up† the reactions were analyzed with TLC, without complications due to the complexation of BINAM or 2-aminonaphthalene to $FeCl_3$. Increasing the reaction temperature or increasing the reaction time had no effect on the yield of the product ratio, which remained fairly constant at 60 : 40 2-aminonaphthalene–BINAM. We reasoned that the BINAM may coordinate strongly with the Fe(III) and inactivate it. Alternatively, acid may form during the reaction conditions and form 2-naphthylammonium chloride which cannot coordinate with Fe(III) and allow the oxidative coupling reaction to proceed. The amount of $FeCl_3{\cdot}6H_2O$ was increased in an effort to optimize the yields of the oxidative coupling reaction.

We found that the amount of BINAM produced could be optimized with 8 equivalents of $FeCl_3{\cdot}6H_2O$. Solid-phase reactions of 2-aminonaphthalene with 2, 4, and 8 equivalents of $FeCl_3{\cdot}6H_2O$ produced 60 : 40, 20 : 80, and 10 : 90 ratios of 2-aminonaphthalene–BINAM respectively. The latter reaction was carried out on a 1 g scale by co-grinding 2-aminonaphthalene with 8 equivalents of $FeCl_3{\cdot}6H_2O$ for 5 minutes at 21 °C to produce analytically pure BINAM in 33% yield after work-up,† without chromatography. An aqueous acid work-up did not increase the yield of recovered BINAM.[4]

Notes and references

† Solid-phase reactions were worked up by partitioning the reaction mixture between ether and water, filtering through celite to remove insoluble material, and washing the precipitate with ether. The ether solution was separated and evaporated to afford the binaphthyl product, 1,1′-binaphthyl-2,2′,3,3′-tetraol: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 (d, J = 8.4 Hz, 1H), 6.96 (ddd, J = 1.2, 6.8, 8.2 Hz, 1H), 7.15 (ddd, J = 1.2, 6.8, 9.1 Hz, 1H), 7.23 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 8.38 (bs, 1H), 10.04 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.8, 145.3, 129.2, 129.0, 126.3, 124.7, 123.1 (2), 116.7, 109.1; IR (ATR): 3459, 3400 cm^{-1}; mp >275 °C.

1 (*a*) G. W. V. Cave, C. L. Raston and J. L. Scott, *Chem. Commun.*, 2001, 2159; (*b*) F. Toda, *Acc. Chem. Res.*, 1995, **28**, 480.
2 L. Williams, *Chem. Commun.*, 2000, 435.
3 F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.*, 1989, **54**, 3007.
4 M. A. Smrcina, M. Lorenc, V. Hanus and P. Kocovsky, *Synlett*, 1991, 231.
5 H. Seeboth, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 307–317.