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Catalysis Communications 9 (2008) 1291–1296
CATALYSIS COMMUNICATIONS
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Perfluoroalkylated pyridine catalyzed Knoevenagel condensation: An important complement of fluorous catalysis without fluorous solvent

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Received 25 September 2007; received in revised form 9 November 2007; accepted 17 November 2007
Available online 24 November 2007

Abstract

Knoevenagel condensation proceeds efficiently in the presence of catalytic amount of perfluoroalkylated pyridine under homogeneous conditions in *n*-octane at 80 °C. The catalyst can be recovered by simple cooling and precipitation and used again. The protocol avoids the use of fluorous solvents during the reaction or workup, which is expensive and can leach in small amounts.

Keywords: Perfluoroalkylated pyridine; Knoevenagel condensation; Fluorous catalysis; Fluorous-solvent-free

1. Introduction

Recently, reactions carried out in a fluorous biphasic system (FBS) have become one of the most important methods for facile catalyst separation from the reaction mixture and recycling of the catalyst since FBS was introduced by Horváth and Rábai in 1994 [1]. In this catalytic system (Fig. 1), the fluorous catalyst with perfluoroalkylated “pony tails” can dissolve into the fluorous phase containing the product after the reaction [2]. Furthermore, FBS has the advantage of possible use for water-sensitive reactions unlike aqueous biphase systems [3].

No catalyst recovery method is without potential drawbacks [4,5]. Accordingly, the fluorous solvent requirement in Fig. 1 has prompted various concerns involving cost, solvent leaching, and environmental persistence [6]. Small amounts of fluorous solvents are similarly found in the organic layers of fluorous/organic liquid/liquid biphase systems. This makes losses unavoidable upon phase separation. Therefore, the development of the strategy to eliminate the fluorous solvent requirement for fluorous catalysis is a topic of enormous importance.

Fluorous catalysis without fluorous solvent suggested that fluorous catalyst might be utilized under one-liquid-phase conditions involving ordinary organic solvents as shown in Fig. 2 [6]. The system would first be warmed to achieve monophasic reaction conditions. Subsequent cooling would precipitate the catalyst, and recovery would involve a simple liquid/solid phase separation. Thus, design and synthesis of the fluorous catalyst that exhibit strongly temperature-dependent properties are important strategy for the application of this catalytic system to organic reactions. However, to our knowledge, example of the applicability of this concept to fluorous catalysis was very limited. Gladysz’s group introduced the solubility based thermomorphic properties of heavy fluorous phosphines **1** and **2** (Scheme 1) in nonpolar organic solvent as a new strategy to perform homogeneous fluorous catalysis without fluorous solvent in conjugate additions of alcohols to methyl propiolate [6,7]. Yamamoto et al. reported the thermomorphic fluorous catalysts **3** and **4** (Scheme 1) as Brønsted acid for the condensation of carboxylic acid with amine [8] and the acetal formation [9], respectively under fluorous-solvent-free conditions. Otera has reported that fluorous distannoxanes such as **5** (Scheme 1) catalyzed transesterifications in toluene [10]. The catalyst precipitated upon cooling, but a fluorous solvent extraction was utilized for

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1566-7367/$ - see front matter
doi:10.1016/j.catcom.2007.11.020

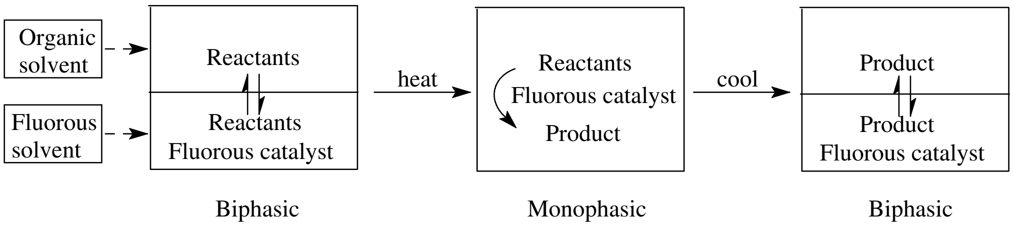


Fig. 1. Fluorous biphasic catalysis with fluorous solvent (the liquid/liquid FBS).

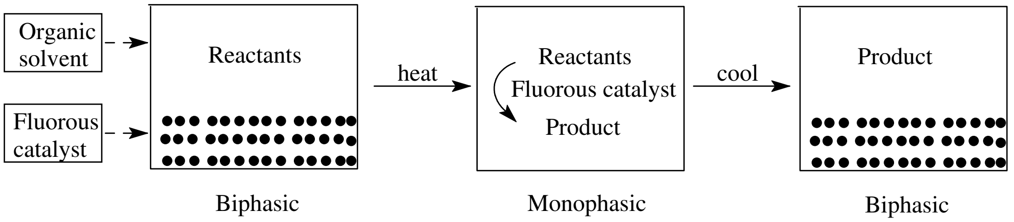
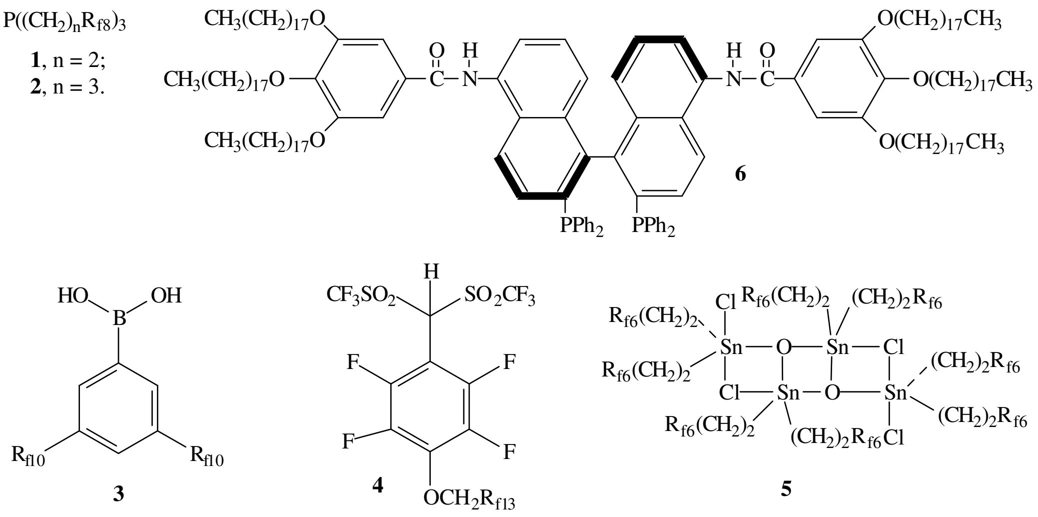


Fig. 2. Fluorous biphasic catalysis without fluorous solvent (the liquid/solid FBS).



Scheme 1. Some thermomorphic fluorous or nonfluorous catalysts.

recovery. Jessop and co-workers described a new method for fluorous biphasic catalysis (FBC), in which the fluorous solvent was replaced by fluorinated silica, and the fluorous catalyst was dissolved in organic solvent by the presence of CO_2 pressure and could be recovered after the reaction by release of the CO_2 pressure [11]. Fan's group report the first example of a thermomorphic system for asymmetric hydrogenation and liquid/solid separation of the chiral catalyst [12]. Their strategy employed alkyl "pony tails" instead of the expensive fluorous ones as the "phase-tags" of the immobilized chiral catalyst. This nonfluorous phase tagged Ru(BINAP)-6 (Scheme 1) catalyst exhibited both the advantages of very simple catalyst recycling and high enantioselectivity due to its homogeneous manner at high temperature. In addition, Bergbreiter and others developed some novel thermomorphic systems consisting of nonfluorous polymer-supported catalysts via properly choosing of organic solvent mixtures [13–18]. These thermomorphic catalyst performed homogeneous catalytic reactions and could be easily recovered by simple cooling or heating.

In the course of our extensive synthetic and physical investigations involving perfluoroalkylated pyridines **7**–**9** (Scheme 2) [19–21], we noticed that they were very poorly soluble in less polar hydrocarbon solvents at room temperature. This drew our attention to the many types of Lewis base catalyzed organic reactions in the literature.

On the other hand, the Knoevenagel condensation is one of the most useful and widely employed methods for carbon–carbon formation in organic synthesis, with numerous applications in the synthesis of fine chemicals, hetero Diels–Alder reactions, and carbocyclic as well as heterocyclic compounds of biological significance [22]. The reactions are usually catalyzed by bases such as amines, ammonia, or sodium ethoxide in organic solvents [22]. Lewis acids [23], surfactants [24], zeolites [25], and ionic liquids [26,27] have also been employed to catalyze