



Continuous-flow synthesis using a column reactor packed with heterogeneous catalysts: A convenient production of nitroolefins by using amino-functionalized silicagel



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ABSTRACT

A continuous-flow synthesis of β -nitroolefins by using heterogeneous base catalysts has been developed. Although the use of an excess amount of nitro-donor such as nitromethane is required in conventional methods, nearly equimolar amounts of nitro-donors and carbonyl compounds are sufficient for high-yielding production of nitroolefins. Catalysts for this flow protocol are inexpensive and abundant, and high durability and high productivity were also realized by using an appropriate second support.

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1. Introduction

Continuous manufacturing of fine chemicals is one of the most important areas of current synthetic chemistry and chemical engineering.^{1,2} For truly efficient continuous production of chemical materials, continuous-flow chemistry has become a powerful solution; the approach offers several benefits such as environmental compatibility, efficiency, and safety.^{3–7} In addition to high value-added specialty chemical products such as APIs, mid-range valued fine chemicals such as common intermediates for the above valuable products can be produced in a sustainable way by employing continuous-flow techniques.^{8,9} To realize continuous-flow synthesis of nonspecialty chemicals, utilization of catalytic processes with inexpensive, abundant, and readily available heterogeneous catalysts is required for realistic prospects of commercialization.¹⁰ Nitroolefins are one of the most important classes of nitrogen-containing intermediates.^{11,12} They provide various types of nitro compounds through addition to carbon–carbon double bonds, and the nitro compounds that are obtained can be converted into a wide range of nitrogen-containing compounds including amines, amides, and lactams by applying further transformations.^{13–15} For straightforward and systematic assembly of such chemical systems

using key intermediates and another reactants, sequential flow reactions are an ideal approach; these systems provide several advantages over one-pot assembly in terms of selectivity and compatibility of substrates and/or catalysts.^{16–22} Our group has focused on the application of heterogeneous catalysts for continuous-flow reactions.²⁰ Our recent efforts on sequential and continuous-flow asymmetric synthesis of (*R*)- and (*S*)-Rolipram²³ revealed that commercially available aminopropyl-functionalized silicagel was quite effective for the synthesis of nitrostyrenes from near equimolar amounts of aromatic aldehyde and nitromethane; however, a remaining challenge is the utilization of other aldehydes including aliphatic aldehydes as substrates for nitro-group acceptors. Nitroolefins including nitrostyrenes are usually synthesized by using either 1) a multistep reaction²⁴ involving condensation and dehydration reactions between a carbonyl compound and an excess of nitroalkane, or 2) a single-step reaction between these reactants catalyzed by supported amines,^{16,25–29} a Lewis acid/amine system,³⁰ or an amino acid lithium salt,¹⁷ and so on.^{31–33} Major issues are the requirements for harsh reaction conditions and the large amount of nitro-donating substrate required. The use of an excess amount of nitromethane involves some particular difficulties with respect to the utilization of the product nitroolefins because of the need to remove the excess after the reaction, especially for continuous-flow conditions.³⁴ Moreover, the limited range of readily available nitroalkanes is a bottleneck for their use in such an approach. In this study, we have improved our packed-catalyst

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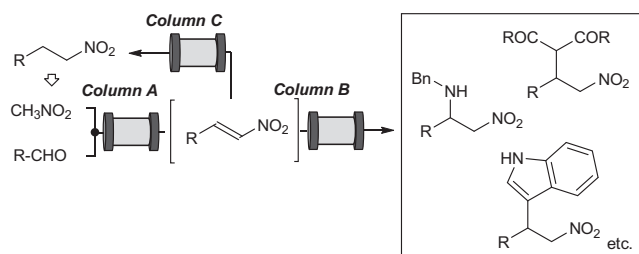


Fig. 1. Nitroolefination and sequential use for various nitro-containing compounds.

system for nitroolefination and expand the scope of the reaction with respect to the aldehyde to increase the versatility of the method. In addition, our flow synthesis of nitroolefins is shown to be applicable for nitroalkane preparation through successive partial hydrogenation of carbon–carbon double bond moieties (Fig. 1).

2. Results and discussion

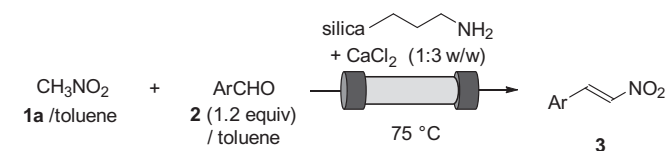
2.1. Continuous-flow synthesis of nitrostyrenes

We began to investigate efficient and scalable production of β -nitrostyrene by examining the effects of flow conditions in the reaction of nitromethane (**1a**) with benzaldehyde (**2a**, Ar = Ph). A SUS column of 300 mm length and 10 mm diameter with column ends was filled with a mixed catalyst system consisting of commercially available primary amine-functionalized silicagel (AP-SiO₂; CHROMATOREX DM1020 NH[®]) and anhydrous calcium chloride (Scheme 1). Toluene solutions of the substrate mixture (**1a/2a** = 1:1.2) were fed by using a plunger pump at a rate of 0.05–1.00 mL/min. For this first series of investigations, the total amount of nitromethane fed into the column was 40 mmol or more. Conversions of **2a** at the point of 36 mmol of **1a** supplied to the catalyst column in eight experiments are plotted in Fig. 2. It was shown that high concentration of substrates did not affect the conversion, although the application of a flow rate of >0.10 mL/min strongly suppressed the reaction. Clearly, sufficient productivity was secured by supplying 0.5 M substrate solution at 0.05 mL/min flow rate.

With these flow conditions in hand, we then examined five kinds of aromatic and heteroaromatic aldehydes: **2a** (Ar = Ph), **2b** (Ar = 4-MeOC₆H₄), **2c** (Ar = 4-MeC₆H₄), **2d** (Ar = 4-CF₃C₆H₄), and **2e** (Ar = 2-thiophene) were successfully employed under the above flow conditions. The yields of **3** remained at around 90% while more than 100 mmol of **1a** and 120 mmol of **2** were supplied, and the catalyst system was stable for more than 80–100 h. In the case of 2-thiophenecarboxaldehyde (**2e**), lower concentrations (0.3 M for **1a** and 0.36 M for **2e**) were required to secure good yields (Scheme 2).

2.2. Continuous-flow synthesis of aliphatic nitroolefins

Our focus then moved to the synthesis of aliphatic nitroolefins by using the present flow method. A preliminary investigation on



Scheme 1. Flow nitroolefination.

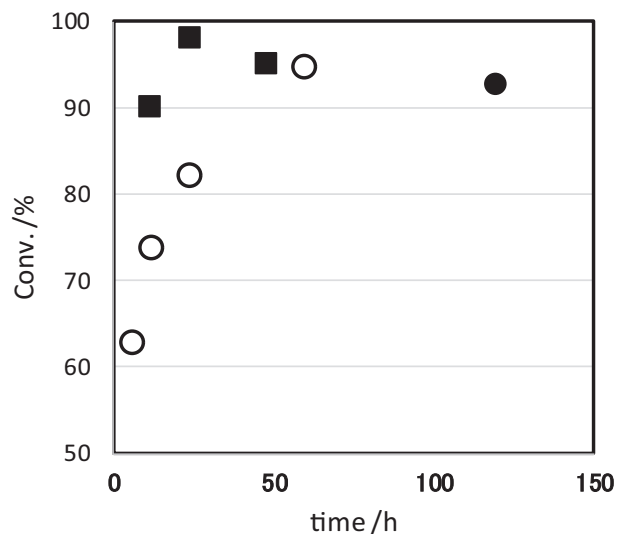
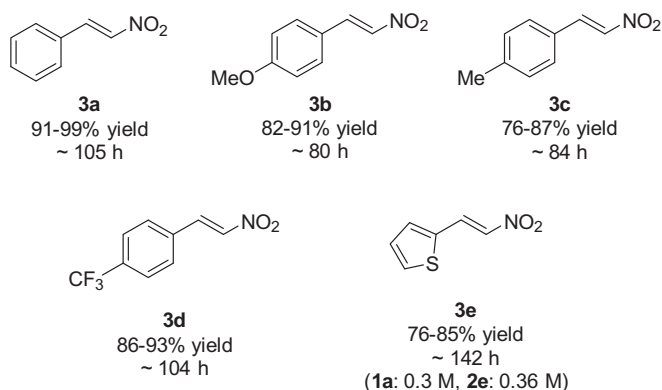


Fig. 2. Time/conversion diagram for supplying 36 mmol of **1a** + **2a**. Note: Closed circle [0.1 M, 0.05 mL/min], closed square [0.2, 0.5, 1.0 M (from right to left) solution at 0.05 mL/min], open circle [with 0.1 M solution at 0.1, 0.25, 0.5, 1.0 mL/min (from right to left)].



Scheme 2. Scope of the reaction with respect to the aromatic aldehyde.

such substrates highlighted some difficulties,⁶ therefore, we reexamined the use of several solid bases that were suitable for the reaction of cyclohexanecarboxaldehyde (**2f**) with 1.5 equivalent of nitromethane (**1a**) at 50 °C under batch conditions (Table 1). The reaction in the presence of 200 mg/mmol of AP-SiO₂, which corresponded to 0.14 equivalent of NH₂ to the aldehyde, proceeded well to afford the dehydrated nitroolefin **3f** irrespective of the level of conversion, and the yield of **3f** at 12 h was 92% (entry 2). Typical solid bases such as CaO, KF supported alumina (KF/Al₂O₃), and anion-exchange resins (Amberlite) gave nitroaldol adduct **4f** predominantly (entries 3–5). Clearly, product **3f** in the AP-SiO₂-catalyzed reaction was not a sequential product that was formed via **4f** as an intermediate, and an aza-Henry pathway that proceeded through imine formation was strongly suggested. The ratio of AP-SiO₂ to the substrates was found to be crucial; the use of 150 mg/mmol of AP-SiO₂ gave 80% yield (entry 6), whereas 100 mg/mmol of AP-SiO₂ resulted in a poor yield (entry 7). We then examined the use of suitable second supports. Whereas anhydrous calcium chloride gave 45% yield of **3f** (entry 8), the use of 4Å molecular sieves (MS4A) gave a better result (entry 9). Thus, our investigation on continuous-flow synthesis of aliphatic nitroolefin derivatives was conducted by using a catalyst column containing AP-SiO₂ and MS4A.

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