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Continuous Microflow Synthesis of Butyl Cinnamate by a Mizoroki−Heck Reaction Using a Low-Viscosity Ionic Liquid as the Recycling Reaction Medium

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Abstract:

A continuous microflow system was developed with efficient catalyst recycling for a Mizoroki−Heck reaction of iodobenzene with butyl acrylate, using a low-viscosity ionic liquid ([bmim]-NTf_2) as the reaction medium. Using a CPC CYTOS Lab System as the microreaction apparatus, in combination with an originally developed microextraction/catalyst recycling system, the reaction medium, which contained Pd catalyst could be continuously recycled to provide a total of 115.3 g (80%, 10 g/h) of the desired product.

Introduction

Microreaction (miniaturized chemical reaction) technology has opened up new perspectives for chemistry and the chemical industry.[1] Microreactors are expected to have a significant impact on chemical synthesis and production because of their many advantageous characteristics, such as highly efficient micromixing, a high volume-to-area ratio, efficient heat transfer ability, the avoidance of "hot spots" by effective temperature control, and a high operational safety.[2] Transition-metal-catalyzed reactions have previously been performed using a microflow system.[3] For example, hydrogenation,[3a,b] oxidation,[3c,d] Suzuki−Miyaura coupling,[3e] and the Kumada−Corriu reaction[3f] have been reported. Most of them dealt with *heterogeneous* catalysts, and this is probably because heterogeneous catalysis can take advantage of the high volume-to-surface ratio ensured by the microchannels. However, we focus on the potential of this new technology for use in reactions using *homogeneous* catalysts.

Ionic liquids are considered to be environmentally benign alternatives for traditional volatile organic solvents in terms of their low vapor pressure and tunable miscibility with other organic or inorganic chemicals.[4] The immobilization of the catalyst in the ionic liquid is another attractive advantage of this new reaction system, since this would facilitate the separation of both the catalyst and reaction media from the products. Our interest has focused on the use of a microflow system in *homogeneous* catalysis using ionic liquids as the reaction media. We previously reported on the application of a microflow system to the Sonogashira coupling reaction using an ionic liquid, which was particularly useful, when an IMM micromixer with a channel width of 40 μm was employed.[5]

If a *flow* reactor, irrespective of whether it is "micro" or "conventional", was to be applied to a continuous recycling process, the need to discontinue the reaction because of the subsequent separation processes after the reaction (extraction of product from the resulting reaction mixture and separation), has to be eliminated. The Mizoroki−Heck reaction,[6] one of the most useful of the palladium-catalyzed reactions, has already been carried out successfully in ionic liquids,[7] such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) and ammonium salts. [Bmim]PF_6 functions well, not only for the reaction itself but also for efficient recovery of the catalyst.[7a] Both product and ammonium salts can be readily separated from the ionic liquid containing Pd catalyst by successive biphasic workup procedures, and the Pd catalyst, retained in the ionic liquid, can be recycled (Scheme 1). [Bmim]PF_6, however, is a highly viscous liquid, and as an alternative, we focused on the use of a low-

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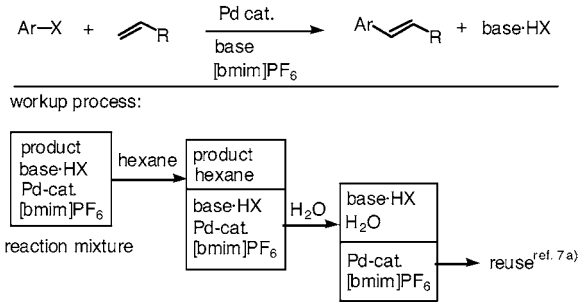
Scheme 1. **Typical workup process for Mizoroki−Heck reaction in ionic liquids**



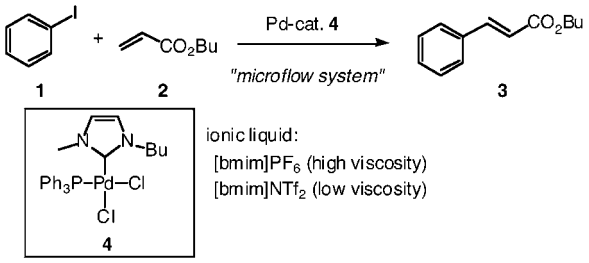
viscosity ionic liquid, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim]NTf_2),[8,9] for this study,[10] since it diffuses in microchannels more rapidly and less pressure drop and higher extraction efficiency would be expected for low-viscous reaction media.

We report herein that the Mizoroki−Heck reaction using ionic liquids can be successfully conducted in a microflow system. We also report on a model study, which achieved the multi-ten gram-scale production of butyl cinnamate using a continuous microflow reactor, a CPC CYTOS Lab System,[11] combined with our originally developed workup system, based on a dual micromixer assisting extraction system.

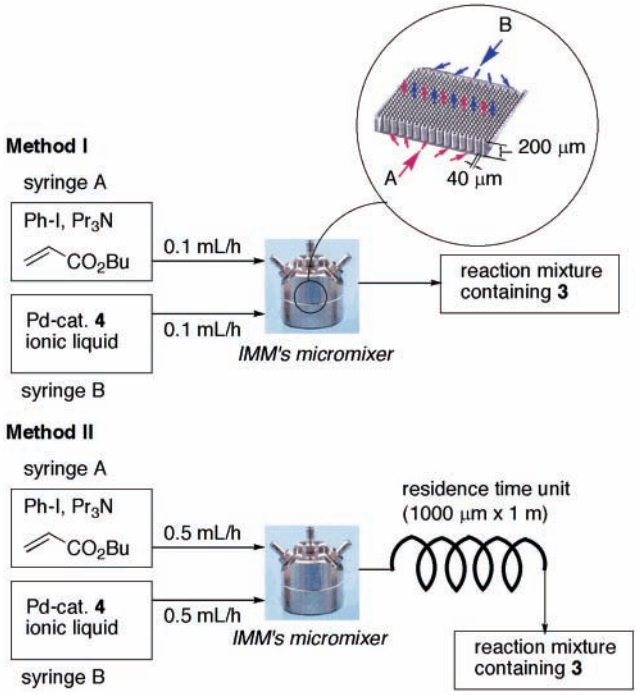
Results and Discussion

Mizoroki−Heck Reaction in a Microflow System. The reaction of iodobenzene (**1**) with butyl acrylate (**2**) in an ionic liquid was examined in a microflow system as a model reaction, to produce butyl cinnamate (**3**) as the product (Scheme 2). Both high- and low-viscosity ionic liquids, [bmim]PF_6 (312 mPa·s, 303 K)[12] and [bmim]NTf_2 (52 mPa·s, 293 K),[8] were tested for comparison. In many Pd-catalyzed reactions using ionic liquids, Pd−carbene complexes, which are generated in situ by the reaction of Pd complexes with ionic liquids, are thought to be the key catalyst species.[13] However, such an in situ procedure would make the microflow system vulnerable to clogging, because the initial

Scheme 2. **Pd−carbene complex 4 and ionic liquids used in a microflow system**



Scheme 3. **Two methods for a microflow reaction using an IMM micromixer**



Pd complexes, such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$, are insoluble in ionic liquids. Because of this, we used a Pd−carbene complex **4**,[14] which is soluble in these ionic liquids. Initially, we employed an IMM micromixer having 2 × 15 interdigitated channels (channel width = 40 μm) (Scheme 3) and found that it worked reasonably well. The results obtained using the microflow system are summarized in Table 1.

The mixture of reactants (iodobenzene (**1**), butyl acrylate (**2**), tripropylamine, and tetradecane as an internal standard) were loaded in syringe A. A solution of 5 mol % of Pd catalyst **4** dissolved in an ionic liquid, was loaded in syringe B (Scheme 3). These two syringes were operated by syringe pumps. When the reaction was performed using an IMM micromixer alone (method I) at a flow rate of 0.1 mL/h in [bmim]PF_6 at 130 °C, the reaction was sluggish, resulting in only a 12% yield of the desired coupling product with the recovery of a large amount of starting substrates (entry

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(11) The CYTOS Lab System was developed by CPC-Cellular Process Chemistry Systems GmbH, Germany. Schwalbe, T.; Golbig, K.; Hohmann, M.; Georg, P.; Oberbeck, A.; Dittmann, B.; Stasna, J.; Oberbeck, S. (Cellular Process Chemistry Inc., U.S.A.) Eur. Pat. Appl. EP 1 123 734, 2001; *Chem. Abstr.* **2001**, *135*, 154468b. The effective reaction volume of the CYTOS microreactor is 1.2 mL; however, along with the feed lines inside the cell, the total volume results in 2.0 mL. In the standard configuration additional reaction volume is provided by equipping the residence time unit of 15 mL. Further information is available on the Internet: www.cpc-net.com. CYTOS is registered by CPC-Systems GmbH. See also ref 2k.

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(14) The Pd−carbene complex **4** was prepared from $PdCl_2(CH_3CN)_2$ with 1-butyl-3-methylimidazolium chloride and triphenylphosphine in THF. The details will be published in a separate paper.

Table 1. **Mizoroki−Heck reaction using ionic liquids in a microflow system in conjunction with an IMM micromixer[a]**

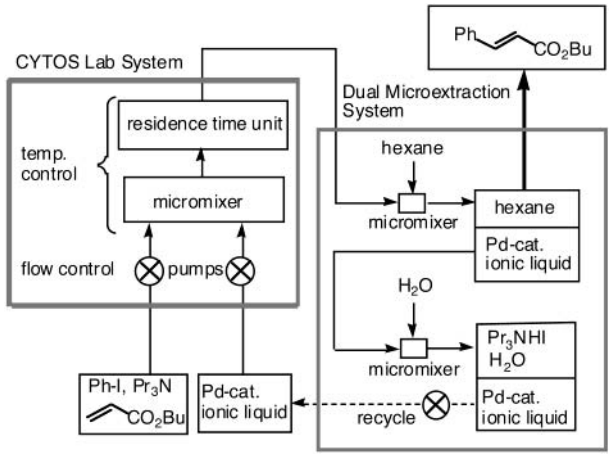
entry	ionic liquid	method[b]	temp (°C)	Pd cat. (mol %)	residence time (min)[c]	yield of **3** (%)[d]
1	[bmim]PF_6	I	130	5	10	12
2	[bmim]PF_6	I	150	5	10	67
3	[bmim]PF_6	II	150	5	50	87
4	[bmim]PF_6	II	150	2	50	98
5	[bmim]NTf_2	II	150	2	50	88
6	[bmim]NTf_2	II	150	recovered[e]	50	65
7	[bmim]NTf_2	II	130	5	50	97
8	[bmim]NTf_2	II	130	recovered[f]	50	99

[a] Reaction conditions; iodobenzene (**1**):butyl acrylate (**2**):tripropylamine = 1:1.2:1.5. [b] Method I: IMM micromixer (40 μm), flow rate, 0.1 mL/h. Method II: IMM micromixer (40 μm) + stainless tube reactor (1000 μm × 1 m), flow rate, 0.5 mL/h. [c] The residence time was determined by the total volume of the microreactor and the flow rates of both A and B. [d] Yields were determined by GC using tetradecane as an internal standard. [e] Recycled Pd catalyst in the ionic liquid from entry 5 was used. [f] Recycled Pd catalyst in ionic liquid from entry 7 was used.

1). Increasing the reaction temperature to 150 °C gave a 67% yield of the desired product **3** (entry 2). Since the low yields are due simply to low conversions, we attached an additional stainless steel tube reactor (diameter = 1000 μm, length = 1 m) to extend the residence time in order to ensure the completion of the reaction (method II). With an increased flow rate, 0.5 mL/h, the extended system, comprising a micromixer plus a tube reactor, resulted in a smooth reaction to give an 87% yield of product within 50 min at 100 °C in [bmim]PF_6 (entry 3). With a decreased amount of Pd catalyst (2 mol %), heating to 150 °C was necessary, but yields as high as 98% were obtained (entry 4). Comparable yields were obtained when the reaction was conducted in a low-viscosity ionic liquid, [bmim]NTf_2 (entry 5). After the reaction, the product and ammonium salts were separated by successive extraction with hexane and water, and the remaining ionic liquid containing Pd catalyst was employed in the next reaction. Although the second run, using a mixture of [bmim]-NTf_2 and catalyst recovered from prior reactions and conducted at 150 °C resulted in a low efficiency (entry 6), we were pleased to find that 130 °C is a suitable temperature for both the reaction and the reuse of the catalyst (entries 7 and 8).

A Continuous Flow System Using an Automated Microflow Apparatus. With these favorable results in hand, we embarked on work to construct an automated continuous microflow system for use in the Mizoroki−Heck reaction. To achieve such a continuous microflow system, which involves the reaction, separation of the product and catalyst, and reuse of the catalyst, the problem of designing a continuous workup system arose. For the continuous reaction system, we used an automated microflow apparatus, CPC CYTOS Lab System,[11] which is equipped with pumps, a micromixer (channel width = 100 μm, inner volume = 2 mL), and a residence time unit (inner volume = 15 mL), with an intelligent control unit (left-hand side of Scheme 4). To realize a flow of 0.5 mL/min in the microchannels, the use of the low-viscosity ionic liquid [bmim]NTf_2, was essential, since a high-viscosity ionic liquid [bmim]PF_6 did not flow smoothly and overburdened the pumps.

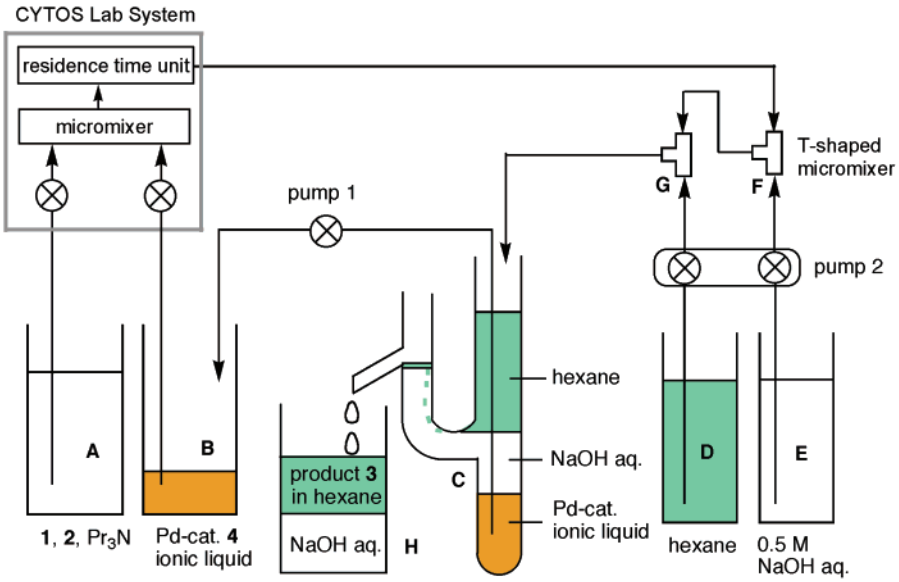
Scheme 4. **Schematic drawing of the automated microflow apparatus, CPC CYTOS lab system and flow workup processes**



Using this automated microflow apparatus, a neat liquid containing iodobenzene (**1**), butyl acrylate (**2**), and tripropylamine was introduced from one inlet of the micromixer (0.5 mL/min), and the low-viscosity ionic liquid containing the Pd catalyst **4** was introduced from the other inlet (0.5 mL/min). The catalytic reaction took place after the two solutions were mixed at the CPC microreactor and was brought to completion in the residence time unit (residence time, 17 min at a total flow rate of 1.0 mL/min). The temperature of both the microreactor and the residence time unit was controlled at 130 °C. From the resulting mixture, the product, butyl cinnamate, was obtained by conventional extraction with hexane. The yields were consistently higher than 90%. The byproduct, an ammonium salt, was removed from the resulting ionic liquid layer by washing with copious amount of water. The ionic liquid recovered in this procedure could be used again in the next run without any drop in product yield (90−99%), suggesting that the Pd catalyst remained active in the ionic liquid even after completion of the recycling procedure. The repeated use of the Pd catalyst in the ionic liquid led us to explore a totally automated flow system with continuous catalyst recycling.

To achieve such a flow workup system, we used T-shaped micromixers (channel diameter = 300 μm) to facilitate the extraction of the product and ammonium salt. The setup is schematically outlined in the right-hand side of Scheme 4. In Scheme 5, we present a totally automated catalytic flow system with microextraction units attached to the microflow reaction system. The ionic liquid solution exiting from the microflow reaction apparatus was introduced into a T-shaped static micromixer, where the ammonium salt was washed by mixing with 0.5 M NaOH aqueous solution. The mixture solution was then mixed by another T-shaped static micromixer, where hexane was mixed to extract the product. On standing in the Y-shaped glass flask, the resulting mixture separated into three phases, a hexane layer containing the product and tripropylamine, an aqueous layer containing the inorganic salt, and the ionic liquid layer containing the Pd catalyst. The ionic liquid in the bottom layer was pumped back to container **B** for recycling the Pd catalyst. After running the complete system for 11.5 h, where 144.8 g (0.71

Scheme 5. **Detailed continuous workup process with flow workup/catalyst recycling system**



mol) of iodobenzene together with the corresponding amount of acrylate and amine were consumed (total volume 408 mL), 115.3 g of *trans*-butyl cinnamate was obtained in an 80% (10 g/h) yield after purification by silica gel chromatography. This corresponds to a performance in which the ionic liquid with the Pd catalyst (90 mL) was recycled about five times during this overall catalytic reaction.

Conclusions

A Pd-catalyzed Mizoroki−Heck reaction was successfully carried out in a microflow system using ionic liquids as the reaction media. A continuous flow system was achieved with efficient catalyst recycling by using a low-viscosity ionic liquid, [bmim]NTf_2, and an automated microreactor system, CYTOS Lab System, in conjunction with an efficient self-designed microextraction/catalyst recycling system. The desired coupled product, butyl cinnamate, was produced in an overall yield of 80% (115.3 g, 10 g/h), in which the ionic liquid containing Pd catalyst was continuously recycled. In this continuous microflow system, the Pd catalyst is immobilized in the ionic liquid phase and circulates around the system analogous to a heterogeneous catalyst. We believe that the continuous microflow system described here is for use in reactions involving homogeneous catalysts.

Experimental Section

General. The ionic liquids used in this work were synthesized according to the literature,[8,12] dried under vacuum at 50 °C for 4 h, and saturated with N_2 before use. Other reagents were used as purchased. The product was confirmed by ^{1}H- and^{13}C NMR, GC−MS, and HPLC. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JMN-AL400 spectrometer in $CDCl_3$ operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements. Mass spectra were obtained on a Shimadzu GCMS-QP 5050A instrument. Analytical HPLC was carried out on JAI LC-908. Analytical GC was carried out on a Shimadzu GC-17A gas chromatography equipped with a flame ionization detector using a fused capillary column (J & W DB-1). IMM's static micromixer was purchased from the Institute of Microtechnology Mainz, in which the central micromixing device with 2 × 15 interdigitated channels (40 μm width and 200 μm depth) was made of silver. The CPC CYTOS Lab System was made by CPC-Cellular Process Chemistry System GmbH. The T-shaped micromixer for extraction, which has a channel diameter of 300 μm, was designed by us and manufactured by Sanko Seiki Co., Ltd. The syringe pump was purchased from KD Scientific Inc. Pump (SP-D-2501V), and Pump (RP-NB) were purchased from Nihon Seimitsu Kagaku Co., Ltd. and Fulue Science Co., Ltd., respectively.

Typical Procedure for the Reaction Using the IMM Micromixer in a Flow System (Table 1, entry 7). A mixture of neat liquid (1.9 mL) containing iodobenzene (**1**) (0.612 g, 3 mmol), butyl acrylate (**2**) (0.461 g, 3.6 mmol), tripropylamine (0.645 g, 4.5 mmol), and tetradecane (0.149 g, 0.7 mmol) as an internal standard was loaded in syringe **A**. The Pd catalyst **4** (0.087 g, 0.15 mmol) in [bmim]NTf_2 (1.9 mL) was loaded in syringe **B**. Syringes **A** and **B** were each connected to the two inlets of the IMM microreactor by a Teflon tube. At the outlet of the microreactor, a 1.0 m length of stainless tube (diameter = 1000 μm) was attached to create additional residence time unit by a short Teflon tube. The Teflon tube was connected to the end of the stainless steel tube for product collection. The entire reactor was submerged in an oil bath, which was maintained at 130 °C, followed by switching on the two syringe pumps at the rate of 0.5 mL/h. The mixture of the product was collected from the outlet. The reaction mixture (ca. 0.2 mL) from the first 1 h was discarded, and the subsequent portion was collected. The product was separated from the reaction mixture by extraction with hexane (5 × 5 mL). The yield of the desired product **3** was determined by GC analysis to be 97%. The resulting ionic liquid layer, containing the Pd catalyst and ammonium salt, was washed with water (5 × 5 mL) to remove the ammonium salt. The resulting

ionic liquid layer was dried under vacuum at 50 °C for 4 h and used in the next experiment.

Typical Procedure for the Microflow Reaction Using a CYTOS Lab System. Prior to the reaction, the CYTOS Lab System was filled with solvent and the temperature inside the microreactor and the residence time unit adjusted using the thermostat of the system. Pumps A and B of the microreaction system were calibrated independently to the desired flow rates using nonane and ionic liquid [bmim]NTf_2, respectively. The residence time *t* was calculated according to the equation: *t* (min) × total flow rate (mL/min) = volume (2 mL (micromixer) + 15 mL (residence time unit)). The mixture of neat liquid (30 mL) comprising iodobenzene (**1**) (9.2 g, 45 mmol), butyl acrylate (**2**) (7.0 g, 54 mmol), tripropylamine (9.8 g, 68 mmol), and tetradecane (3.2 g, 16 mmol) as an internal standard was loaded in container **A**. Pd catalyst **4** (1.29 g, 2.25 mmol) in [bmim]NTf_2 (30 mL) was loaded in container **B**. The reaction temperature was controlled at 130 °C using a Huber Unistat Tango temperature controller attached to the CPC CYTOS Lab System. The flow rate (0.5 mL/h) was controlled by a PC terminal. The reactants were pumped through the two inlet pipes into the microreaction system from the graduated cylinders. The consistency of the flow rate was periodically verified by measuring the volume of starting material consumed over a given certain period. The product was separated from the reaction mixture by extraction with hexane (5 × 30 mL). The yield of the desired product **3**, as determined by GC analysis, was 90%. The resulting ionic liquid layer, which containing the Pd catalyst and ammonium salt, was washed with water to remove the ammonium salt (5 × 30 mL). The resulting ionic liquid layer was dried under vacuum at 50 °C for 4 h and used in the next experiment.

Typical Procedure for the Reaction in a Continuous Microflow/Catalyst Recycling System. The apparatus for an automated catalytic flow system was set up as shown in Scheme 5. The mixture of neat liquid (408 mL) comprised of iodobenzene (**1**) (144.8 g, 0.71 mol), butyl acrylate (**2**) (110.0 g, 0.85 mol), and tripropylamine (154.0 g, 1.06 mol) was loaded in container **A**. The Pd catalyst **4** (3.9 g, 6.75 mmol) in [bmim]NTf_2 (90 mL) was loaded in container **B**. For this experiment aiming at a larger scale production, two standard residence time units were attached to the CPC CYTOS Lab System. Correspondingly, the flow rates were adjusted to 0.8 mL/min for the substrates in **A** and 1.0 mL/min for the Pd catalyst solution in **B**. Hexane was placed in container **D**, and an aqueous solution of 0.5 M NaOH was placed in container **E**. N_2 was bubbled through all four solutions to remove O_2 during the reaction. A Y-shaped glass flask **C** was inserted in the flow line to ensure good phase separation. The ionic liquid layer containing the Pd catalyst was moved to container **B** by pump **1** (SP-D-2501V), which was operated at 1.0 mL/min. Pump **2** (RP-NB), which has two flow lines, was used at a flow rate of 1.6 mL/min to introduce the NaOH aqueous solution and hexane to each T-shaped micromixer. After the reaction, the combined hexane phase was evaporated, and the residual oil was purified by column chromatography on silica gel to give the desired product **3** in 80% (115.3 g) yield.

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