Modular Microreaction Systems for Homogeneously and Heterogeneously Catalyzed Chemical Synthesis

by **Daniel A. Snyder**[1]), **Christian Noti**, and **Peter H. Seeberger***[1])

Department of Chemistry, Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich

and **Frank Schael**, **Thomas Bieber**, **Guido Rimmel**, and **Wolfgang Ehrfeld**

Ehrfeld Mikrotechnik AG , D-55342 Wendelsheim

Until now, microreaction devices designed for a specific type of reaction were used mainly for highly exothermic, very fast reactions. Described is a modular microreaction system and its application to representative homogeneous and heterogeneous reactions important in organic synthesis. The modular microreaction system allows continuous flow processes to be optimized and employed effectively in the chemical laboratory. The modular microreaction systems proved also versatile for syntheses requiring moderate reaction times, thus extending their application to a large fraction of organic reactions. The use of the modular and cleanable microreaction systems to rapidly develop optimized reaction conditions provides an excellent basis for the development of many chemical transformations scalable from milligram to ton production quantities.

1. Introduction. – Microfabricated reaction systems (microreaction systems) have generated much interest in recent years for use in analysis in the chemical and biological sciences [1]. The reduced size of such microanalytical systems minimizes the required sample size and facilitates experimental throughput and automation. Microreaction systems have also been explored for use in chemical synthesis [2], where high heat- and mass-transfer rates have been exploited to perform reactions otherwise considered dangerous [3]. Initial explorations in combinatorial chemistry have been reported as well [4]. The use of microreaction systems for fine chemical synthesis is just evolving [5]. The synthesis of key intermediates or active drug molecules in the chemical and pharmaceutical industries could benefit from microreaction systems by enabling cost-effective transition from bench-top to production scale. Microstructured reactors (microreactors) are essential parts of microreaction systems and have been explored extensively [6]. However, to fully benefit from microreaction technology, microreaction systems should incorporate common unit operations of chemical engineering such as mixing and heat exchange in one unit. Ideally, such microreaction systems would be *i*) fully modular to allow for quick transfer of reactions developed for batch operation mode, be *ii*) easily assembled for experimental flexibility, and *iii*) enable significant production rates for both homogeneous and heterogeneous reactions at elevated temperatures and high pressures on a table top.

Here, we describe a modular microreaction system and its application to representative homogeneous and heterogeneous reactions important in organic

[1]) Former address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.

synthesis. The modular microreaction system allows continuous flow processes to be optimized and employed effectively in the chemical laboratory. Syntheses enabled by the modular microreaction system in the laboratory environment are readily scalable. The continuous operation mode avoids scale-up difficulties typically encountered when lab-scale batch processes are be transferred to production-scale processes [7]. In addition, the microstructures inserted in the modules of the modular microreaction system are scalable by increasing the number of parallel microstructures without changing the characteristic dimensions. In this way, process conditions may be maintained while adjusting modular microreaction systems to the desired production rates.

2. Results and Discussion. – The modular design of the microreaction system allows one set of components to be used for a variety of purposes, thus accelerating the development of protocols for new reactions. The modules of the modular microreaction system were composed of mechanically machined approximately cubic stainless steel blocks (25 mm) containing stainless steel inserts with characteristic dimensions of 50–100 μm for fluid-handling functions. The passive total fluidic volume of the modular microreaction system was minimized by avoiding any connectors or pipes between the unit operation modules, which were sealed against each other by chemically resistant O-rings that withstand pressures of up to 100 bar. The modular microreaction system employed here was designed for flow rates of up to 100 ml/min.

Basic features of the modular microreaction system are the ability for reactive mixing of components on a μm length scale, followed by subsequent diffusional and secondary flow mixing in micromixers. The micromixers operate *via* interdigitating streams of solvent. They allow for the combination of reactant streams in milliseconds to seconds depending on the diffusion coefficients and flow conditions, thereby minimizing local concentration gradients that may result in side-product formation. In general, reaction selectivity and yield can be sensitive to mixing effects when the reaction rate is higher than the mixing rate [8]. For the reactions described below, it was assured that mixing rates of the micromixers were 1–2 orders of magnitude higher than the reaction rates. The modular microreaction systems allow also for precise control of reaction conditions including temperature, pressure, and residence time. The cross-type heat-exchangers facilitate rapid, intensive heating and cooling to reach the optimal reaction temperature. The capillary reactor used as general-purpose residence time module for liquids employed a temperature controlled stainless steel capillary reactor consisting of a capillary with 1-mm internal diameter. The multiple-turn coiling of the reactor capillary was designed to result in a residence-time distribution of the reaction medium in the reactor that is half as broad as the corresponding residence-time distribution in a non-coiled capillary of the same length. A cartridge reactor allows a solid catalyst to be enclosed in a temperature controlled, flow-through stainless steel cartridge.

The simple modular microreaction system employed here included two heat-exchangers, a micromixer, and a temperature-controlled capillary reactor consisting of either a 1.7 and 4 ml volume capillary, respectively, or a 0.5-ml cartridge reactor charged with solid catalyst (*Fig. 1*).

Two reactant solutions were fed through the micromixer into the reactor using HPLC pumps with flow rates between 0.07 and 4 ml/min, and the eluent from the micro-

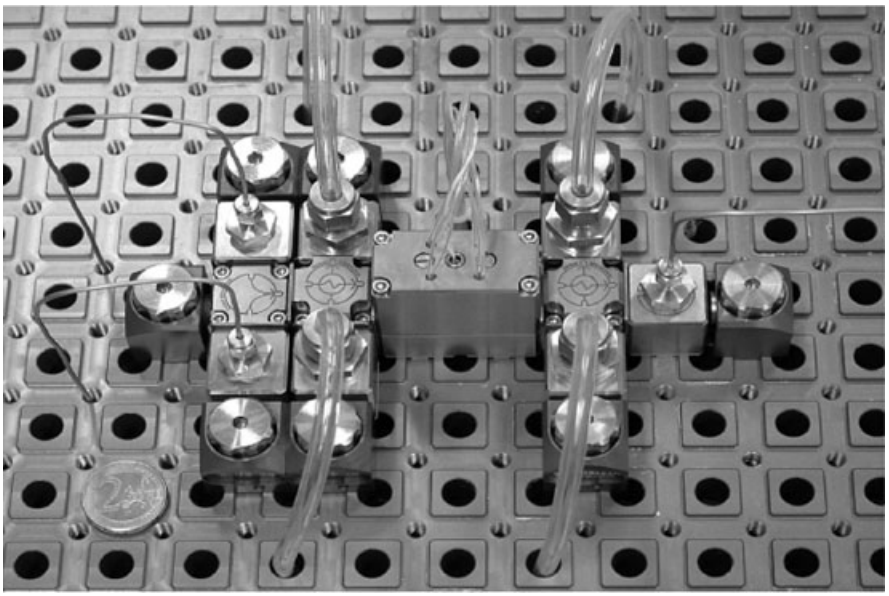

Fig. 1. *Modular microreaction system with a 0.5-ml cartridge reactor* (module equipped with electrical cables) *for employment of solid catalysts.* Alternatively, an arrangement with a capillary reactor (not shown) was used for homogeneous and heterogeneous liquid/liquid reactions.

reaction system was quenched immediately. Exemplary, *Fourier* transform infrared (FT-IR) absorbance spectra of modular microreaction systems eluents were collected in-line *via* an attenuated total reflection (ATR) flow-through cell with adjacent FT-IR spectrometer.

Several representative chemical transformations were carried out including acylation, alkylation, cycloaddition, olefination, and cross-coupling reactions (*Table*).

For the aldol condensation, a more-complex reactor configuration was employed. In a first micromixer, acetone and PhCHO were mixed before KOH was added in a second mixer. The mixture was subsequently fed into the capillary reactor. After passing through the reactor, AcOH was added by a third micromixer to quench the reaction. Finally, $CHCl_3$ was added in a fourth micromixer to extract the product, and the eluent was collected in a flask to allow for phase separation.

Initially, acetylation of 2-phenylethanol using excess Ac_2O and 4-(dimethylamino)pyridine (DMAP) as catalyst was explored; with a residence time of 15 min in the capillary reactor, the reaction resulted in 95% yield of product as measured by GC-FID of the quenched, extracted, and dried reactor eluant[2]). Alkylation of PhOK by $PhCH_2Br$ with an excess of PhOK in DMF was found to be extremely rapid (residence

[2]) To produce 2-phenylethyl acetate, a solution of Ac_2O (0.7 ml, 7.70 mmol) in pyridine (25 ml) and a solution of 2-phenylethanol (0.33 ml, 2.76 mmol) and DMAP (25 mg, 0.20 mmol) in pyridine (25 ml) were combined during a residence time of 15 min at 30°. A 1.8-ml portion of the reactor eluant was collected into 1M HCl (20 ml) for analysis; this was extracted with Et_2O (15 ml), and the organic layer was washed with 5% Na_2CO_3 (3 ml), dried (Na_2SO_4), and analyzed by GC, which showed the product to have been formed in 95% yield.

Table. *Summary of Reactions Performed in the Modular Microreaction System*[a])

Reaction	Reactant 1 (c_i)	Reactant 2 (c_i)	Catalyst	Product	Solvent	T/K	τ/min	φ/%	ϕ/%	η/%	g/h[b])
Acylation	2-Phenylethanol (0.08M)	Ac_2O (0.16M)	DMAP	2-Phenylethyl acetate	Pyridine	303	15	95	95	100	3.4
Alkylation (*Williamson* ether synthesis)	PhOH (0.19M)/KOH (0.23M)	$PhCH_2Br$ (0.1M)	Bu_4NI	$PhCH_2OPh$	DMF	323	1	100	100	100	110
Alkylation (*Williamson* ether synthesis)	PhOH (0.19M)/KOH (0.23M)	$PhCH_2Br$ (0.1M)	Bu_4NI	$PhCH_2OPh$	$CHCl_3$/ H_2O	323	60	99	93	94	2.4
Cycloaddition (*Diels–Alder*)	2,3-Dimetylbuta-1,3-diene (0.99M)	Maleic anhydride (0.48M)	–	DBFD	NMP	333	30	100	98	98	17
Olefination (*Horner–Wadsworth–Emmons*)	Triethyl phosponoacetate (1M)	PhCHO (0.09M)	TBD	Ethyl cinnamate	MeCN	323	10	n.d.	91	n. d.	5.2
Nitroaldol addition (*Henry*)	$MeNO_2$ (1.87M)	PhCHO (0.99M)	TBD	2-Nitro-1-phenyl-ethanol	i-PrOH	278	10	76	76	100	77.7
Aldol condensation	Acetone (0.5M)	PhCHO (0.25M)	NaOH	Benzylidene-acetone; dibenzylidene-acetone	EtOH	298	7	89	59; 22	66; 28	185 110
C,C Coupling (*Heck*)	PhI (0.17M)	Ethyl acrylate (0.17 M)	Pd/C	Ethyl cinnamate	NMP	363	30	99	99	100	5.7

[a]) *Abbreviations:* c_i : initial concentration, τ : residence time in microreactor, φ : conversion of reactant (referred to the stoichiometrically limiting component, estimated error of φ was $\pm 1\%$, measured by GC-FID in quenched, extracted, and dried eluant, *cf.* [3]), ϕ : actual yield of non-isolated product (estimated error of ϕ was $\pm 1\%$, measured by GC-FID in quenched, extracted and dried eluant, *cf.* [3]), η: Selectivity ($\eta = \phi/\varphi$), g/h: yield in grams/hour, DMAP: 4-(dimethylamino)pyridine, TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene, NMP: *N*-methylpyrrolidin-2-one, DBFD: 3a,4,7,7a-tetrahydro-5,6-dimethylisobenzofuran-1,3-dione. [b]) Extrapolation, in the assumption that the yield increases linearly with time.

time 1 min) and resulted in quantitative yield. Interestingly, this reaction could also be carried out under biphasic conditions ($CHCl_3/H_2O$) in the presence of Bu_4NI (TBAI) as phase-transfer catalyst, but required a longer reaction time. It should be noted that the capillary reactor was not explicitly designed for biphasic liquid–liquid reaction media, which tend to separate spontaneously. While reactors designed for such media were described previously [9], these media were not further investigated in the present work.

Next, we demonstrated the utility of the microreaction systems to carry out C–C bond-forming reactions at elevated temperatures. The *Diels–Alder* reaction of maleic anhydride with excess 2,3-dimethylbuta-1,3-diene proceeded readily [10]. *Horner–Wadsworth–Emmons* olefination of PhCHO with triethyl phosphonoacetate also caused no problems; 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was found to perform better than 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), resulting in 91% yield in 10 min at 50°. For a conventional batch process under slightly different conditions, a yield of 85% was reported [11]. TBD also efficiently catalyzed a *Henry* nitroaldol addition, whereby the reaction temperature showed little influence between 0 and 50° [12].

Metal-catalyzed cross-couplings are key transformations for the assembly of complex molecules. Therefore, we explored the applicability of microreaction systems to these important modes of bond formation. *Heck* coupling of PhI and ethyl acrylate using Pd on charcoal on 20-mmol scale without preconditioning afforded 99% yield of the desired ethyl cinnamate in 30 min at 130° [13][14]. Batch methods had resulted in 100% conversion after 30 min at 140° with preconditioned catalyst [15].

During the optimization of chemical syntheses and the development of industrial processes, it is important to gain a sound understanding of the reaction mechanism. The aldol condensation of acetone and PhCHO was studied and optimized using modular microreaction systems with regard to reactant concentrations and reaction time. The dependence of the yield of benzylidene-acetone (=4-phenylbut-3-en-2-one; *Table* and *Fig. 2*) for various reaction times and stoichiometric ratios of the reactants was recorded.

The highest yield of benzylidene-acetone (59%) and dibenzylidene-acetone (=1,5-diphenylpenta-1,4-dien-3-one; 20%) was obtained with a reaction time of just 7 min and a twofold excess of PhCHO. Under these conditions, acetone was almost completely consumed (99% conversion).

Yield and selectivity of a reaction can be optimized readily using modular microreaction systems but required a total of 34 h in the laboratory to perform 59 measurements in 13 set-ups. A similar optimization carried out with conventional laboratory equipment would require 65 h of laboratory work when assuming that each set-up would require 5 h of work. It should be mentioned that other parameters such as pressure can be varied and optimized with the modular microreaction system within the same time-frame. High yields and selectivities were observed throughout the series of homogeneous and heterogeneous reactions (*Table*) underlining the broad applicability of the modular microreaction systems.

GC Analysis was the most time-consuming part of these studies. In-line spectrometric techniques may further accelerate reaction optimization as demonstrated for the *Henry* reaction (*Fig. 3*, and *Table*), where in-line FT-IR was applied. Conversion was measured by FT-IR as a function of process parameters such as

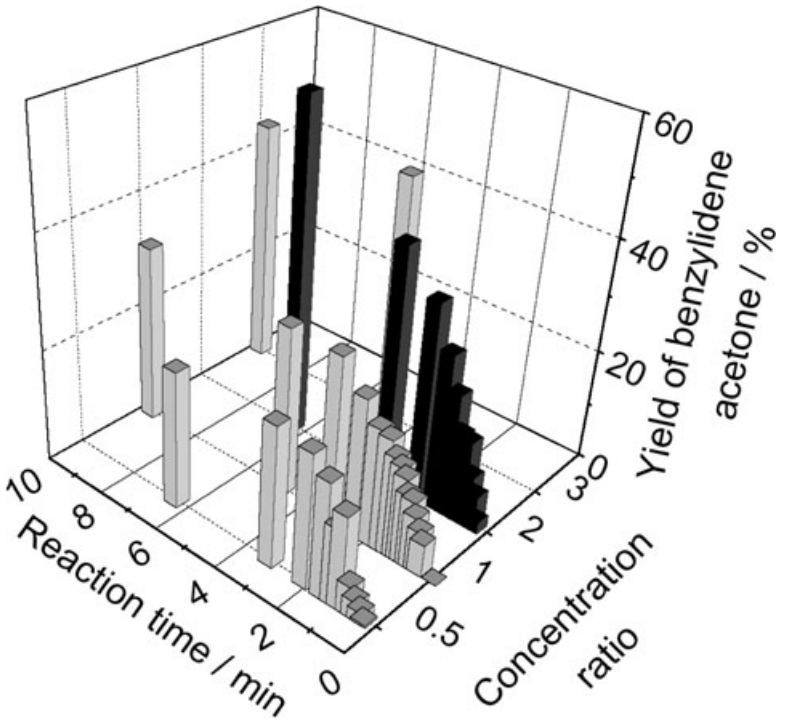

Fig. 2. *Actual yield of non-isolated benzylidene-acetone obtained with the modular microreaction system for various concentrations of acetone and benzaldehyde, and reaction times.* The reaction time was varied by variation of the total flow through the modular microreaction system. The black bars indicate the results with maximized yield of benzylidene-acetone.

reaction time (see inset of *Fig. 3*). The results were in good agreement with results obtained by GC. The combination of modular microreaction systems with rapid, non-invasive analysis methods provides an elegant way for on-line optimization and statistical analyses of chemical syntheses.

3. Conclusions. – Until now, microreaction devices designed for a specific type of reaction were used mainly for highly exothermic, very fast reactions. The modular microreaction systems proved also versatile for syntheses requiring moderate reaction times, thus extending their application to a large fraction of organic reactions. The use of the modular and cleanable microreaction systems to rapidly develop optimized reaction conditions provides an excellent basis for the development of many chemical transformations scalable from milligram to ton production quantities.

Experimental Part

General. All microreaction modules were manufactured by *Ehrfeld Mikrotechnik* (*Ehrfeld Mikrotechnik AG*, D-55342 Wendelsheim). The cross-current flow heat-exchangers are built from wet-etched, stacked, and bonded 1.4571 stainless steel platelets. The multilamination micromixers contain either wet-etched, stacked, and bonded 1.4571 stainless steel platelets or comb-shaped inlets with a diaphragm defining the mixing zone. The

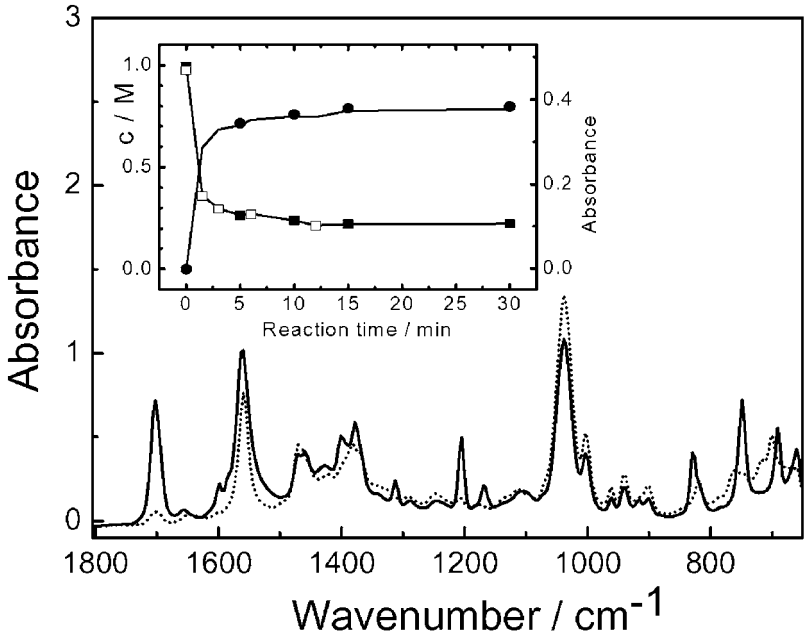

Fig. 3. *On-line FT-IR studies of the* Henry *reaction performed in the modular microreaction system*. FT-IR Spectra of a mixture of 1.87M $MeNO_2$ and 0.99M PhCHO in i-PrOH before the reaction (*solid line*) and in equilibrium after 30 min of reaction time (*broken line*). *Insert:* Concentration of PhCHO (*squares*) and of 2-nitro-1-phenylethanol (*circles*) *vs.* reaction time as measured by GC-FID (*left axes*, *filled symbols*). FT-IR Absorbance (*right axis*, *open squares*) detected at 1702 cm^{-1} (C=O stretching mode of PhCHO) *vs.* reaction time.

temp.-controlled cap. reactor has electric heating and consists of a specially twisted (eight shaped) stainless steel capillary. The cartridge reactor has an integrated temp.-controlled heating system and a removable cartridge for easy and fast exchange of catalyst. The sealing plates consist of stainless steel with an FFKM O-ring for fluid-tight connection. The delivery of the reaction solns. was performed by *Knauer K-501* HPLC pumps equipped with ceramic valves. For the heating and cooling of the thermal fluid, *Thermo Haake DC30* and *DC30-K20* thermostats were used. All starting materials were purchased from *Aldrich* and used without further purification. GC Measurements were executed with a *Thermo Finnigan Trace GC* equipped with a *Macherey & Nagel Optima 5* cap. column (∅0.25 mm, 0.25 μm, length 30 m). He was used as a carrying gas, eluted materials were detected by a *Thermo Finnigan* flame-ionization detector (FID). The quantification of reaction yields was performed using GC and alkanes as internal standards.

Synthesis of 2-Phenylethyl Acetate (Alkylation). The microreaction system consisted of three cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled cap. reactor. A soln. (50 ml) of Ac_2O (1.46 ml, 15.4 mmol) in pyridine, and a soln. (50 ml) of 2-phenylethanol (900 μl, 5.52 mmol) and 4-(dimethylamino)pyridine, (DMAP; 50 mg, 0.40 mmol) in pyridine were combined for a residence time of 15 min at 30°, cooling to 20° after reaction. For GC analysis, the reactor eluent was collected into 1M HCl, extracted with Et_2O, washed with 5% Na_2CO_3, and dried (Na_2SO_4) to afford 2-phenylethyl acetate in 93% yield.

*Synthesis of Benzyl Phenyl Ether (*Williamson *Ether synthesis)*. For both methods, the microreaction plant consisted of three cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled capillary reactor.

Method 1. A soln. (50 ml) of PhOH (1,85 g, 19.6 mmol), KOH (1,09 g, 19.5 mmol), and H_2O (2 ml) in DMF was combined with a soln. (50 ml) of $PhCH_2Br$ (1.20 ml, 10.1 mmol) in DMF, with a total residence time of 1 min at 50°, cooling to 20° after reaction. For GC analysis, the reactor eluent was collected into 0.1M HCl, extracted with Et_2O, washed with 5% Na_2CO_3, and dried (Na_2SO_4) to afford benzyl phenyl ether in 100% yield.

Method 2. A soln. (50 ml) of PhOH (1.852 g, 19.7 mmol) and KOH (1.245 g, 22.2 mmol) in H_2O, and a soln. (50 ml) of $PhCH_2Br$ (1.20 ml, 10.1 mmol) and Bu_4NI (TBAI; 848 mg, 2.30 mmol) in $CHCl_3$ were used; with a residence time of 40 min at 50°. For GC analysis, the reactor eluant collected into 0.1M HCl, extracted with $CHCl_3$, washed with H_2O, and dried (Na_2SO_4) to afford benzyl phenyl ether in 87% yield.

*Synthesis of 3a,4,7,7a-Tetrahydro-5,6-dimethylisobenzofuran-1,3-dione (*Diels–Alder *Reaction).* The microreaction plant consisted of three cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled cap. reactor. A soln. (50 ml) of maleic anhydride (4.67 g, 48 mmol) in 1-methylpyrolidin-2-one (NMP) and a soln. (50 ml) of 2,3-dimethylbuta-1,3-diene (8.1 g, 100 mmol) in NMP were combined and flowed with a residence time of 30 min at 60°, cooling to 20° after reaction. For GC analysis, the reactor eluant was collected into $CHCl_3$ and analyzed immediately to afford the title compound in 98% yield.

Synthesis of Ethyl Cinnamate.(= Ethyl 3-Phenylprop-2-enoate). Method 1: Horner–Wadsworth–Emmons *Reaction.* The microreaction plant consisted of three cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled cap. reactor. A soln. (30 ml) of PhCHO (650 µl, 6.40 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD; 898 mg, 6.45 mmol) in MeCN was combined with a soln. (30 ml) of triethyl phosphonoacetate (1.228 g, 5.48 mmol) in MeCN, and flowed at 50° with a residence time of 10 min, cooling to 20° after reaction. For GC analysis, the reactor eluant was collected into 10% NH_4Cl soln., extracted with AcOEt, and dried (Na_2SO_4) to afford the title compound in 91% yield.

Method 2: Heck *Reaction.* The microreaction plant consist of two cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled cartridge reactor. A soln. (50 ml) of ethyl acrylate (2.70 g, 26.9 mmol) in NMP and a soln. (50 ml) of PhI (3.46 g, 16.9 mmol) and Et_3N (1.69 g, 16,7 mmol) in NMP were flowed through a solid-phase cartridge reactor loaded with 10% Pd on C (116 mg) at 130° with a residence time of 30 min. For GC analysis, the reactor eluant was collected in H_2O, extracted with Et_2O, and dried (Na_2SO_4) to afford the ethyl cinnamate in 95% yield.

Synthesis of 2-Nitro-1-phenylethanol (Nitroaldol Addition, Henry *Reaction).* The microreaction plant consisted of two cross-flow heat-exchangers, a stack-type micromixer, and a temp.-controlled cap. reactor. A soln. (50 ml) of PhCHO (10.5 g, 99.3 mmol) and 11.4 g (186 mmol) $MeNO_2$ in i-PrOH was combined with a soln. (50 ml) of TBD (2.78 g, 20.0 mmol) in i-PrOH at 2°, and flowed at 20° with a residence time of 10 min. For GC analysis, the reactor eluant was collected into 10% NH_4Cl soln., extracted with Et_2O, and dried (Na_2SO_4) to afford the title compound in 78% yield.

Synthesis of Benzylidene-acetone (=4-Phenylbut-3-en-2-one) and Dibenzylidene-acetone (=1,5-Diphenyl-penta-1,4-dien-3-one) (Aldol Condensation). The microreaction plant consisted of three micromixers and a cap. reactor. In the first micromixer, a soln. of 0.5M acetone in EtOH is mixed with a soln. of 0.25M PhCHO in EtOH. Subsequently, the obtained mixture is mixed with a soln. of 1.5M KOH in EtOH and is allowed to pass through the cap. reactor at 20°. For GC analysis, the eluant was quenched by 50% AcOH and extracted by CH_2Cl_2 to afford benzylidene-acetone in 59% yield and dibenzylidene-acetone, in 20% yield.

This research was supported by *GlaxoSmithKline* (*Scholar Award* to *P.H.S.*), the *Alfred P. Sloan Foundation* (Fellowship to *P.H.S.*), and *Merck* (*Academic Development Program Award* to *P.H.S.*). Fruitful cooperation with Dr. *M. Adamczyk* of *Mettler Toledo GmbH* concerning the FT-IR measurements is gratefully acknowledged.

REFERENCES

[1] P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. Zhang, *Tetrahedron* **2002**, *58*, 4735; G. M. Greenway, S. J. Haswell, P. H. Petsul, *Anal. Chim. Acta.* **1999**, *387*, 1; D. J. Harrison, K. Fluri, K. Seiler, Z. Fan, C. S. Effenhauser, A. Manz, *Science* **1993**, *261*, 895.

[2] W. Ehrfeld, *Chimia* **2002**, *56*, 598; W. Ehrfeld, in 'Process Intensification through Microreaction Technology', in 'Re-Engineering the Chemical Processing Plant: Process Intensification', Eds. A. Stankieewicz, A. Moulijin, Marcel Dekker, New York, 2003; C. de Bellefon, N. Tanchoux, S. Caravieilhes, P. Grenouillet, V. Hessel, *Angew. Chem., Int. Ed.* **2000**, *39*, 3442.

[3] S. K. Ajmera, M. W. Losey, K. F. Jensen, M. A. Schmidt, *AIChE J.* **2001**, *47*, 1639; K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293.

[4] S. M. Senkan, *Angew. Chem., Int. Ed.* **2001**, *40*, 312; S. M. Senkan, S. Ozturk, *Angew. Chem., Int. Ed.* **1999**, *38*, 791; S. M. Senkan, *Nature* **1998**, *394*, 350.

[5] T. Schwalbe, V. Autze, G. Willie, *Chimia* **2002**, *56*, 636.

[6] W. Ehrfeld, V. Hessel, 'Microreactors', VCH-Wiley, Weinheim, 2000; W. Ehrfeld, V. Hessel, V. Haferkamp, 'Microreactors', in 'Ullmann's Encyclopedia of Industrial Chemistry', Sixth Editon, Wiley-VCH, Weinheim, 1999; K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem., Int. Ed.* **2004**, *43*, 406.
[7] N. G. Anderson, *Org. Process Res. Dev.* **2001**, *5*, 613.
[8] J. R. Bourne, *Org. Process Res. Dev.* **2003**, *7*, 471.
[9] J. Schiewe, W. Ehrfeld, V. Haverkamp, V. Hessel, H. Löwe, Ch. Wille, M. Altvater, R. Neubert, in 'IMRET 4: 4th International Conference on Microreaction Technology, Topical Conference Proceedings', AIChE Spring National Meeting March 5 – 9, 2000, Atlanta, GA, p. 467 – 477. AIChE, New York, NY.
[10] Z. Zhu, J. H. Espenson, *J. Am. Chem. Soc.* **1997**, *119*, 3507.
[11] M. W. Rathke, M. Howak, *J. Org. Chem.* **1985**, *50*, 2624.
[12] D. Simoni, F. P Invidiata, S. Manfredini, R. Ferroni, I. Lampronti, M. Roberti, G. P. Pollini, *Tetrahedron Lett.* **1997**, *38*, 2749; D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607.
[13] T. Schwalbe, V. Autze, M. Hohmann, W. Stirner, *Org. Process Res. Dev.* **2004**, *8*, 440.
[14] S. Liu, T. Fukuyama, M. Sato, I. Ryu, *Org. Process Res. Dev.* **2004**, *8*, 477.
[15] F. Zhao, B. M. Bhanage, M. Shirai, M. Arai, *Chem. – Eur. J.* **2000**, *6*, 843.

Received September 13, 2004