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Umpolung Reactions of α-Tosyloximino Esters in a Flow System

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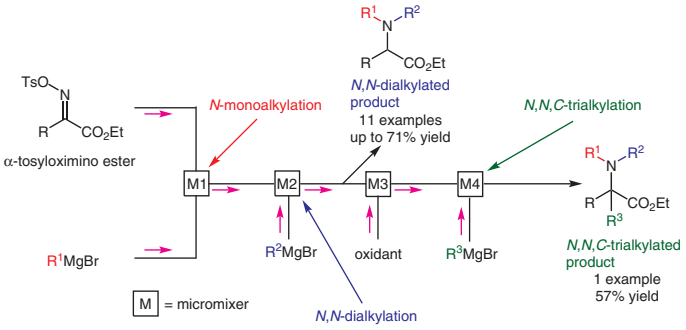

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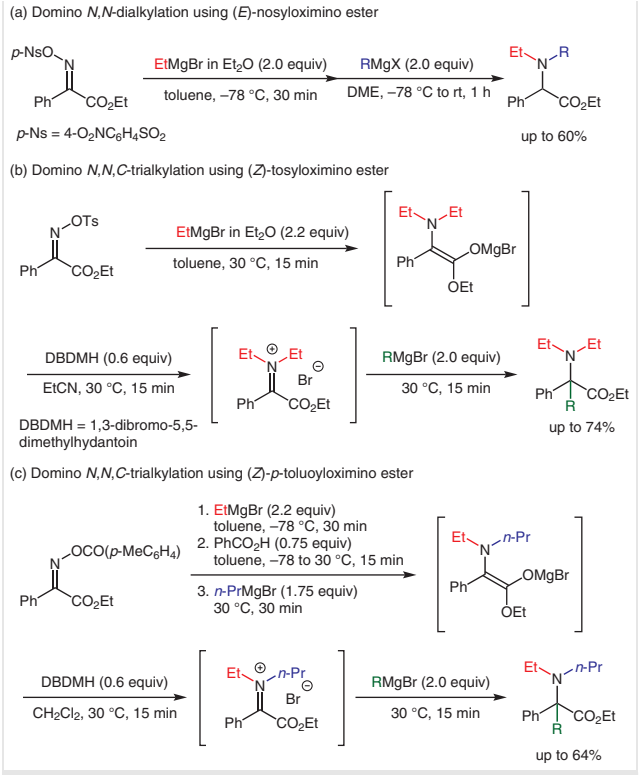
Abstract An umpolung reaction of α-tosyloximino esters in a flow system is disclosed. Tandem *N*,*N*-dialkylations with two different Grignard reagents gave the desired *N*,*N*-dialkylated products in moderate to good yields. In addition, a tandem *N*,*N*,*C*-trialkylation of an α-tosyloximino ester with three different Grignard reagents has been successfully achieved to afford the desired *N*,*N*,*C*-trialkylated product in moderate yield.

Key words umpolung, tosyloximino esters, tandem, alkylation, Grignard reagents, flow reactor

Natural products, pharmaceuticals, and the basic skeletons of other important biologically active compounds frequently include nitrogen-containing organic moieties. Among nitrogen-containing compounds, α-amino acids and their derivatives, including amino esters and amino alcohols, have attracted considerable attention. Consequently, there has been a considerable desire to develop reactions that efficiently synthesize compounds with various substituents on both the nitrogen and the carbon atoms at the α-positions of α-amino acid moieties. α-Imino esters are among the most useful nitrogen-containing starting materials for the synthesis of various natural and nonnatural α-amino acid derivatives.[1,2]

We have previously reported that the *N*-alkylation reaction of α-imino esters with Grignard reagents proceeds smoothly to give the *N*-alkylated products,[3] and that *N*,*N*-dialkylations and *N*,*N*,*C*-trialkylations of α-sulfoximino esters give the corresponding α-amino acid derivatives.[4] There are some limitations on these reactions; for example, the use of an (*E*)-nosyloximino ester was needed for the synthesis of *N*,*N*-dialkylated α-amino acid derivatives having two different substituents on the amino nitrogen. However, when reaction was conducted at the extremely low temperature of –78 °C problems were encountered in introducing a second substituent onto the imino nitrogen atom to give an *N*,*N*-dialkylated amino ester (Scheme 1a). In *N*,*N*,*C*-trialkylations of (*Z*)-tosyloximino esters, *N*,*N*,*C*-trialkylated α-amino acid derivatives with two identical substituents on the amino nitrogen were obtained (Scheme 1b). In 2015, we reported that *N*,*N*,*C*-trialkylated α-amino acid derivatives with two different alkyl substituents on the nitro-



Scheme 1 Previous tandem *N*,*N*-dialkylation and *N*,*N*,*C*-trialkylation reactions

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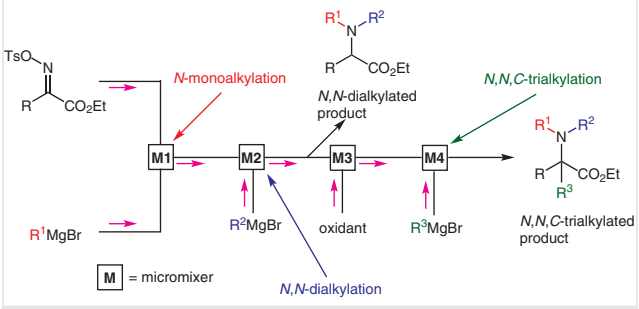
gen atom could be synthesized by using α-*N*-*p*-toluoyloximino esters as highly efficient starting α-imino esters (Scheme 1c).[5]

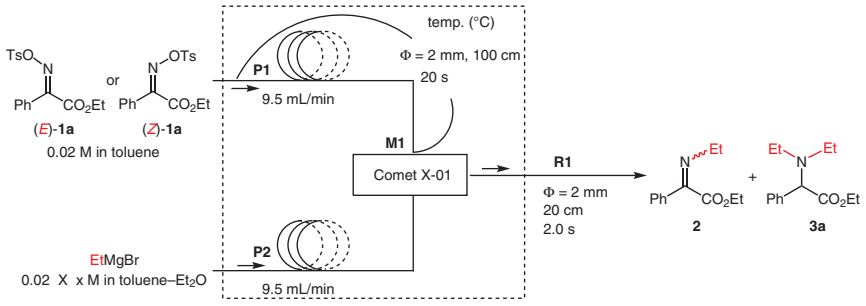
Flow systems can provide conditions different from those of batch processes conducted in flasks. A reaction field in micro-space can increase the efficiency of heat exchange, permitting better control of the reaction temperature than in a batch reaction. In addition, because tandem reactions can be easily carried out, it becomes possible to use unstable intermediates and to synthesize products efficiently and rapidly.[6,7] Here, we report *N*,*N*-dialkylation, and *N*,*N*,*C*-trialkylation reactions of α-tosyloximino esters in a flow system; this has such advantages as high efficiency and rapid heat transfer compared with conventional batch reactions (Scheme 2).



Scheme 2 Tandem *N*,*N*-dialkylation and *N*,*N*,*C*-trialkylation reactions in a flow system

First, we screened the reaction conditions for *N*-monoethylation of the α-tosyloximino ester (*E*)-**1a** by using a Comet X-01 micromixer (Figure S1).[8,9] The results are summarized in Table 1. A solution of (*E*)-**1a** in toluene and a solution of ethylmagnesium bromide (EtMgBr) in toluene–diethyl ether were mixed by using the Comet X-01 at various temperatures. When the reaction was carried out at room temperature, the desired *N*-monoethylated product **2** was obtained in 37% yield, accompanied by the diethylated product **3a** in 18% yield (Table 1, entry 1). Lower reaction temperatures gave better yields (entries 2–5). Although the best yield (70%) was obtained at –78 °C, we continued to examine the effects of various concentrations of EtMgBr at the milder temperature of –40 °C (entries 6–10). The use of 1.4 equivalents of EtMgBr slightly improved the yield (entry 7). The use of the isomer (*Z*)-**1a** was then examined under several reaction conditions, but the desired monoethylated product **2** was not obtained (entries 11–13).

Table 1 Optimization of the *N*-Monoethylation of α-Tosyloximino Ester **1a**



Entry	*E*/*Z*	Temp (°C)	EtMgBr (equiv)	Yield (%)		
				2 (*Z*/*E*)	**3a**	**1a**
1	*E*	rt	1.0	37 (83:17)	18	16
2	*E*	0	1.0	34 (88:12)	4	12
3	*E*	–20	1.0	51 (92:8)	10	8
4	*E*	–40	1.0	58 (89:11)	6	9
5	*E*	–78	1.0	70 (90:10)	10	10
6	*E*	–40	1.2	56 (89:11)	5	9
7	*E*	–40	1.4	61 (91:9)	17	3
8	*E*	–40	1.6	49 (92:8)	22	1
9	*E*	–40	1.8	41 (93:7)	37	0

Entry	*E*/*Z*	Temp (°C)	EtMgBr (equiv)	Yield (%)		
				2 (*Z*/*E*)	**3a**	**1a**
10	*E*	–40	2.0	23 (85:15)	40	0
11	*Z*	–40	1.0	0	3	90
12	*Z*	–40	2.0	0	4	95
13	*Z*	rt	2.2	0	41	52

Because the starting material (*E*)-**1a** was recovered in some cases, we next examined the use of two connected Comet X-01 micromixers to increase the mixing efficiency (Figure 1).

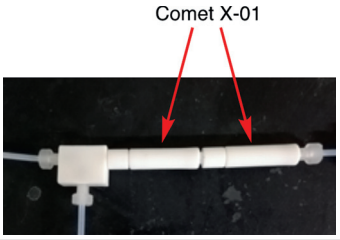
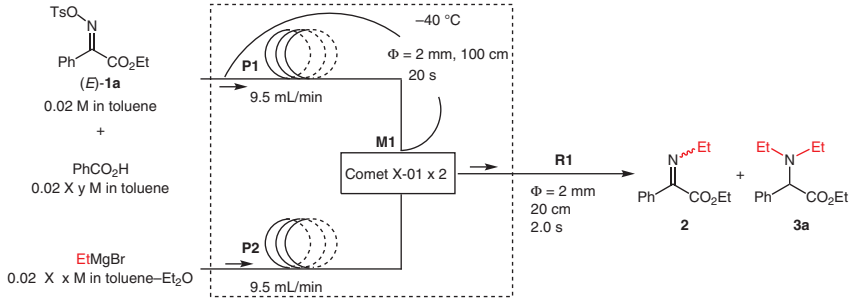


Figure 1 Connected Comet X-01 micromixers

The results are summarized in Table 2. The formation of the diethylated product **3a** increased and (*E*)-**1a** was not recovered (entries 2–6). Benzoic acid (BzOH) was examined as an additive to quench excess EtMgBr and to activate (*E*)-**1a**. A solution of (*E*)-**1a** containing BzOH in toluene and a solution of EtMgBr in toluene–diethyl ether were mixed by using the two connected Comet X-01 micromixers. The use of 2.0 equivalents of EtMgBr and 0.5 equivalents of BzOH gave the desired *N*-monoethylated product **2** in the best yield of 69% (entry 9).[9]

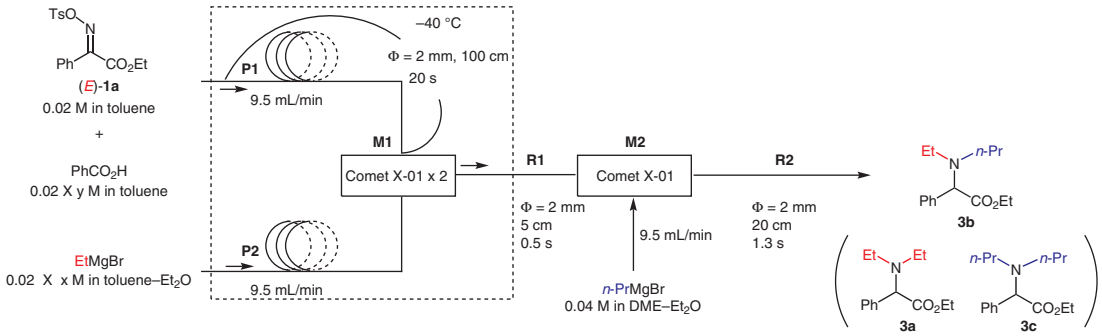
Tandem *N*,*N*-dialkylations with two different Grignard reagents were next examined. The reaction conditions were screened by using ethyl and propyl Grignard reagents. The results are summarized in Table 3. The use of 2.0 equivalents of EtMgBr, 0.5 equivalents of BzOH, and 2.0 equivalents of PrMgBr gave the desired *N*-ethyl *N*-propyl product **3b** in the best yield of 71% (entry 3).[10,11]

Table 2 Optimization of the *N*-Monoethylation of α-Tosyloximino Ester (*E*)-**1a** in Two Connected Comet X-01 Micromixers



Entry	EtMgBr (equiv)	BzOH (equiv)	Yield (%)		
			2 (*Z*/*E*)	**3a**	(*E*)-**1a**
1	1.0	–	56 (94:6)	8	13
2	1.2	–	67 (89:11)	12	0
3	1.4	–	60 (95:5)	20	0
4	1.6	–	57 (93:7)	22	0
5	1.8	–	48 (90:10)	30	0
6	2.0	–	40 (93:7)	38	0
7	1.2	0.5	36 (92:8)	3	27
8	1.4	0.5	44 (89:11)	4	23
9	2.0	0.5	69 (92:8)	15	0

Table 3 Optimization of the Tandem *N*,*N*-Dialkylation of α-Tosyloximino ester (*E*)-**1a**

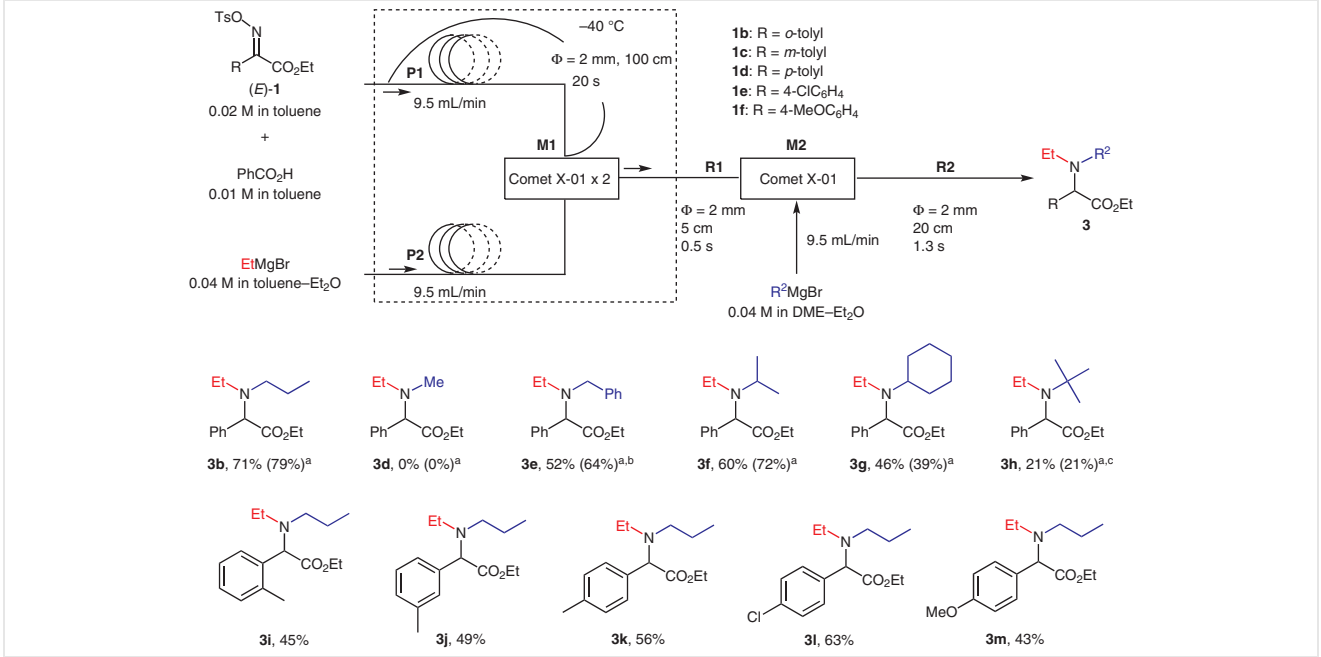


Entry	EtMgBr (equiv)	BzOH (equiv)	Yield (%)		
			3b	**3a**	**3c**
1	1.6	0.5	49	5	4
2	1.8	0.5	62	12	3
3	2.0	0.5	71	6	0
4	2.2	0.5	58	10	6
5	2.0	1.0	50	7	13
6	2.0	0.7	57	15	0
7	2.0	0.6	61	9	5
8	2.0	0.4	65	9	0
9	2.0	0.3	61	16	1
10	2.5	1.0	63	8	5
11	2.5	1.5	54	12	14

With the optimized reaction conditions in hand, we used a variety of second Grignard reagents and α-tosyloximino esters **1** in the tandem *N*,*N*-dialkylation (Scheme 3). Methyl Grignard reagent as the second nucleophile did not give the desired product **3d**, as previously reported.[3] The use of primary benzyl Grignard reagent afforded the product **3e** in 52% yield. Secondary alkyl (isopropyl and cyclohexyl) Grignard reagents gave the corresponding products **3f** and **3g** in yields of 60 and 46%, respectively. The use of *tert*-butyl Grignard reagent afforded product **3h** in a lower yield of 21% as a result of steric hindrance. The scope of the aromatic group was next examined. α-Tosyloximino esters (*E*)-**1b–d** containing tolyl groups gave the desired products **3i–k** in moderate yields. α-Tosyloximino esters (*E*)-**1e** and **1f**, with electron-withdrawing and electron-donating groups respectively, gave the corresponding products **3l** and **3m** in yields of 63 and 43%, respectively.

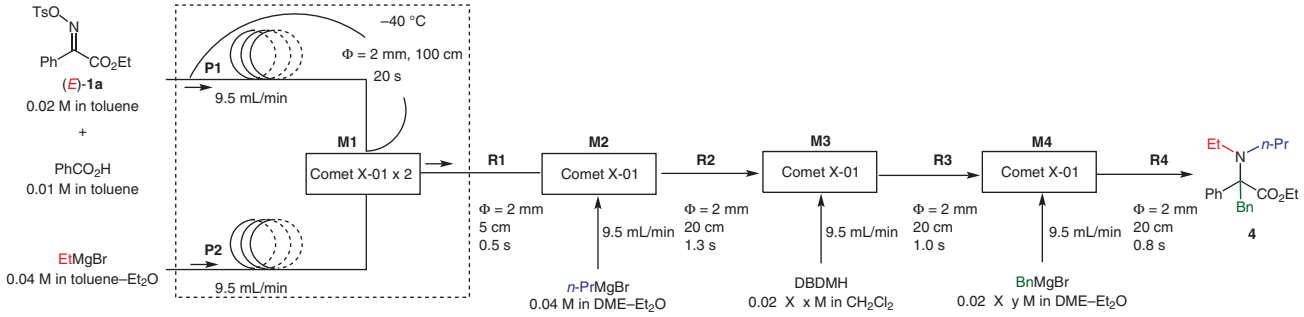
Finally, we examined the tandem *N*,*N*,*C*-trialkylation of α-tosyloximino ester **1a** with three different Grignard reagents. Effects of the number of equivalents of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as an oxidant and of BnMgBr as the third nucleophile were examined (see Supporting Information, Figure S2).[9] The results are summarized in Table 4. The use of 1.2 equivalents of DBDMH and 2.5 equivalents of BnMgBr afforded the desired *N*-ethyl *N*-propyl *C*-benzyl product **4** in the best yield of 57% (entry 6).

Based on our previous study,[5] a plausible reaction mechanism for the *N*-mono-, *N*,*N*-di-, and *N*,*N*,*C*-trialkylations of α-tosyloximino ester (*E*)-**1a** is shown in Scheme 4. The addition of the first Grignard reagent gives (*Z*)-**2** through either an addition–elimination reaction (path a) or an S_N2 reaction (path b). With regard to the role of benzoic acid, we presume that it coordinates to the tosyloxy group of intermediate **A** or **B** to facilitate its elimination. (*Z*)-**2** might isomerize to (*E*)-**2** in the presence of benzoic acid or bromomagnesium tosylate. The addition of the second Grignard reagent gives the magnesium enolate **D** via the five-membered intermediate **C**. The magnesium enolate **D** is hydrolyzed to afford the *N*,*N*-dialkylated product **3**. Oxidation of the magnesium enolate **D** with DBDMH generates the iminium salt **E**, which undergoes an addition reaction with the third Grignard reagent to give the *N*,*N*,*C*-trialkylated product **4**.



Scheme 3 Tandem *N*,*N*-dialkylations of various α-tosyloximino esters (*E*)-**1**. [a] Yield previously obtained under batch conditions.[5] [b] BnMgBr (0.05 M) was used. [c] *t*-BuMgCl (0.05 M) in DME–THF was used.

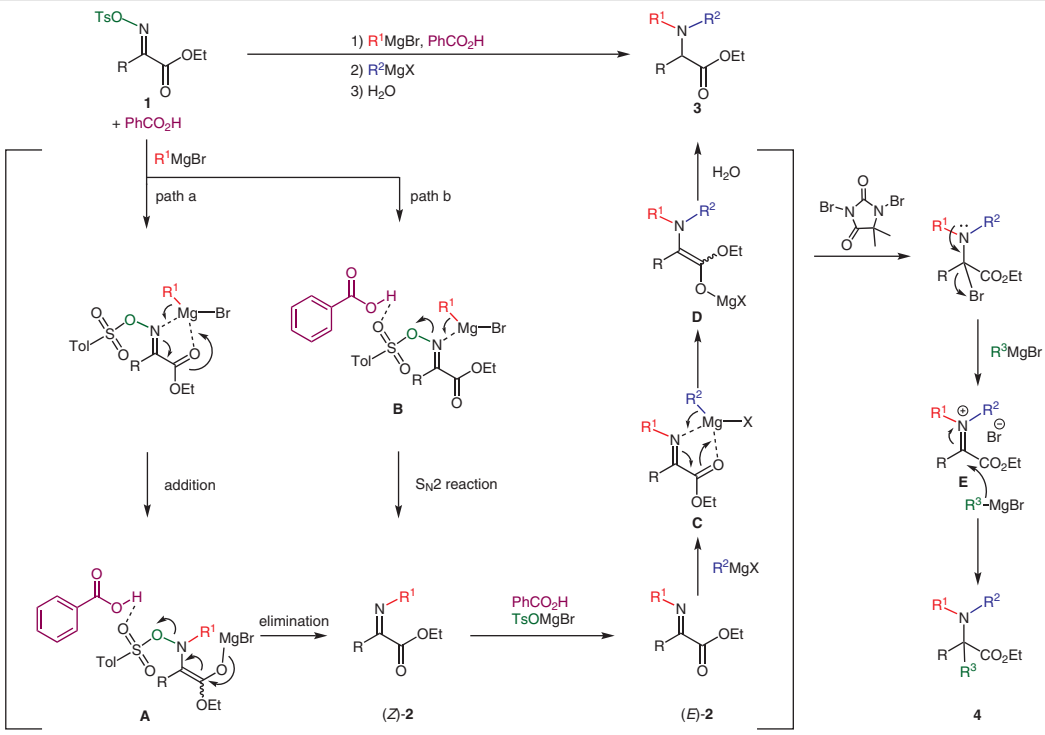
Table 4 Optimization of the Tandem *N*,*N*,*C*-Trialkylation of α-Tosyloximino Ester (*E*)-**1a**



Entry	DBDMH (equiv)	BnMgBr (equiv)	Yield (%) of **4**
1	0.6	2.0	0
2	0.8	2.0	0
3	1.0	2.0	43
4	1.2	2.0	47
5	1.5	2.0	45
6	1.2	2.5	57 (64)[a]
7	1.2	3.0	46

[a] Yield previously obtained under batch conditions.[5]

In conclusion, we have investigated the umpolung reaction of α-tosyloximino esters in a flow system. Tandem *N*,*N*-dialkylations with two different Grignard reagents gave the desired *N*,*N*-dialkylated products in moderate to good yields. In addition, the tandem *N*,*N*,*C*-trialkylation of an α-tosyloximino ester with three different Grignard reagents proceeded successfully to afford the desired *N*,*N*,*C*-trialkylated product in moderate yield. The present flow system is an attractive because one step can be eliminated by simultaneous introduction of benzoic acid. Moreover, the



Scheme 4 Plausible reaction mechanism

N,*N*-dialkylated and *N*,*N*,*C*-trialkylated products are useful intermediates for syntheses of biologically active compounds, and they can be synthesized at the less extreme temperature of –40 °C in a shorter time in comparison with the previously reported batch conditions.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707265.

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(9) See the Supporting Information for details.

(10) Results with other acids as additives are summarized in Table S1 of the Supporting Information.

(11) **Ethyl [Ethyl(propyl)amino](phenyl)acetate (3b)[4]; Typical Procedure**

A flow-microreactor system consisting of two connected Comet X-01 micromixers (**M1**), a Comet X-01 micromixer (**M2**), two pre-cooling units (**P1**: inner diameter = 2000 μm, length = 100 cm; **P2**: inner diameter: 2 mm, length = 100 cm), and two Teflon tube reactors (**R1**: inner diameter = 2 mm, length = 5 cm; **R2**: inner diameter = 2 mm, length = 20 cm) was used. The first flow-microreactor system consisting of the two connected Comet X-01 micromixers together with **P1** and **P2** was immersed in a magnetically stirred constant-temperature bath at –40 °C. The remainder of the system was at rt. A solution of α-tosyloxyimino ester **1a** (0.02 M) and BzOH (0.01 M) in toluene (9.5 mL/min) [prepared from α-tosyloximino ester (*E*)-**1a** (138.9 mg, 0.40 mmol), BzOH (24.4 mg, 0.20 mmol), and toluene (20 mL)] was introduced into **M1** by using a syringe pump. A 0.04 M solution of EtMgBr in toluene–Et_2O (9.5 mL/min) [prepared from a 0.93 M solution of EtMgBr (0.86 mL, 0.80 mmol) in Et_2O and toluene (19.14 mL)] was also introduced into **M1** by using a syringe pump, and the mixed solution was passed through **R1**. A 0.04 M solution of PrMgBr in DME–Et_2O (9.5 mL/min), prepared from a 0.82 M solution of PrMgBr (0.98 mL, 0.80 mmol) in Et_2O and DME (19.02 mL), was introduced into **M2** by using a syringe pump, and the resulting solution was passed through **R2**. Once a steady state was reached, the resulting solution (30 mL) was poured into sat. aq $NaHCO_3$ (10 mL) to quench the reaction. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and filtered. The solvents were evaporated in vacuo, and the residue was purified by preparative TLC [silica gel, hexane–Et_2O (20:1)] three times to give the desired product **3b** [yield: 35.5 mg (71%)], together with the *N*,*N*-diethyl product **3a** [yield: 3.0 mg (6%)].

3b

Yellow oil. IR (neat): 1737, 1453, 1372, 1154, 1067 1029, 728, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 2 H), 7.34–7.25 (m, 3 H), 4.51 (s, 1 H), 4.25–4.13 (m, 2 H), 2.63 (q, *J* = 7.3 Hz, 2 H), 2.55–2.44 (m, 2 H), 1.52–1.35 (m, 2 H), 1.24 (t, *J* = 7.3 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.81 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 137.4, 128.7, 128.2, 127.7, 69.1, 60.4, 52.0, 44.3, 20.4, 14.2, 12.3, 11.7. HRMS (EI): *m/z* [M – $C_3H_5O_2$]$^+$ calcd for $C_{12}H_{18}N$: 176.1434; found: 176.1434.