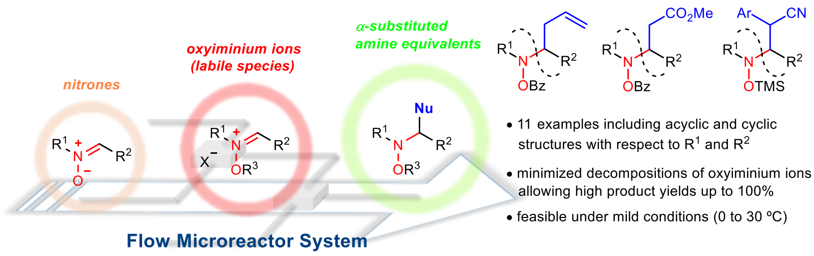
Nucleophilic Addition to Nitrones Using a Flow Microreactor

Yukihiro Arakawa[a]
Shun Ueta[a]
Takuma Okamoto[a]
Keiji Minagawa[a,b]
Yasushi Imada*[a]

[a] Department of Applied Chemistry, Tokushima University, Minamijosanjima, Tokushima 770-8506, Japan

[b] Institute of Liberal Arts and Sciences, Tokushima University, Minamijosanjima, Tokushima 770-8502, Japan

imada@tokushima-u.ac.jp



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Abstract Nucleophilic addition reactions of soft carbon nucleophiles to nitrones in a flow microreactor are reported for the first time. Under microflow conditions at 30 °C to 0 °C, a range of nitrones can be efficiently transformed into the corresponding oxyiminium ions by reacting with either acyl halides or trialkylsilyl triflates, which can subsequently undergo the addition of nucleophiles including allyltributylstannane, ketene methyl *tert*-butyldimethylsilyl acetal, and *N*-silyl ketene imines to afford the corresponding adducts in high yields, while such reactions at a similar temperature under batch conditions have resulted in lowering the yields due to undesired side reactions.

Key words nitrone, flow, microreactor, nucleophilic addition, nitrogen-containing compound

Nitrones **1** (Figure 1) can be attractive intermediates for the synthesis of nitrogen-containing compounds,[1] but their use as electrophiles in nucleophilic addition reactions typically requires the strong activation of α carbon due to its comparatively low electrophilicity. Early studies, indeed, demonstrated that **1** could be electrophilic enough to react with "reactive" nucleophiles such as organomagnesium and organolithium reagents, while "less reactive" nucleophiles such as *O*-silylated enolates could be inactive.[2] To enhance the reactivity and control selectivities, the use of Lewis acid catalysts has proven to be effective.[3] On the other hand, Murahashi and coworkers established a stoichiometric activation of **1** with acyl halides, in which the resulting *N*-oxyiminium ions **Im(OBz)-1** are highly electrophilic to undergo rapid addition of soft carbon nucleophiles **Nu** such as enolates to give the corresponding adduct **2** (Figure 1, upper route).[4] However, the nitrone activation as well as subsequent addition reactions using a batch reactor has to be carefully carried out at a very low temperature such as –78 °C; otherwise, **Im(OBz)-1** readily undergoes undesired rearrangement to amides **3** due to its lability.[5] More recently, Yoshimura and coworkers introduced the nucleophilic addition reactions of *in situ*

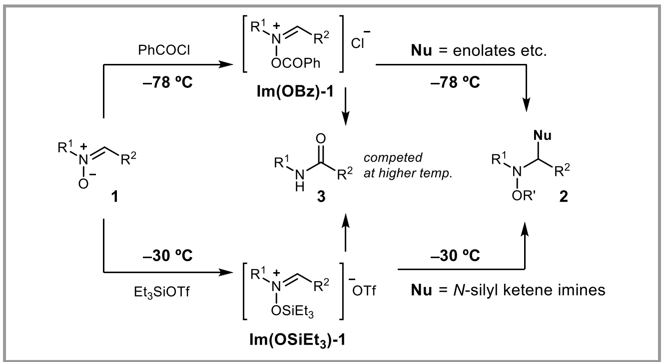
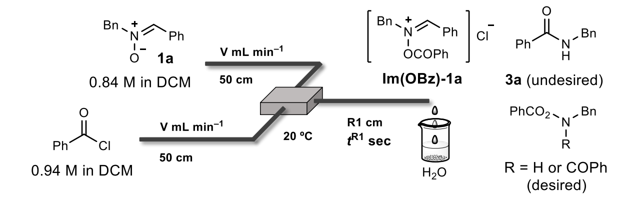


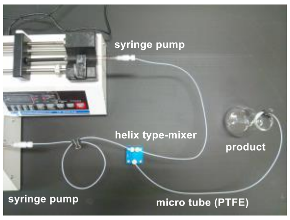
Figure 1 Previous strategies for utilizing nitrones as electrophiles via their *N*-oxyiminium ion forms in batch system.[4,6]

generated *N*-silyl ketene imines to **1** involving activation of substrates with triethylsilyl triflate, which also required –30 °C to fully suppress such an undesired amide formation from the corresponding *N*-oxyiminium ions **Im(OSiEt$_3$)-1** (Figure 1, lower route).[6] As a result, the application of these synthetic methods especially in industry may be significantly limited despite their high generality and reliability under carefully controlled conditions.

Flow microreactor systems allow for efficient reactant mixing, efficient heat and mass transfer, and precise control of reaction times and have therefore been successfully utilized for molecular transformations involving highly labile intermediates, which are difficult to control in batch system.[7] Within this manuscript, we wish to expand the utility of flow microreactor system by adopting it to the nucleophilic addition to **1** via the formation of unstable *N*-oxyiminium intermadiates.

A general and simple flow setup was used in this study, which comprises of syringe pumps and helical channel micromixers connected with each other via PTFE micro tubes as required (Figure 2, photograph). We started our investigation by seeking the optimal residence time (t^{R1} / sec) for deriving *N*-



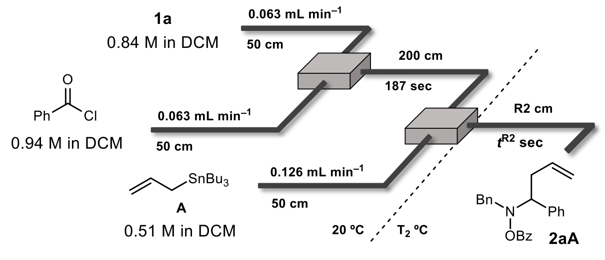


t^{R1} (sec)	V (mL min^{-1})	R1 (cm)	conv. (%)	**3a** (%)
2.95	1.0	50	70	0
5.89	0.5	50	75	0
23.6	0.5	200	84	0
94.2	0.125	200	94	1
187	**0.063**	**200**	**95**	**1**
236	0.125	500	94	2

Figure 2 Determination of the optimum residence time for the generation of Im(OBz)-1a in flow.

benzoyloxyiminium chloride [**Im(OBz)-1a**] from *N*-benzyl-α-phenylnitrone (**1a**) and benzoyl chloride in the flow system at 20 °C, in which t^{R1} was adjusted by changing either the flow rate (V / mL min^{-1}) or the tube length between the mixer and the exit (R1 / cm). Solutions of **1a** (0.84 M) and benzoyl chloride (0.94 M) in dichloromethane (DCM) were fed by the syringe pumps and mixed at the mixer where **Im(OBz)-1a** could start to be produced, which was run in the following microtube and the outflow was poured into water that could quench **Im(OBz)-1a** to detect it as its hydrolyzed form or further benzoylated form (Figure 2, desired products). For example, when t^{R1} was adjusted to be 2.95 seconds, the conversion of **1a** was determined by ^{1}H NMR spectroscopy to be 70% without any occurrence of undesired rearrangement of **Im(OBz)-1a** to the corresponding amide **3a**. Prolonging t^{R1} increased the conversion, and the highest value of 95% was attained with 187 seconds of t^{R1} (V = 0.063 mL min^{-1}, R1 = 200 cm) while the formation of **3a** was still negligible (Figure 2).

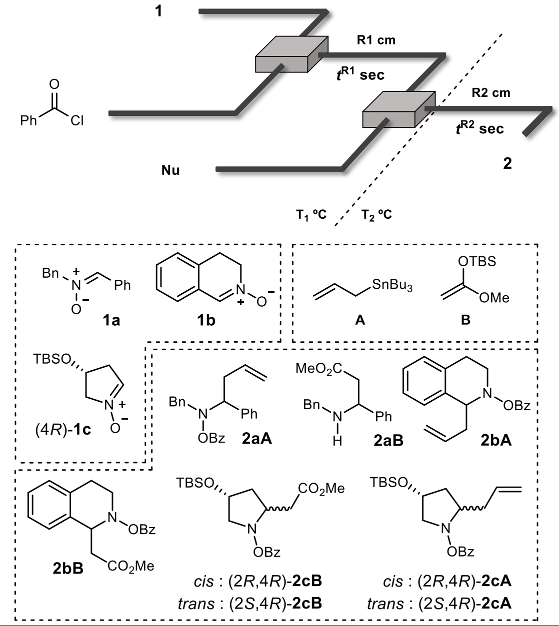
We then connected the outlet of the first flow mentioned above into the second micromixer where **Im(OBz)-1a** could encounter with allyltributylstannane (**A**) chosen as a test nucleophile. A solution of **A** in DCM (0.60 M) was fed by the third syringe pump at a flow rate of 0.126 mL min^{-1} to the second mixer, and the resulting mixture was further run for 234 seconds (t^{R2}) at 20 °C in a 500 cm length of the micro tube prior



t^{R2} (sec)	R2 (cm)	T_2 (°C)	NMR yield (%) by-products	**2aA**
234	500	20	16	84
468	1000	20	11	89
468	**1000**	**30**	**1**	**99**

Figure 3 Optimization of flow system conditions for the addition of A to 1a via the formation of Im(OBz)-1a.

Table 1 Adapting different substrates to the flow microreactor system[a]



Entry	1/Nu	t^{R1} (sec)	t^{R2} (sec)	T_1 (°C)	T_2 (°C)	2	Yield (%)[b]
1	1a/A	187	468	20	30	2aA	84
2	1b/A	187	468	20	30	2bA	89
3	1a/B	187	468	20	30	2aB[c]	73
4	1b/B	187	468	20	30	2bB	60
5	1c/B	187	468	20	30	2cB	38[d]
6	1c/B	0.20	3.93	20	20	2cB	94[d]
7	1c/B	0.20	3.93	0	0	2cB	74[e] (97)[d]
8	1c/A	0.20	3.93	0	0	2cA	2[d]
9[f]	1c/A	0.20	19.6	0	0	2cA	79[d,g]

[a] Solutions of **1** (1.00 M), benzoyl chloride (1.05 M), and the nucleophile (**Nu**, 0.60 M) dissolved in DCM were used unless otherwise noted.
[b] Isolated yield.
[c] Isolated through reduction with zinc/acetic acid after the reaction.
[d] NMR yield.
[e] *cis:trans* = 3.3:1.
[f] Benzoyl bromide was used instead of benzoyl chloride.
[g] *cis:trans* = 10:1.

to being poured into water to quench the reaction (Figure 3). Although the desired adduct **2aA** was obtained in 84% yield, a total of 16% by-products including the hydrolyzed form of **Im(OBz)-1a** (2%) and its benzoylated form (11%), desired in Figure 2, and **3a** (3%) was observed by ^{1}H NMR spectroscopy. The yield of by-products was reduced to 11% by prolonging residence time t^{R2} twice (468 sec) and finally further reduced to only 1% by performing the nucleophilic addition step at 30 °C (T_2) to give **2aA** in 99% NMR yield (Figure 3).

Substrate generality of the present flow microreactor system was explored (Table 1). Solutions of **1** (1.00 M), benzoyl chloride (1.05 M), and **Nu** (0.60 M) were successively mixed with the initially optimized residence times and temperatures. In the case of the combination of **1a** and **A**, the outflow solution was collected for 1469 seconds to afford **2aA** in 84% isolated yield (461 mg) after purification (entry 1). 3,4-Dihydroisoquinoline *N*-oxide (**1b**), a cyclic nitrone, was also efficiently allylated with **A** to give the corresponding adduct **2bA** in 89% isolated yield (319 mg) through collecting the outflow for 1159 seconds (entry 2).[8] The use of silyl ketene acetal **B** instead of **A** as a nucleophile for its addition to **1a** and **1b** allowed for synthesis of β-amino acid derivatives **2aB** and

2bB, respectively, with acceptable isolated yields in a similar production scale (entries 3 and 4). As expected, the rearrangement to the corresponding amides **3** was successfully suppressed in all the above cases. This was also the case when (4*R*)-4-(*t*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**1c**)[9] was used as a chiral substrate, although the desired product **2cB** was obtained only in 38% NMR yield despite full conversion of **1c** (entry 5). We soon became aware that a considerable amount of *N*-benzoyloxypyrrole (Figure 4) was formed through elimination of *t*-butyldimethylsilanol from the corresponding *N*-oxyiminium chloride followed by aromatization to release HCl. This observation led us to reoptimize flow conditions by controlling readily tunable residence times t^{R1} and t^{R2}. To our delight, the yield of **2cB** was dramatically enhanced when t^{R1} and t^{R2} were adjusted to be 0.2 and 3.93 seconds (entry 6), respectively, which was even more improved by executing both steps at 0 °C to give **2cB** in the highest NMR yield of 97% (entry 7). By collecting the outflow for 68 seconds under the suitable conditions, 494 mg (74%) of **2cB** was obtained in a *cis*:*trans* ratio of 3.3:1 after a column chromatographic purification (entry 7), from which 290 mg (43%) of the *cis* isomer was isolated as a result of a single recrystallization. It should be noted that no desired product **2cB** was obtained in a batch reaction system (Figure 4, upper), indicating the obvious utility of the present flow system. On the other hand, an even more challenging issue on the addition to **1c** was the use of **A** as a nucleophile, which resulted in only 2% NMR yield of the corresponding adduct **2cA** under the conditions that was just only optimized for the use of **B** (entry 8). To solve this issue, we attempted to use other acyl halides instead of benzoyl chloride and preliminarily found that the use of benzoyl bromide with an increased t^{R2} (19.6 seconds) could be effective for providing the desired adduct **2cA** in 79% NMR yield in a *cis*:*trans* ratio of 10:1 (entry 9). Also in this case, the reaction in a batch reactor was not efficient at the same reaction temperature (Figure 4, lower).

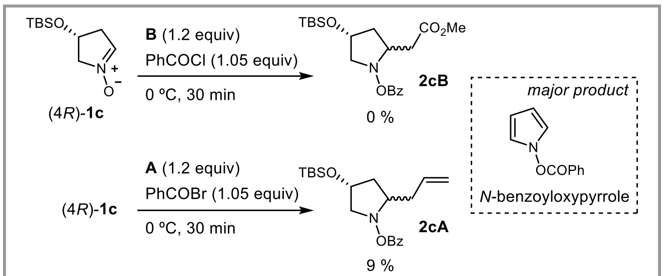
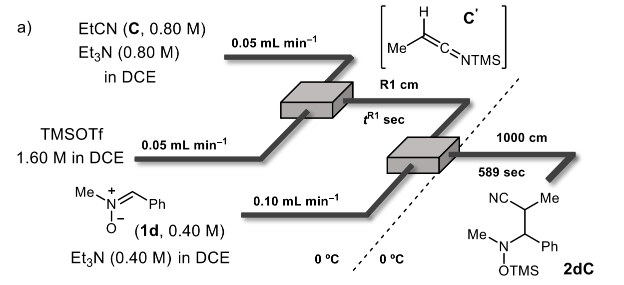


Figure 4 Inefficiency of the nucleophilic additions to (4*R*)-**1c** in batch system.

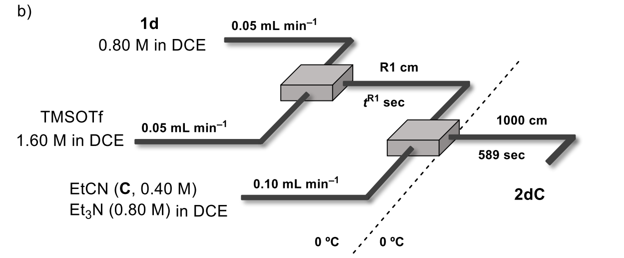
Next, we turned our attention to the addition of nitriles to **1**,[6] for which trialkylsilyl triflate should activate both nitriles and **1** in situ by transforming them into *N*-silyl ketene imines and **Im(OSiR$_3$)-1**, respectively, in the presence of triethylamine (Et_3N). Since both activated forms could be labile and actually the low temperature was required in batch system (Figure 1, lower route),[6] flow microreactor synthesis would be useful for performing the reaction more efficiently under mild conditions. For a start, we set up a flow in which a solution of propionitrile (**C**, 0.80 M) and Et_3N (0.80 M) in dichloroethane (DCE) and that of trimethylsilyl triflate (TMSOTf, 1.60 M) in DCE were mixed in the first mixer to give the corresponding *N*-silyl ketene imine **C'**

a)



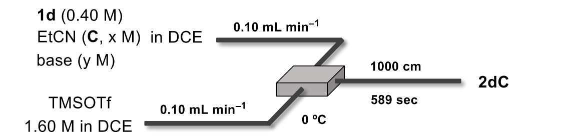
t^{R1} (sec)	R1 (cm)	Conv. of **1d** (%)	NMR yield (%) **3d**	NMR yield (%) **2dC**
59	50	75	10	10
24	20	90	17	31
5.9	**5**	**92**	**21**	**56**

b)



t^{R1} (sec)	R1 (cm)	Conv. of **1d** (%)	NMR yield (%) **3d**	NMR yield (%) **2dC**
59	50	61	19	28
12	**10**	**96**	**16**	**67**

c)



x (M)	y (M)	Conv. of **1d** (%)	NMR yield (%) **3d**	NMR yield (%) **2dC**
0.40	0.80	100	26	62
1.20	**1.60**	**100**	**6**	**79**

Figure 5 Optimization of flow system conditions for the addition of **C** to **1d** via the formation of **Im(OTMS)-1d**.

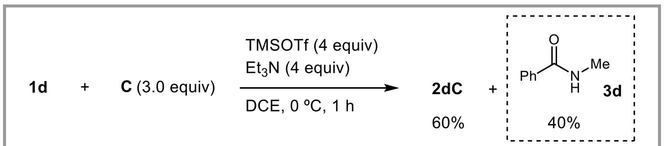
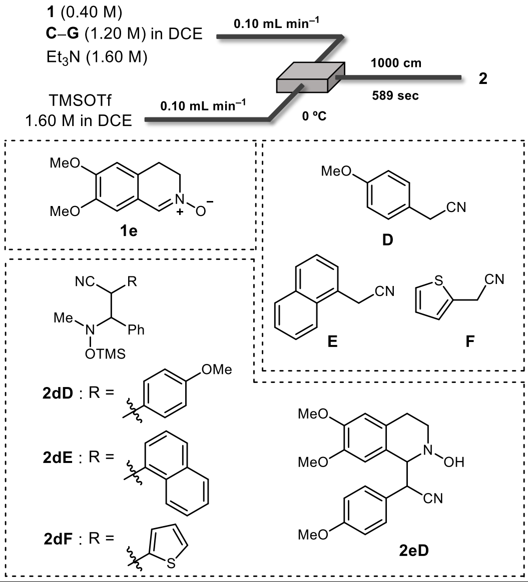


Figure 6 The reaction with **1d** and **C** in batch system.

that was mixed with a DCE solution of *N*-methyl-α-phenylnitrone (**1d**, 0.40 M) and Et_3N (0.40 M) in the second mixer at 0 °C (Figure 5a). The first step's residence time (t^{R1}) was varied, while that for the second step was fixed to be 589 seconds. Although NMR yields of the desired adduct **2dC** were increased up to 56% by shortening t^{R1}, the formation of the undesired amide **3d** was not negligible and **1d** was not fully consumed even with t^{R1} of 5.9 seconds possibly due to the short lifetime of **C'** that could quickly isomerize to the corresponding α-silylnitrile.[10] We therefore attempted to minimize such a deactivation of **C'** by performing the activation of **1d** prior to that of **C** in the stepwise flow system (Figure 5b). However, whereas the yield of **2dC** was slightly improved, a small amount

Table 2 Substrate scope of the addition of nitrones to **1** under the optimized flow conditions



Entry	1/Nu	2	Yield (%)[a]	d.r.[a,b]
1	**1d/C**	**2dC**	79	53:47
2	**1d/D**	**2dD**	100	63:37
3	**1d/E**	**2dE**	78	72:28
4	**1d/F**	**2dF**	67	54:46
5[c]	**1f/D**	**2eD**	74[d]	100:0

[a] Determined by ^{1}H NMR spectroscopy.
[b] Diastereomer ratio.
[c] The collected reaction mixture was treated with aqueous HCl solution.
[d] Isolated yield.

of **1d** still remained unreacted even with a suitable t^{R1}. These results led us to explore their simultaneous activation in flow by means of only a single mixer where a solution of **1d** (0.40 M), **C** (0.40 M), and Et_3N (0.80 M) in DCE and that of TMSOTf (1.60 M) in DCE were mixed (Figure 5c). As expected, complete consumption of **1d** was finally attained, which was further optimized by increasing the concentrations of **C** and Et_3N to 0.80 M and 1.60 M, respectively, to give **2dC** in 79% yield along with only 6% of **3d**. It should be noted that, in a batch reactor, the side reaction took place to afford **3d** in 40% yield under comparable conditions (Figure 6), indicating the effectiveness of the present flow microreactor system.

With the optimized conditions in hand, the substrate scope was evaluated (Table 2). In the flow microreactor system with **1d** as an electrophile, various nitriles including **C**, 4-methoxyphenylacetonitrile (**D**), 1-naphtylacetonitrile (**E**), and 2-thiopheneacetonitrile (**F**) were successfully used as a nucleophile to provide the desired addition products **2dC**–**2dF** in high yields as diastereomer mixtures (entries 1–4). In addition, 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide (**1e**) reacted efficiently with **D** to be transformed into the corresponding adducts **2eD** in good isolated yield as a single diastereomer (entry 5).

In conclusion, we have demonstrated that nucleophilic addition reactions to nitrones via their *N*-oxyiminium intermediates with soft carbon nucleophiles such as allyltributylstannane, silyl ketene acetal, and silyl ketene imine, which has previously required relatively low reaction temperatures (−30 to −78 °C) to carry out in conventional batch systems, can be efficiently performed at milder temperatures (0 to 30 °C) by means of a flow microreactor system that has allowed for minimization of serious side reactions. The results show that suitable flow conditions are quite sensitive to the nature of substrates but can be optimized each time by altering readily tunable parameters such as residence time. We believe that this study will open the way for more practical uses of nitrones as electrophile in organic synthesis.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(8) A DCM solution of **1b** (1.00 M) and that of benzoyl chloride (1.05 M) were fed to the first micromixer (YMC, Deneb, SUS316) by syringe pumps (YMC, YSP-101) equipped with a gastight syringe through 50 cm length of PTFE microtubes (an inside diameter ϕ of 500 μm) at a flow rate of 0.063 mL min^{-1} at 20 °C. The resulting mixture was delivered to the second micromixer through a 200 cm length of the microtube (ϕ = 500 μm), while a DCM solution of **A** (0.60 M) was equally fed to the same mixer at a flow rate of 0.126 mL min^{-1}. The finally resulting mixture was further run through a 1000 cm of the microtube (ϕ = 500 μm) at 30 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1159 seconds onto water and diluted with ethyl acetate (5 mL) and hexane (2 mL), which was washed successively with a saturated $NaHCO_3$ aqueous solution (2 mL × 3) and brine (2 mL × 3), and dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a mixture of hexane and ethyl acetate (95:5) as an eluent to afford **2bA** as a brown oil (0.319 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.71 (t, *J* = 6.5 Hz, 2H), 3.05 (t, *J* = 6.1 Hz, 2H), 3.51 (dt, *J* = 12.5, 6.1 Hz, 1H), 3.69 (dt, *J* = 12.5, 6.1 Hz, 1H), 4.46 (t, *J* = 6.1 Hz, 1H), 5.00–5.07 (m, 1H), 5.05–5.11 (m, 1H), 6.01 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 7.11–7.23 (m, 4H), 7.35–7.44 (m, 2H), 7.50–7.57 (m, 1H), 7.88–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 25.5, 39.2, 49.7, 65.0, 117.0, 126.2, 126.6, 127.0, 128.5, 129.4, 129.5, 133.1, 133.4, 135.2, 135.7, 164.9; Anal. Calcd. for $C_{19}H_{19}NO_2$: C 77.79, H 6.53, N 4.77; found: C 77.68, H 6.61, N 4.87.
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