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Nucleophilic Addition to Nitrones Using a Flow Microreactor

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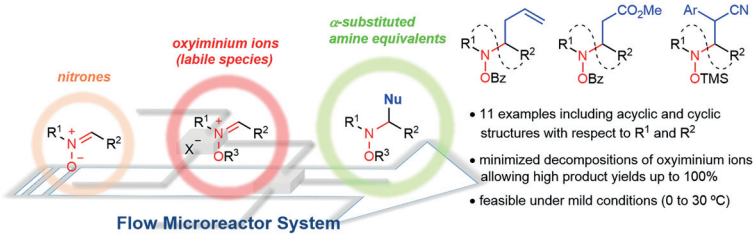

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Abstract Nucleophilic addition reactions of soft carbon nucleophiles to nitrones in a flow microreactor are reported for the first time. Under microflow conditions at 30 to 0 °C, a range of nitrones can be efficiently transformed into the corresponding oxyiminium ions by reaction with either acyl halides or trialkylsilyl triflates. These 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; such reactions at a similar temperature under batch conditions resulted in lower yields because of undesired side reactions.

Key words nitrones, flow, microreactor, nucleophilic addition, nitrogen-containing compounds

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 the α-carbon atom because of 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, whereas '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 co-workers 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 with use of a batch reactor have 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** because of its lability.[5]

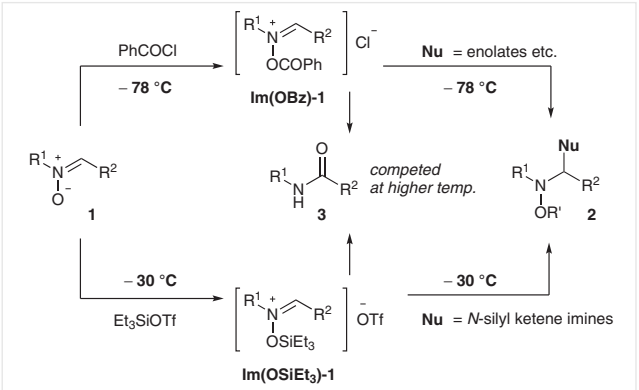


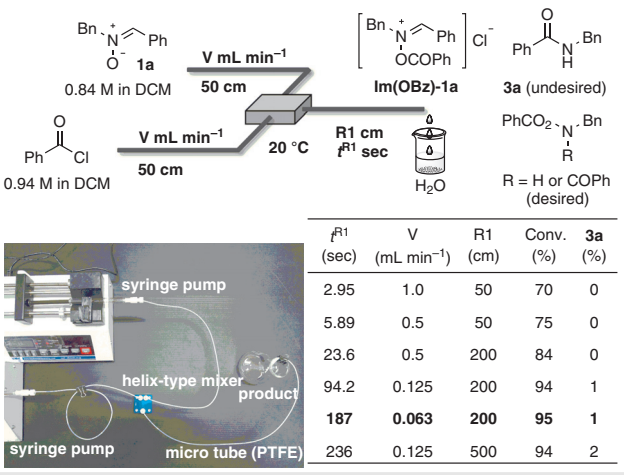
Figure 1 Previous strategies for utilizing nitrones as electrophiles via their *N*-oxyiminium ions formed in a batch system[4,6]

More recently, Yoshimura and co-workers introduced the nucleophilic addition reactions of in situ generated *N*-silyl ketene imines to **1** involving activation of substrates with triethylsilyl triflate, which also required –30 °C to fully suppress 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 that are difficult to control in batch systems.[7] Within this manuscript, we wish to expand the utility of

the flow microreactor system by adopting it to the nucleophilic addition to **1** through the formation of unstable *N*-oxyiminium intermediates.

A general and simple flow setup was used in this study, which comprises of syringe pumps and helical channel micromixers connected with each other through polytetrafluoroethylene (PTFE) micro tubes as required (Figure 2, photograph).

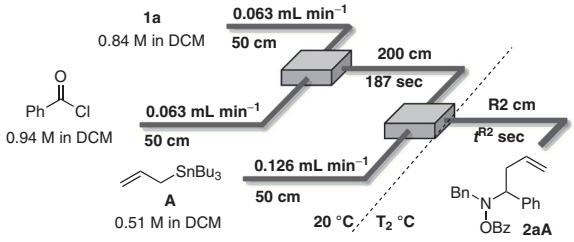


t^{R1} (sec)	V (mL min^{-1})	R1 (cm)	Conv. (%)	**3a** (%)
2.95	1.0	50	70	0
5.89	0.5	50	75	0
23.6	0.5	200	84	0
94.2	0.125	200	94	1
187	**0.063**	**200**	**95**	**1**
236	0.125	500	94	2

Figure 2 Determination of the optimal residence time for the generation of **Im(OBz)-1a** in a flow reactor

We started our investigation by determining the optimal residence time (t^{R1}, given in s) for synthesizing *N*-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, given in mL·min^{-1}) or the tube length between the mixer and the exit (R1, given in cm). Solutions of **1a** (0.84 M) and benzoyl chloride (0.94 M) in dichloromethane (DCM) were fed by the syringe pumps and mixed in the mixer, in which **Im(OBz)-1a** could start to be produced. It 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 to the second micromixer, in which **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 micro tube of 500 cm length prior to being poured into water to quench the reaction (Figure 3).



t^{R2} (s)	R2 (cm)	T_2 (°C)	NMR yield (%) by-products	NMR yield (%) **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** through the formation of **Im(OBz)-1a**

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 amount of by-products was reduced to 11% by prolonging the residence time t^{R2} twice (468 s) 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 and treated under 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) by 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 at 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-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**1c**)[9] was used as a chiral substrate, although the desired product **2cB** was obtained in only 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 *tert*-butyldimethylsilanol from the corresponding *N*-oxyiminium chloride followed by aroma-

tization to release HCl. This observation led us to reoptimize the flow conditions by controlling the 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 0.2 and 3.93 seconds (entry 6), respectively, which was even more improved by performing 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 by a single recrystallization. It should be noted that no desired product **2cB** was obtained in a batch reaction system (Figure 4, top), indicating the obvious utility of the present flow system. On the other hand, an even more challenging issue regarding 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 were just only optimized for the use of **B** (entry 8). To solve this problem, 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, bottom).

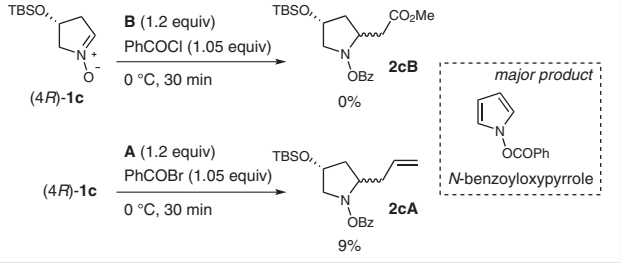
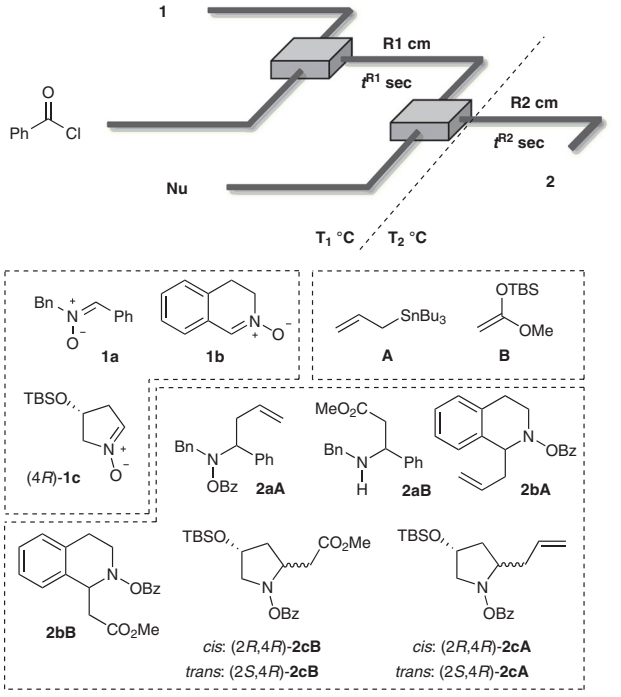


Figure 4 Inefficiency of the nucleophilic additions to (4*R*)-**1c** in a batch system

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 a low temperature was required in the 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 a solution of trimethylsilyl triflate (TMSOTf, 1.60 M) in DCE were mixed in the first mixer to give the corresponding *N*-silyl ketene imine **C′**.

Table 1 Adapting Different Substrates to the Flow Microreactor System[a]

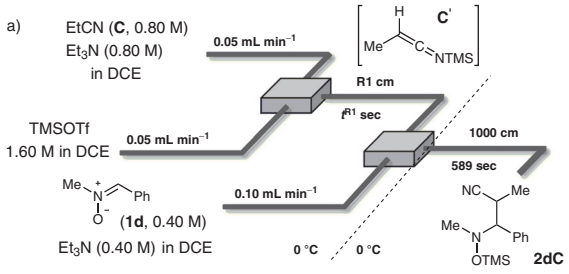


Entry	**1**/**Nu**	t^{R1} (s)	t^{R2} (s)	T_1 (°C)	T_2 (°C)	**2**	Yield (%)[b]
1	**1a**/**A**	187	468	20	30	**2aA**	84
2	**1b**/**A**	187	468	20	30	**2bA**	89
3	**1a**/**B**	187	468	20	30	**2aB**[c]	73
4	**1b**/**B**	187	468	20	30	**2bB**	60
5	**1c**/**B**	187	468	20	30	**2cB**	38[d]
6	**1c**/**B**	0.20	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]

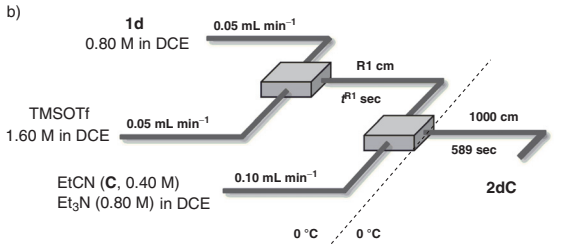
[a] Reaction conditions: Solutions of **1** (1.00 M), benzoyl chloride (1.05 M), and the nucleophile (**Nu**, 0.60 M) dissolved in DCM were used unless otherwise noted.
[b] Isolated yield.
[c] Isolated through reduction with zinc/acetic acid after the reaction.
[d] NMR yield.
[e] *cis*/*trans* = 3.3:1.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

The latter 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 5, a). The first step's residence time (t^{R1}) was varied, whereas 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 a t^{R1} of 5.9 seconds.

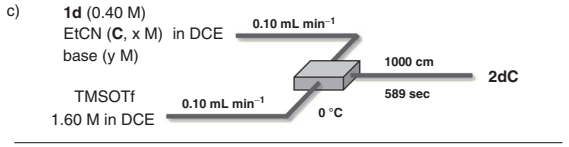
This is possibly due to the short lifetime of **C′** that could quickly isomerize to the corresponding α-silylnitrile.[10] We therefore attempted to minimize such a deactivation of **C′** by performing the activation of **1d** prior to that of **C** in the stepwise flow system (Figure 5, b). However, although the yield of **2dC** was slightly improved, a small amount of **1d** still remained unreacted even with a suitable t^{R1}.



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



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



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

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

These results led us to explore their simultaneous activation in flow by means of only a single mixer, in which a solution of **1d** (0.40 M), **C** (0.40 M), and Et_3N (0.80 M) in DCE and a solution of TMSOTf (1.60 M) in DCE were mixed (Figure 5, c). 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.

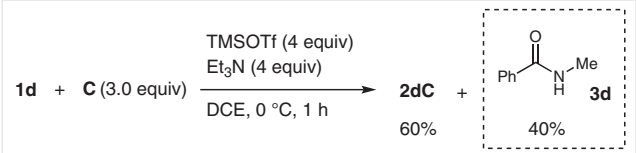
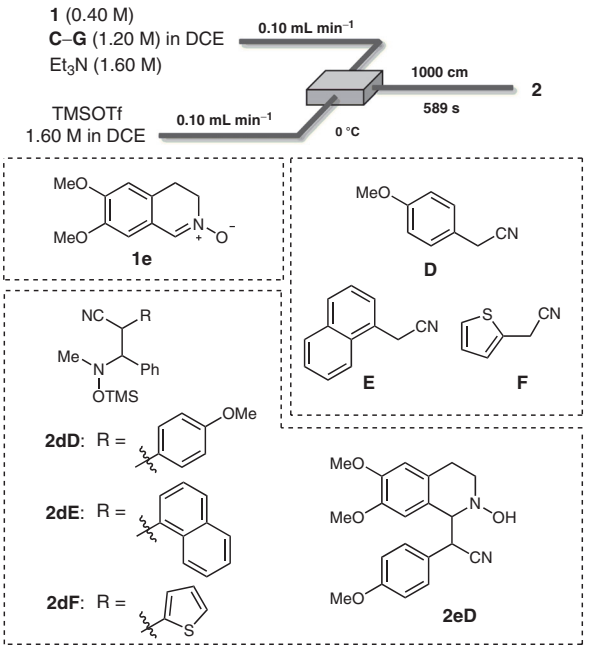


Figure 6 The reaction with **1d** and **C** in a batch system

Having the optimized conditions in hand, we evaluated the substrate scope (Table 2). In the flow microreactor system with **1d** as an electrophile, various nitriles including **C**, 4-methoxyphenylacetonitrile (**D**), 1-naphthylacetonitrile

Table 2 Substrate Scope of the Addition of Nitrones to **1** under the Optimized Flow Conditions



Entry	**1**/**Nu**	**2**	NMR yield (%)[a]	dr[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 ^1H NMR spectroscopy.
[b] Diastereomeric ratio.
[c] The collected reaction mixture was treated with aqueous HCl solution.
[d] Isolated yield.

(**E**), and 2-thiopheneacetonitrile (**F**) were successfully used as nucleophiles to provide the desired addition products **2dC**–**2dF** in high yields as diastereomeric mixtures (entries 1–4). In addition, 3,4-dihydro-6,7-dimethoxyisoquinoline *N*-oxide (**1e**) reacted efficiently with **D** to the corresponding adduct **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, 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. These reactions previously required relatively low reaction temperatures (–30 to –78 °C) to be carried out in conventional batch systems. 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 the residence time. We believe that this study will open the way for more practical uses of nitrones as electrophiles in organic synthesis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691601.

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(8) **(2bA)** A dichloromethane 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 polytetrafluoroethylene microtubes (50 cm length, inside diameter Ø = 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 microtube (200 cm length, Ø = 500 μm), while a dichloromethane 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 the microtube (1000 cm length, Ø = 500 μm) at 30 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1159 s onto water and diluted with EtOAc (5 mL) and hexane (2 mL). The mixture was washed successively with a sat. $NaHCO_3$ aq solution (2 mL × 3) and brine (2 mL × 3), dried with $MgSO_4$, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel (hexane/EtOAc 95:5) to afford **2bA** as a brown oil. Yield: 0.319 g (89%). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.71 (t, *J* = 6.5 Hz, 2 H), 3.05 (t, *J* = 6.1 Hz, 2 H), 3.51 (dt, *J* = 12.5, 6.1 Hz, 1 H), 3.69 (dt, *J* = 12.5, 6.1 Hz, 1 H), 4.46 (t, *J* = 6.1 Hz, 1 H), 5.00–5.07 (m, 1 H), 5.05–5.11 (m, 1 H), 6.01 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1 H), 7.11–7.23 (m, 4 H), 7.35–7.44 (m, 2 H), 7.50–7.57 (m, 1 H), 7.88–7.97 (m, 2 H). ^{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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