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A One-Pot *O*-Sulfinative Passerini/Oxidation Reaction: Synthesis of α-(Sulfonyloxy)amide Derivatives

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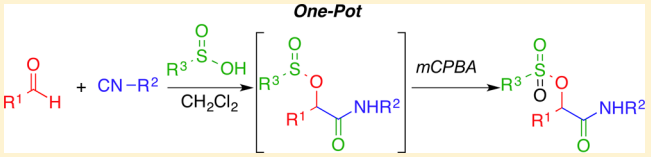
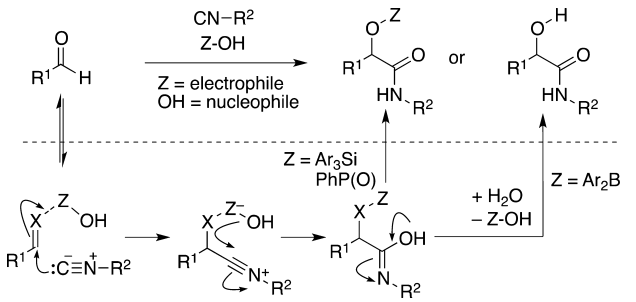
Supporting Information

ABSTRACT: We have developed a one-pot *O*-sulfinative Passerini/oxidation reaction, in which a combination of an aldehyde, an isocyanide, and a sulfinic acid react, followed by the addition of *m*CPBA as an oxidant to give the corresponding α-(sulfonyloxy)amides in high yields. This reaction is the first reported demonstration of an isocyanide-based multicomponent reaction using a sulfinic acid in place of a carboxylic acid. A wide range of aldehydes and isocyanides are applicable to this reaction.



Multicomponent reactions of isocyanides, such as the Passerini and Ugi reactions, are very useful synthetic tools for the construction of diverse complex molecules. The Passerini reaction, in particular, has been found useful for the construction of polyfunctional molecules such as α-acyloxyamide in a practical, one-pot process. Since Passerini's development of this multicomponent reaction in 1921,[1] various modifications have been reported,[2] although it is only recently that other species have been substituted for carboxylic acid. Typically, a carboxylic acid is a crucial component of the mixture due to the specific mechanism by which the Passerini reaction progresses. This mechanism, which has been widely studied, appears to involve activation of an aldehyde by the carboxylic acid, followed by addition of an isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate to afford the final product by migration of the acyl group onto the oxygen atom derived from the aldehyde. Therefore, the presence of carboxylic acid is generally a necessity during the reaction of an isocyanide with an aldehyde, or with an imine, as in the Ugi reaction. This requirement for a carboxylic acid unfortunately limits the application of this reaction to the synthesis of a narrow range of molecules. Several examples using other components in place of carboxylic acids have been reported to date. One example is the *O*-arylative Passerini reaction using nitrophenol derivatives, developed by El Kaim and Grimaud in 2006.[3] A direct alkylative Passerini reaction of an aldehyde, an isocyanide, and a free aliphatic alcohol, catalyzed by In(III), was reported by Taguchi.[4] Acetals and ketals are also useful for the reaction of isocyanides when catalyzed by Lewis or Brønsted acids, affording α-alkoxyimidates.[5] Because, as described above, the acyl group of a carboxylic acid acts as an electrophile while its OH group acts as a nucleophile for the nitrilium intermediate, other molecules containing both electrophilic and nucleophilic groups (Z−OH) could potentially act in a similar manner to a carboxylic acid in the Passerini reaction. Based on this hypothesis, we previously developed an *O*-silylative Passerini reaction, borinic-acid-catalyzed α-addition of an isocyanide, and an *O*-phosphinative Passerini reaction (Scheme 1).[6] In this work, we demonstrated the use of sulfinic acid as a carboxylic acid equivalent to afford the desired products from three components.

Scheme 1. *O*-Silylative Passerini Reaction, *O*-Phosphinative Passerini Reaction, and Borinic Acid Catalyzed α-Addition of an Isocyanide



We initially examined whether sulfinic acid was capable of participating in a three-component coupling reaction with an aldehyde and an isocyanide to afford the corresponding α-(sulfinyloxy)amide (eq 1, step 1). We further investigated the reaction of the resulting α-(sulfinyloxy)amide with an oxidizing reagent to generate α-(sulfonyloxy)amide derivatives in a one-pot operation (eq 1, step 2). Generally, α-(sulfonyloxy)alkanoic acid derivatives are important precursors of α-amino acids.[7] In addition, α-(sulfonyloxy)amides may be useful as useful building blocks in S_N2 reactions to convert other functional groups.

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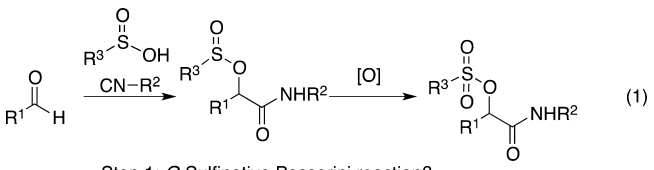


(1)

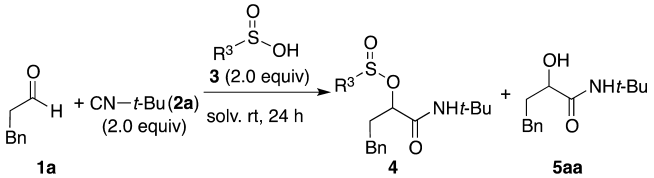
In our initial studies, we used a combination of phenylpropionaldehyde (**1a**), *tert*-butyl isocyanide (**2a**) (1.0 equiv), and (4-tolyl)sulfinic acid (**3a**) (1.0 equiv) in CH_2Cl_2 at room temperature (entry 1, Table 1). The expected α-(sulfinyloxy)-amide **4aaa** was obtained in 40% yield after 24 h; however, the hydrolysis product **5aa**[6c] was also obtained in 20% yield. When 1.0 equiv of isocyanide and 2.0 equiv of sulfinic acid were used, **4aaa** was obtained in 50% yield, but the yield of **5aa** increased to 49% (entry 2). The hydrolysis side reaction was suppressed using 1.5 equiv of isocyanide and 2.0 equiv of sulfinic acid, giving the desired **4aaa** in 79% yield as well as **5aa** in 11% yield (entry 3). Finally, we were pleased to observe that **4aaa** was obtained in 87% yield, while the yield of **5aa** was decreased to 8%, when 2 equiv of **2a** were used (entry 4). This reaction proceeded efficiently in both toluene and diethyl ether to afford **4aaa** in high yields (entries 5 and 6). Use of the cyclic ether THF as a solvent was less effective, resulting in the formation of α-hydroxyamide **5aa** in 27% yield, probably due to hydrolysis of **4aaa** (entry 7). Methanol, which has been used in the Ugi reaction as a protic solvent, produced a very sluggish reaction from which only **5aa** was obtained in 20% yield after 24 h (entry 8).

Having established a method for the *O*-sulfinative Passerini reaction, we then set out to evaluate the effectiveness of sulfinic acids bearing other substituents (entries 9−12). When (4-trifluoromethylphenyl)sulfinic acid (**3b**), (4-chlorophenyl)-sulfinic acid (**3c**), or phenylsulfinic acid (**3d**) was used, the product was obtained in high yield (entries 9−11). Methanesulfinic acid (**3e**) could also be used, giving the product **4aae** in 88% yield (entry 12).

We also attempted to expand the range of isocyanides and aldehydes that could be used in the *O*-sulfinative Passerini reaction, using (4-tolyl)sulfinic acid (**3a**) in all cases. The results are shown in Table 2. Throughout these experiments, optimal amounts of aldehydes **1a−i** (1.0 equiv) and isocyanides **2a−h** (2.0 equiv) were used in the presence of 2.0 equiv of (4-tolyl)sulfinic acid (**3a**). The results demonstrate that these conditions allow the reaction to proceed when using a wide variety of aliphatic aldehydes and isocyanides and that most reactions were complete within 24 h. The reactions of aliphatic isocyanides (R^2 = *t*-Oct, *c*-Hex, and Bn) with **1a** and **3a** gave the products in good to high yields (entries 2−4). When *tert*-octyl isocyanide (**2b**) and cyclohexyl isocyanide (**2c**) were used, the products were obtained in 90% and 63% yields, respectively (entries 2 and 3). In the case of benzyl isocyanide (**2d**), the desired product **4ada** was afforded in 52% yield (entry 4). Aromatic isocyanides generally showed low reactivity. Thus, in the case of aromatic isocyanides bearing an electron-withdrawing group at the *para* position, 4-bromophenyl isocyanide (**2e**) and phenyl isocyanide (**2f**), the reaction did not proceed at all (entries 5 and 6). Aromatic isocyanides bearing an electron-donating group at the *para* position also exhibited low reactivity; for example, the reaction using 4-methoxyphenyl isocyanide (**2g**) gave a trace amount of product (entry 7). Finally, 4-(*N*,*N*-dimethylamino)phenyl isocyanide (**2h**) showed moderate reactivity, affording the corresponding product **4aha** in 67% yield (entry 8).

The reactivity of various aldehydes with *tert*-butyl isocyanide (**2a**) was next examined. Aliphatic aldehydes **1b**, **1c**, and **1d** gave the products in 94%, 90%, and 79% yield, respectively (entries 9−11). Cinnamaldehyde (**1e**) and benzaldehyde (**1f**)

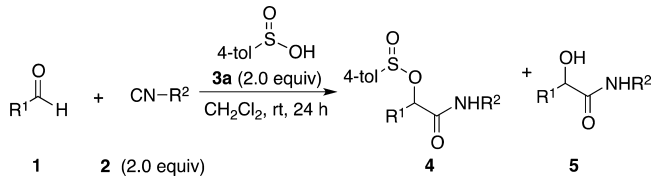
Table 1. Results of *O*-Sulfinative Passerini Reaction under Various Conditions



entry[a]	R^3	solvent	4/yield (%)	5/yield (%)
1[b]	4-MeC_6H_4 (**3a**)	CH_2Cl_2	40 (**4aaa**)	20
2[c]	4-MeC_6H_4 (**3a**)	CH_2Cl_2	50 (**4aaa**)	49
3[d]	4-MeC_6H_4 (**3a**)	CH_2Cl_2	79 (**4aaa**)	11
4	4-MeC_6H_4 (**3a**)	CH_2Cl_2	87 (**4aaa**)	8
5	4-MeC_6H_4 (**3a**)	toluene	83 (**4aaa**)	14
6	4-MeC_6H_4 (**3a**)	Et_2O	78 (**4aaa**)	19
7	4-MeC_6H_4 (**3a**)	THF	66 (**4aaa**)	27
8	4-MeC_6H_4 (**3a**)	MeOH	–	20
9	4-$CF_3C_6H_4$ (**3b**)	CH_2Cl_2	81(**4aab**)	11
10	4-ClC_6H_4 (**3c**)	CH_2Cl_2	89 (**4aac**)	9
11	C_6H_5 (**3d**)	CH_2Cl_2	82 (**4aad**)	8
12	Me (**3e**)	CH_2Cl_2	88 (**4aae**)	–

[a]The reaction was carried out using 2.0 equiv of **2a** and 2.0 equiv of **3** for 24 h unless otherwise mentioned. [b]Using 1.0 equiv of **2a** and 1.0 equiv of **3a**. [c]Using 1.0 equiv of **2a** and 2.0 equiv of **3a**. [d]Using 1.5 equiv of **2a** and 2.0 equiv of **3a**.

Table 2. Range of Isocyanides and Aldehydes Applicable to the *O*-Sulfinative Passerini Reaction



entry	R^1	R^2	4/yield (%)	5/yield (%)
1	$BnCH_2$ (**1a**)	*t*-Bu (**2a**)	87 (**4aaa**)	8 (**5aa**)
2	$BnCH_2$ (**1a**)	*t*-Oct (**2b**)	90 (**4aba**)	7 (**5ab**)
3	$BnCH_2$ (**1a**)	*c*-Hex (**2c**)	63 (**4aca**)	18 (**5ac**)
4	$BnCH_2$ (**1a**)	Bn (**2d**)	52 (**4ada**)	21 (**5ad**)
5	$BnCH_2$ (**1a**)	4-BrC_6H_4 (**2e**)	nr	–
6	$BnCH_2$ (**1a**)	Ph (**2f**)	nr	–
7	$BnCH_2$ (**1a**)	4-$MeOC_6H_4$ (**2g**)	trace	–
8	$BnCH_2$ (**1a**)	4-$Me_2NC_6H_4$ (**2h**)	67 (**4aha**)	32 (**5ah**)
9	*c*-Hex (**1b**)	*t*-Bu (**2a**)	94 (**4baa**)	–
10	*i*-Pr (**1c**)	*t*-Bu (**2a**)	90 (**4caa**)	9 (**5ca**)
11	*t*-Bu (**1d**)	*t*-Bu (**2a**)	79 (**4daa**)	20 (**5da**)
12	2-phenylethenyl (**1e**)	*t*-Bu (**2a**)	nr	–
13	Ph (**1f**)	*t*-Bu (**2a**)	nr	–
14	4-$F_3CC_6H_4$ (**1g**)	*t*-Bu (**2a**)	15 (**4gaa**)	–
15	4-BrC_6H_4 (**1h**)	*t*-Bu (**2a**)	13 (**4haa**)	–
16	4-$O_2NC_6H_4$ (**1i**)	*t*-Bu (**2a**)	17 (**4iaa**)	–

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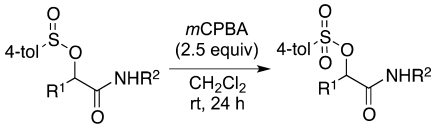
both demonstrated quite low reactivity, and their reactions did not produce any of the desired product (entries 12 and 13). However, aromatic aldehydes bearing an electron-withdrawing group at the *para* position also showed low reactivity, affording products with yields of around 15% (entries 14−16).

During the course of this investigation, we anticipated that subsequent oxidation of the sulfinyl groups could be achieved using an oxidizing reagent. We investigated oxidants including *m*CPBA, oxone, and DMDO. After examination of the reaction conditions, we found that α-(sulfinyloxy)amide derivatives **4** were oxidized by *m*CPBA easily and cleanly in CH_2Cl_2 to afford the corresponding α-(sulfonyloxy)amide derivatives **6** in good to high yields (Table 3).[8]

Table 3. Oxidation Reaction To Give α-(Sulfonyloxy)amides

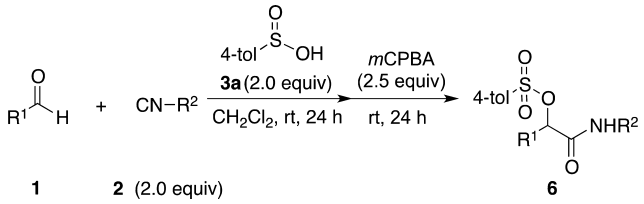


4 **6**

entry	R^1, R^2	yield/%
1	$BnCH_2$, *t*-Bu (**4aaa**)	88 (**6aaa**)
2	*c*-Hex, *t*-Bu (**4baa**)	85 (**6baa**)
3	*i*-Pr, *t*-Bu (**4caa**)	87 (**6caa**)
4	*t*-Bu, *t*-Bu (**4daa**)	89 (**6daa**)
5	$BnCH_2$, *t*-Oct (**4aba**)	95 (**6aba**)
6	$BnCH_2$, *c*-Hex (**4aca**)	80 (**6aca**)
7	$BnCH_2$, Bn (**4ada**)	77 (**6ada**)

Furthermore, we expanded these stepwise reactions to give a one-pot reaction (Table 4). A three-component reaction of **1**, **2**, and **3a** in CH_2Cl_2, followed by addition of *m*CPBA, gave the α-(sulfonyloxy)amides **6** in moderate to good yields.

Table 4. One-Pot *O*-Sulfinative Passerini/Oxidation Reactions



1 **2** (2.0 equiv) **6**

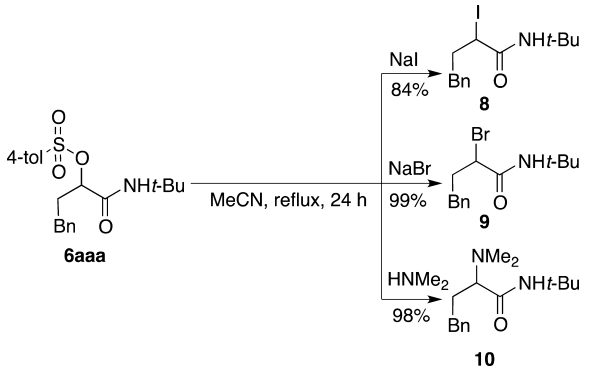
entry	R^1, R^2	yield/%
1	$BnCH_2$, *t*-Bu (**4aaa**)	69 (**6aaa**)
2	*c*-Hex, *t*-Bu (**4baa**)	73 (**6baa**)
3	*i*-Pr, *t*-Bu (**4caa**)	57 (**6caa**)
4[a]	*t*-Bu, *t*-Bu (**4daa**)	56 (**6daa**)
5	$BnCH_2$, *t*-Oct (**4aba**)	75 (**6aba**)
6	$BnCH_2$, *c*-Hex (**4aca**)	40 (**6aca**)
7	$BnCH_2$, Bn (**4ada**)	36 (**6ada**)

[a]$NaHCO_3$ (3 equiv) was also added to the reaction mixture.

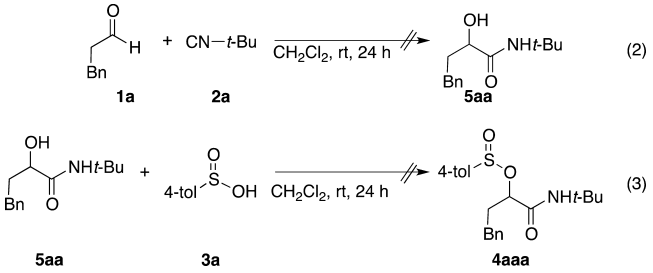
The sulfonyl group of the product **6aaa** was readily converted to other functional groups via an S_N2 reaction (Scheme 2). NaI, NaBr, and dimethylamine were employed as nucleophiles in the substitution reaction to afford the α-haloamides **8** and **9** as well as α-aminoamide **10** in high yields.

To reveal the reaction mechanism, we conducted a series of controlled experiments. These showed that addition of

Scheme 2. S_N2 Reaction Giving α-Substituted Amide Derivatives



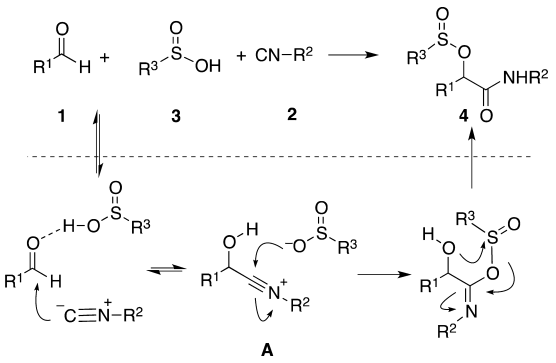
isocyanide **2a** to aldehyde **1a** in the absence of (4-tolyl)sulfinic acid (**3a**) did not proceed in CH_2Cl_2 over a period of 24 h (eq 2). In addition, when the reaction of α-hydroxyamide **5aa** with



(4-tolyl)sulfinic acid (**3a**) was attempted in CH_2Cl_2 with room temperature, the desired product **4aaa** was not obtained, and **5aa** was instead recovered (eq 3). These results indicate that α-(sulfinyloxy)amides cannot be formed by a dehydration reaction between an α-hydroxyamide **5** and a sulfinic acid **3**.

Based on these results, we propose a reaction mechanism for the *O*-sulfinative Passerini reaction, shown in Scheme 3. In this

Scheme 3. Proposed Reaction Mechanism



mechanism, the aldehyde is activated by the acidic proton of the sulfinic acid **3a** (pK_a = 2.80 in H_2O)[9] through coordination with the carbonyl oxygen. Subsequently, nucleophilic attack of the carbonyl group by isocyanide provides a nitrilium intermediate **A**, which is trapped by the sulfinate anion to afford the adduct **4** through migration of the sulfinate group onto the oxygen atom originating from the aldehyde.

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CONCLUSION

In summary, we have developed a one-pot *O*-sulfinative Passerini/oxidation reaction, in which a combination of an aldehyde, an isocyanide, and a sulfinic acid react, followed by addition of *m*CPBA as an oxidant to give the corresponding α-(sulfonyloxy)amides in high yields. This reaction is the first reported demonstration of an isocyanide-based multicomponent reaction using a sulfinic acid in place of a carboxylic acid. A wide range of aldehydes and isocyanides are applicable to this reaction.

EXPERIMENTAL SECTION

General Method. ^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*), and integration. ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (DART) was measured with a quadrupole and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation.

General Procedure. To a solution of **1** (0.5 mmol) and **3** (1.0 mmol) in CH_2Cl_2 (1 mL), **2** (1.0 mmol) was added, and the whole was stirred at room temperature. After reaction completion (monitored by TLC), satd. $NaHCO_3$ aq was added. The aqueous layer was separated and extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl 4-methylbenzenesulfinate (4aaa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4aaa** (163 mg, 87% yield) as a pale yellow oil. The The diastereomeric ratio was determined to be 10:7 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.22 (s, 9H), 1.27 (s, 9H), 1.88 (m, 2H), 2.09 (m, 1H), 2.23 (m, 1H), 2.37 (s, 3H), 2.38 (s, 3H), 2.49 (m, 2H), 2.63 (m, 2H), 4.45 (dd, *J* = 4.4, 6.4 Hz, 1H), 4.59 (dd, *J* = 4.0, 8.4 Hz, 1H), 6.07 (s, 1H), 6.23 (s, 1H), 7.02 (d, *J* = 6.8 Hz, 2H), 7.09−7.22 (m, 8H), 7.30 (m, 4H), 7.57 (m, 4H). ^{13}C NMR ($CDCl_3$): 21.3, 28.2, 28.4, 30.4, 30.7, 34.6, 34.8. 51.0, 51.1, 76.1, 77.2, 124.5, 124.6, 125.8, 125.9, 128.0, 128.1, 128.4, 129.7, 129.8, 140.5, 140.6, 141.1, 141.6, 143.5, 143.6, 168.5, 168.8. IR (KBr): 3340, 2970, 1680, 1590, 1520, 1500, 1460, 1360, 1220, 1180, 1080 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{21}H_{28}NO_3S$ [M + H]$^+$: 374.1790. Found: 374.1784.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl 4-(trifluoromethyl)benzenesulfinate (4aab). Silica gel column chromatography (hexane/ethyl acetate = 8/1) gave **4aab** (174 mg, 81% yield) as a white amorphous solid. The diastereomeric ratio was determined to be 5:4 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.21 (s, 9H), 1.27 (s, 9H), 1.92 (m, 2H), 2.12 (m, 1H), 2.23 (m, 1H), 2.52 (m, 2H), 2.64 (m, 2H), 4.46 (dd, *J* = 5.2, 11.2 Hz, 1H), 4.62 (dd, *J* = 4.0, 7.2 Hz, 1H), 5.95 (s, 1H), 6.15 (s, 1H), 7.00 (d, *J* = 6.8 Hz, 2H), 7.05−7.21 (m, 10H), 7.72−7.82 (m, 6H). ^{13}C NMR ($CDCl_3$): 28.3, 28.4, 30.4, 30.9, 34.7, 34.8, 51.3, 51.4, 77.2, 78.8, 123.1 ($^1J_{C-F}$ = 271.7 Hz), 125.3, 125.5, 126.0, 126.1, 126.2 ($^3J_{C-F}$ = 3.8 Hz), 128.3, 128.3, 128.4, 128.5, 134.2 ($^2J_{C-F}$ = 33.4 Hz), 140.2, 140.3, 148.1, 148.3, 168.1, 168.4. IR (KBr): 3340, 2970, 1680, 1600, 1520, 1500, 1460, 1370, 1320, 1220, 1170, 1140, 1080, 1060 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{21}H_{25}F_3NO_3S$ [M + H]$^+$: 428.1507. Found: 428.1504.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl 4-Chlorobenzenesulfinate (4aac). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4aac** (175 mg, 89% yield) as a yellow oil. The diastereomeric ratio was determined to be 4:3 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.31 (s, 9H), 1.35 (s, 9H), 1.98 (m, 2H), 2.17 (m, 1H), 2.30 (m, 1H), 2.58 (m, 2H), 2.70 (m, 2H), 4.50 (dd, *J* = 6.0, 11.6 Hz, 1H), 4.67 (dd, *J* = 4.0, 7.2 Hz, 1H), 6.04 (s, 1H), 6.25 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.17−7.28 (m, 10H), 7.56 (m, 3H), 7.68 (m, 3H). ^{13}C NMR ($CDCl_3$): 28.3, 28.5, 30.4, 30.8, 34.6, 34.8, 51.2, 51.3, 76.5, 78.2, 126.0, 126.1, 126.3, 128.3, 128.4, 129.4, 129.5, 139.1, 140.4, 142.3, 143.1, 168.2, 168.5. IR (KBr): 3340, 2970, 1680, 1580, 1520, 1480, 1460, 1390, 1370, 1220, 1140, 1090 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{20}H_{25}ClNO_3S$ [M + H]$^+$: 394.1244. Found: 394.1248.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl Benzenesulfinate (4aad). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4aad** (148 mg, 82% yield) as a yellow oil. The diastereomeric ratio was determined to be 6:5 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.28 (s, 9H), 1.32 (s, 9H), 1.95 (m, 2H), 2.15 (m, 1H), 2.28 (m, 1H), 2.56 (m, 2H), 2.70 (m, 2H), 4.52 (dd, *J* = 5.2, 11.6 Hz, 1H), 4.66 (dd, *J* = 4.0, 7.6 Hz, 1H), 6.08 (s, 1H), 6.27 (s, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.14−7.28 (m, 12 H), 7.58 (m, 3H), 7.73 (m, 3H). ^{13}C NMR ($CDCl_3$): 28.3, 28.4, 30.4, 30.8, 34.6, 34.8, 51.1, 51.2, 76.6, 77.7, 124.5, 124.6, 125.9, 126.0, 128.2, 128.3, 128.3, 129.2, 129.2, 132.7, 132.8, 140.5, 140.6, 144.2, 144.6, 168.4, 168.7. IR (KBr): 3340, 2970, 1680, 1520, 1490, 1460, 1390, 1360, 1230, 1140, 1090 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{20}H_{26}NO_3S$ [M + H]$^+$: 360.1633. Found: 360.1632.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl Methanesulfinate (4aae). Silica gel column chromatography (hexane/ethyl acetate = 4/1) gave **4aae** (131 mg, 88% yield) as a yellow oil. The diastereomeric ratio was not determined by ^{1}H NMR due to overlap of the diastereomers. ^{1}H NMR ($CDCl_3$): 1.29 (s, 18H), 2.15 (m, 4H), 2.25 (m, 2H), 2.57 (s, 3H), 2.58 (m, 2H), 2.65 (s, 3H), 4.43 (m, 2H), 5.98 (s, 1H), 6.44 (s, 1H), 7.08−7.21 (m, 10H). ^{13}C NMR ($CDCl_3$): 28.3, 28.5, 30.5, 30.9, 33.9, 35.0, 44.7, 51.3, 51.3, 78.5, 80.5, 125.9, 126.0, 128.2, 128.3, 128.4, 140.3, 140.5, 168.5, 168.6. IR (KBr): 3330, 2970, 1680, 1530, 1490, 1460, 1390, 1360, 1300, 1230, 1140, 1030 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{15}H_{24}NO_3S$ [M + H]$^+$: 298.1477. Found: 298.1471.

1-Oxo-4-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)-butan-2-yl 4-Methylbenzenesulfinate (4aba). Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **4aba** (193 mg, 90% yield) as a yellow oil. The diastereomeric ratio was determined to be 5:4 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 0.97 (s, 9H), 0.97 (s, 9H), 1.34 (s, 3H), 1.38 (s, 3H), 1,39 (s, 3H), 1.41 (s, 3H), 1.67 (m, 4H), 1.94 (m, 2H), 2.16 (m, 1H), 2.34 (m, 1H), 2.44 (s, 3H), 2.46 (s, 3H), 2.57 (m, 2H), 2.72 (m, 2H), 4.52 (dd, *J* = 5.6, 11.2 Hz, 1H), 4.64 (dd, *J* = 4.4, 8.0 Hz, 1H), 6.24 (s, 1H), 6.45 (s, 1H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.14−7.35 (m, 10 H), 7.36 (m, 3H), 7.64 (m, 3H). ^{13}C NMR ($CDCl_3$): 21.5, 28.3, 28.4, 28.9, 30.5, 31.0, 31.4, 31.5, 34.6, 34.7, 51.9, 52.2, 55.2, 76.4, 78.4, 124.5, 124.7, 125.9, 126.0, 128.3, 128.4, 128.5, 129.9, 140.7, 140.8, 141.4, 141.9, 143.6, 143.7, 168.1, 168.4. IR (KBr): 3340, 2960, 1680, 1530, 1500, 1460, 1390, 1370, 1230, 1140, 1030 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{25}H_{36}NO_3S$ [M + H]$^+$: 430.2416. Found: 430.2406.

1-(Cyclohexylamino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfinate (4aca). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4aca** (126 mg, 63% yield) as a brown solid of mp = 80.0−82.0 °C (hexane/ethyl acetate). The diastereomeric ratio was determined to be 4:3 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.06−2.02 (m, 22H), 2.15 (m, 1H), 2.30 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 2.53 (m, 2H), 2.69 (m, 2H), 3.72 (m, 2H), 4.58 (dd, *J* = 4.8, 11.2 Hz, 1H), 4.72 (dd, *J* = 4.4, 7.6 Hz, 1H), 6.18 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 2H), 7.12−7.29 (m, 10H), 7.35 (m, 3H), 7.61 (m, 3H). ^{13}C NMR ($CDCl_3$): 21.4, 24.5, 25.3, 30.4, 30.8, 32.5, 32.6, 32.7, 32.8, 34.7, 34.9, 47.9, 75.9, 77.9, 124.6, 124.8, 125.8, 126.0, 128.2, 128.3, 128.4, 129.8, 140.5, 140.7, 141.0, 141.6, 143.5, 143.6, 168.3, 168.7. IR (KBr): 3320, 2930, 1680, 1640, 1540, 1500, 1450, 1350, 1220, 1140, 1080, 1040 cm^{-1}. HRMS−DART (*m*/*z*): Calcd for $C_{23}H_{30}NO_3S$ [M + H]$^+$: 400.1946. Found: 400.1950.

1-(Benzylamino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfinate (4ada). Silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **4ada** (107 mg, 52% yield) as a pale yellow solid of mp = 82.6−84.5 °C (hexane/ethyl acetate). The diastereomeric ratio was determined to be 10:9 by ^{1}H NMR. ^{1}H NMR

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($CDCl_3$): 2.01 (m, 2H), 2.23 (m, 1H), 2.40 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 2.55 (m, 2H), 2.73 (m, 2H), 4.32−4.52 (m, 4H), 4.68 (dd, J = 5.2, 10.8 Hz, 1H), 4.82 (dd, J = 4.0, 7.6 Hz, 1H), 6.65 (m, 1H), 6.84 (m, 1H), 7.07 (d, J = 7.6 Hz, 2H), 7.18−7.35 (m, 22H), 7.58 (m, 4H). ^{13}C NMR ($CDCl_3$): 21.4, 30.5, 30.9, 34.6, 34.9, 43.1, 43.2, 75.4, 77.8, 124.6, 124.8, 125.9, 126.0, 127.3, 127.5, 127.6, 128.3, 128.3, 128.3, 128.4, 128.5, 128.6, 129.8, 137.6, 137.7, 140.4, 140.6, 140.8, 141.4, 143.6, 143.7, 169.5, 169.8. IR (KBr): 3330, 2930, 1670, 1530, 1500, 1450, 1390, 1360, 1260, 1180, 1080, 1030 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{24}H_{26}NO_3S$ $[M + H]^+$: 408.1633. Found: 408.1636.

1-((4-(Dimethylamino)phenyl)amino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfinate (4aha). Silica gel column chromatography (hexane/ethyl acetate = 4/1) gave **4aha** (147 mg, 67% yield) as a brown amorphous solid. The diastereomeric ratio was determined to be 6:5 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 2.06 (m, 2H), 2.29 (m, 1H), 2.42 (m, 1H), 2.44 (s, 3H), 2.46 (s, 3H), 2.62 (m, 2H), 2.78 (m, 2H), 2.92 (s, 6H), 2.93 (s, 6H), 4.73 (dd, J = 6.0, 11.6 Hz, 1H), 4.87 (dd, J = 3.6, 7.2 Hz, 1H), 6.74 (brs, 4H), 7.10 (d, J = 7.2 Hz, 2H), 7.14−7.42 (m, 16H), 7.68 (m, 4H), 7.94 (s, 1H), 8.06 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.4, 21.5, 30.5, 30.9, 34.5, 34.8, 40.7, 76.0, 77.7, 112.7, 112.8, 121.5, 121.7, 124.6, 124.8, 125.9, 126.0, 126.6, 126.7, 128.1, 128.2, 128.3, 128.3, 129.9, 130.0, 140.5, 140.6, 140.9, 141.4, 143.7, 143.8, 148.1, 167.1, 167.3. IR (KBr): 3310, 2920, 1670, 1520, 1500, 1450, 1360, 1320, 1220, 1130, 1080, 1030 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{25}H_{29}N_2O_3S$ $[M + H]^+$: 437.1899. Found: 437.1897.

2-(*tert*-Butylamino)-1-cyclohexyl-2-oxoethyl 4-Methylbenzenesulfinate (4baa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4baa** (166 mg, 94% yield) as a a brown amorphous solid. The diastereomeric ratio was determined to be 10:7 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 0.97−2.02 (m, 22H), 1.24 (s, 9H), 1.26 (s, 9H), 2.37 (s, 6H), 4.22 (d, J = 3.6 Hz, 1H), 4.40 (d, J = 3.2 Hz, 1H), 5.86 (s, 1H), 6.12 (s, 1H), 7.29 (d, J = 7.6 Hz, 4H), 7.58 (d, J = 7.6 Hz, 4H). ^{13}C NMR ($CDCl_3$): 21.4, 25.7, 25.8, 26.0, 26.2, 26.5, 28.3, 28.5, 28.9, 29.6. 40.4, 40.5, 51.0, 51.1, 81.6, 82.6, 124.4, 124.5, 129.7, 129.7, 141.7, 141.9, 143.3, 143.4, 168.2, 168.7. IR (KBr): 3390, 2930, 1660, 1520, 1450, 1370, 1230, 1140, 1080 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{19}H_{30}NO_3S$ $[M + H]^+$: 352.1946. Found: 352.1951.

1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 4-Methylbenzenesulfinate (4caa). Silica gel column chromatography (hexane/diethyl ether = 3/1) gave **4caa** (140 mg, 90% yield) as a yellow oil. The diastereomeric ratio was determined to be 5:3 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 0.83 (d, J = 7.2 Hz, 6H), 0.87 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.29 (s, 9H), 1.32 (s, 9H), 2.19 (m, 1H), 2.41 (m, 1H), 2.44 (s, 6H), 4.31 (d, J = 3.2 Hz, 1H), 4.51 (d, J = 3.2 Hz, 1H), 5.96 (s, 1H), 6.24 (s, 1H), 7.37 (d, J = 8.4 Hz, 4H), 7.65 (d, J = 8.4 Hz, 4H). ^{13}C NMR ($CDCl_3$): 15.8, 16.3, 18.6, 19.1, 21.4, 28.3, 28.4, 30.9, 31.0, 51.0, 51.1, 82.3, 82.5, 124.4, 124.6, 129.7, 141.7, 141.9, 143.4, 143.5, 168.3, 168.7. IR (KBr): 3340, 2970, 1670, 1640, 1520, 1460, 1370, 1230, 1140, 1080 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{16}H_{26}NO_3S$ $[M + H]^+$: 312.1633. Found: 312.1632.

1-(*tert*-Butylamino)-3,3-dimethyl-1-oxobutan-2-yl 4-Methylbenzenesulfinate (4daa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4daa** (128 mg, 79% yield) as a yellow solid of mp = 85.6−87.0 °C (hexane/ethyl acetate). The diastereomeric ratio was determined to be 4:3 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 0.95 (s, 9H), 1.00 (s, 9H), 1.24 (s, 9H), 1.31 (s, 9H), 2.43 (s, 3H), 2.45 (s, 3H), 4.13 (s, 1H), 4.26 (s, 1H), 5.72 (s, 1H), 5.91 (s, 1H), 7.36 (m, 4H), 7.65 (m, 4H). ^{13}C NMR ($CDCl_3$): 21.4, 21.5, 26.3, 26.5, 28.3, 28.5, 34.4, 34.8, 50.9, 51.1, 83.4, 85.6, 124.5, 124.6, 129.7, 129.7, 141.9, 142.1, 143.3, 143.4, 167.5, 167.9. IR (KBr): 3330, 2970, 1680, 1540, 1520, 1460, 1370, 1230, 1120, 1090 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{17}H_{28}NO_3S$ $[M + H]^+$: 326.1790. Found: 326.1787.

2-(*tert*-Butylamino)-2-oxo-1-(4-(trifluoromethyl)phenyl)-ethyl 4-Methylbenzenesulfinate (4gaa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **4gaa** (32 mg, 15% yield) as a yellow solid of mp = 82.8−84.8 °C (hexane/ethyl acetate). The diastereomeric ratio was determined to be 11:10 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.22 (s, 9H), 1.30 (s, 9H), 2.29 (s, 3H), 2.38 (s, 3H), 5.33 (s, 1H), 5.51 (s, 1H), 6.28 (s, 1H), 6.35 (s, 1H), 7.09 (m, 4H), 7.30−7.60 (m, 12H). ^{13}C NMR ($CDCl_3$): 21.3, 21.5, 28.3, 28.5, 51.5, 51.6, 74.3, 76.8, 123.1 ($^1J_{C-F}$ = 271.7 Hz), 124.7, 125.1 ($^3J_{C-F}$ = 3.3 Hz), 125.2, ($^3J_{C-F}$ = 3.8 Hz), 127.6, 127.7, 129.6, 130.0, 130.2 ($^2J_{C-F}$ = 32.4 Hz), 130.8 ($^2J_{C-F}$ = 32.4 Hz), 140.1, 140.3, 140.4, 141.3, 143.9, 144.0, 166.6, 167.0. IR (KBr): 3300, 2970, 1660, 1590, 1520, 1460, 1370, 1330, 1220, 1130, 1070 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{20}H_{23}F_3NO_3S$ $[M + H]^+$: 414.1351. Found: 414.1348.

1-(4-Bromophenyl)-2-(*tert*-butylamino)-2-oxoethyl 4-Methylbenzenesulfinate (4haa). Silica gel column chromatography (hexane/ethyl acetate = 8/1) gave **4haa** (28 mg, 13% yield) as a yellow oil. The diastereomeric ratio was determined to be 11:10 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.22 (s, 9H), 1.29 (s, 9H), 2.34 (s, 3H), 2.37 (s, 3H), 5.23 (s, 1H), 5.43 (s, 1H), 6.26 (s, 1H), 6.30 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.15−7.30 (m, 8H), 7.42 (m, 4H), 7.50 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 21.5, 28.4, 28.5, 51.4, 51.5, 75.2, 77.3, 122.5, 122.9, 124.7, 125.1, 129.0, 129.1, 129.6, 130.0, 131.3, 131.7, 135.3, 135.6, 140.3, 141.4, 143.7, 143.8, 166.8, 167.2. IR (KBr): 3340, 2970, 1680, 1520, 1460, 1370, 1290, 1220, 1140, 1070 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{19}H_{23}BrNO_3S$ $[M + H]^+$: 424.0582. Found: 424.0585.

2-(*tert*-Butylamino)-1-(4-nitrophenyl)-2-oxoethyl 4-Methylbenzenesulfinate (4iaa). Silica gel column chromatography (hexane/ethyl acetate = 8/1) gave **4iaa** (34 mg, 17% yield) as a yellow oil. The diastereomeric ratio was determined to be 1:1 by ^{1}H NMR. ^{1}H NMR ($CDCl_3$): 1.21 (s, 9H), 1.29 (s, 9H), 2.30 (s, 3H), 2.93 (s, 3H), 5.37 (s, 1H), 5.53 (s, 1H), 6.27 (s, 1H), 6.35 (s, 1H), 7.16 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.53 (m, 4H), 7.97 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 21.6, 28.4, 28.5, 51.7, 51.8, 73.9, 76.0, 123.2, 123.7, 124.7, 125.1, 128.1, 128.2, 129.7, 130.1, 140.1, 141.1, 143.3, 143.5, 144.2, 144.3, 147.5, 147.9, 166.1, 166.5. IR (KBr): 3340, 2970, 1680, 1520, 1460, 1390, 1350, 1290, 1220, 1180, 1080 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{19}H_{23}N_2O_5S$ $[M + H]^+$: 391.1328. Found: 391.1333.

General Procedure for the Oxidation of Sulfinates 4. To a solution of **4** in CH_2Cl_2 (10 mL), *m*CPBA (2.5 equiv) was added and the whole was stirred at room temperature. After reaction completion (monitored by TLC), the reaction mixture was washed with 1 M NaOH aq and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

General Procedure for the One-Pot *O*-Sulfinative Passerini/Oxidation Reaction. To a solution of **1** (0.5 mmol) and **3** (1.0 mmol) in CH_2Cl_2 (1 mL), **2** (1.0 mmol) was added, and the whole was stirred at room temperature. After reaction completion (monitored by TLC), *m*CPBA (2.5 equiv) was added and the whole was stirred at room temperature. After reaction completion (monitored by TLC), 1 M NaOH was added. The aqueous layer was separated and extracted with $CHCl_3$ (5 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

1-(*tert*-Butylamino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfonate (6aaa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **6aaa** (106 mg, 88% yield, 0.31 mmol scale) as a white solid of mp = 109.4−110.9 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.25 (s, 9H), 2.08 (m, 2H), 2.46 (s, 3H), 2.57 (m, 2H), 4.74 (t, J = 5.6 Hz, 1H), 5.97 (s, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.18 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.81 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 28.2, 30.4, 34.1, 51.3, 80.2, 126.0, 127.8, 128.2, 128.3, 130.0, 132.8, 140.1, 145.5, 166.9. IR (KBr): 3300, 2970, 1650, 1560, 1460, 1370, 1220, 1180, 1100, 1020, 980 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{21}H_{28}NO_4S$ $[M + H]^+$: 390.1739. Found: 390.1736.

2-(*tert*-Butylamino)-1-cyclohexyl-2-oxoethyl 4-Methylbenzenesulfonate (6baa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **6baa** (96 mg, 85% yield, 0.31 mmol scale) as a white solid of mp = 142.8−144.1 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.96−1.64 (m, 10H), 1.12 (s, 9H), 1.82 (m, 1H), 2.39 (s, 3H), 4.49 (d, J = 4.0 Hz, 1H), 5.71 (s, 1H), 7.30 (d, J

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= 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 25.6, 25.8, 26.3, 28.2, 28.9, 40.1, 51.2, 84.9, 127.8, 130.0, 133.1, 145.3, 166.6. IR (KBr): 3400, 2930, 1660, 1530, 1450, 1370, 1230, 1180, 1100, 1070, 970 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{19}H_{30}NO_4S$ $[M + H]^+$: 368.1896. Found: 368.1899.

1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl 4-Methylbenzenesulfonate (6caa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **6caa** (115 mg, 87% yield, 0.41 mmol scale) as a white solid of mp = 106.5−107.1 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.85 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.21 (s, 9H), 2.28 (m, 1H), 2.46 (s, 3H), 4.59 (d, J = 3.6 Hz, 1H), 5.84 (s, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): 16.0, 18.5, 21.5, 28.2, 30.8, 51.2, 85.2, 127.8, 130.0, 133.0, 145.3, 166.8. IR (KBr): 3390, 2980, 1660, 1520, 1460, 1370, 1340, 1230, 1190, 1090, 970 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{16}H_{26}NO_4S$ $[M + H]^+$: 328.1583. Found: 328.1582.

1-(*tert*-Butylamino)-3,3-dimethyl-1-oxobutan-2-yl 4-Methylbenzenesulfonate (6daa). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **6daa** (91 mg, 89% yield, 0.30 mmol scale) as a white solid of mp = 141.0−142.0 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.95 (s, 9H), 1.17 (s, 9H), 2.45 (s, 3H), 4.36 (s, 1H), 5.65 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 26.1, 28.2, 34.5, 51.2, 88.0, 127.9, 130.0, 133.1, 145.3, 165.8. IR (KBr): 3400, 2970, 1660, 1520, 1480, 1360, 1330, 1230, 1190, 1100, 960 cm^{-1} HRMS−DART (m/z): Calcd for $C_{17}H_{28}NO_4S$ $[M + H]^+$: 342.1739. Found: 342.1734.

1-Oxo-4-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)-butan-2-yl 4-Methylbenzenesulfonate (6aba). Silica gel column chromatography (hexane/ethyl acetate = 8/1) gave **6aba** (112 mg, 95% yield, 0.27 mmol scale) as a white solid of mp = 75.6−77.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 0.91 (s, 9H), 1.26 (s, 3H), 1.28 (s, 3H), 1.53 (d, J = 15.2 Hz, 1H), 1.60 (d, J = 15.2 Hz, 1H), 2.00 (m, 2H), 2.39 (s, 3H), 2.50 (m, 2H), 4.67 (dd, J = 4.8, 6.0 Hz, 1H), 6.01 (s, 1H), 6.99 (d, J = 6.8 Hz, 2H), 7.09 (m, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.6, 28.3, 28.6, 30.4, 31.4, 31.5, 34.0, 52.1, 55.5, 80.3, 126.1, 127.8, 128.3, 128.4, 130.0, 133.0, 140.2, 145.5, 166.6. IR (KBr): 3430, 2960, 1680, 1530, 1460, 1370, 1220, 1190, 1100, 980 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{25}H_{36}NO_4S$ $[M + H]^+$: 446.2365. Found: 446.2376.

1-(Cyclohexylamino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfonate (6aca). Silica gel column chromatography (hexane/ethyl acetate = 6/1) gave **6aca** (138 mg, 80% yield, 0.42 mmol scale) as a white solid of mp = 132.6−134.6 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.03−1.84 (m, 10H), 2.09 (m, 2H), 2.46 (s, 3H), 2.55 (m, 2H), 3.70 (m, 1H), 4.83 (t, J = 5.6 Hz, 1H), 6.09 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 7.6 Hz, 2H), 7.16 (m, 1H), 7.23 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.5, 24.5, 25.2, 30.3, 32.4, 32.6, 34.1, 48.0, 80.0, 126.0, 127.8, 128.2, 128.3, 130.0, 132.7, 140.1, 145.5, 166.8. IR (KBr): 3260, 2930, 1650, 1570, 1450, 1360, 1340, 1190, 1180, 1100, 1020, 980 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{23}H_{30}NO_4S$ $[M + H]^+$: 416.1896. Found: 416.1895.

1-(Benzylamino)-1-oxo-4-phenylbutan-2-yl 4-Methylbenzenesulfonate (6ada). Silica gel column chromatography (benzene/ethyl acetate = 100/1) gave **6ada** (49 mg, 77% yield, 0.15 mmol scale) as a white solid of mp = 101.9−103.6 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.12 (m, 2H), 2.45 (s, 3H), 2.55 (m, 2H), 4.40 (m, 2H), 4.91 (t, J = 5.6 Hz, 1H), 6.57 (s, 1H), 7.04 (d, J = 6.8 Hz, 2H), 7.15−7.36 (m, 10H), 7.70 (d, J = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): 21.7, 30.4, 34.1, 43.3, 79.9, 126.2, 127.6, 127.9, 128.3, 128.4, 128.7, 130.1, 132.6, 137.3, 140.1, 145.6, 167.9. IR (KBr): 3370, 2920, 1650, 1530, 1460, 1380, 1350, 1190, 1180, 1100, 1020, 980 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{24}H_{26}NO_4S$ $[M + H]^+$: 424.1583. Found: 424.1580.

General Procedure. The mixture of **6aaa** and sodium salt (NaI, or NaBr) in MeCN (1 mL) was refluxed for 24 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography.

***N*-(*tert*-Butyl)-2-iodo-4-phenylbutanamide (8).** Silica gel column chromatography (hexane/diethyl ether = 3/1) gave **8** (58 mg, 84% yield, 0.2 mmol scale) as a white solid of mp = 97.0−98.0 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 1.28 (s, 9H), 2.21 (m, 2H), 2.60 (m, 1H), 2.69 (m, 1H), 3.98 (t, J = 7.2 Hz, 1H), 5.45 (s, 1H), 7.11−7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): 27.2, 28.3, 35.1, 38.1, 51.6, 126.3, 128.5, 140.0, 169.1. IR (KBr): 3310, 2970, 1650, 1540, 1460, 1360, 1280, 1220, 1180 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{14}H_{21}INO$ $[M + H]^+$: 346.0668. Found: 346.0667.

***N*-(*tert*-Butyl)-2-bromo-4-phenylbutanamide (9).** Silica gel column chromatography (hexane/diethyl ether = 3/1) gave **9** (59 mg, 99% yield, 0.2 mmol scale) as a white solid of mp = 79.0−80.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$):1.37 (s, 9H), 2.28 (m, 1H), 2.44 (m, 1H), 2.81 (m, 2H), 4.14 (dd, J = 5.2, 8.8 Hz, 1H), 6.12 (s, 1H), 7.20−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 28.4, 33.1, 37.3, 51.6, 51.7, 126.2, 128.5, 128.6, 140.1, 167.5. IR (KBr): 3300, 2970, 1650, 1550, 1450, 1360, 1220, 1030 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{14}H_{21}BrNO$ $[M + H]^+$: 298.0807. Found: 298.0804.

The mixture of **6aaa** (0.13 mmol) and dimethylamine (50% aqueous solution, 1.3 mmol) in MeCN (2 mL) was refluxed for 24 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, and the organic layer was separated. The organic layer was washed with water and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

***N*-(*tert*-Butyl)-2-(dimethylamino)-4-phenylbutanamide (10).** Silica gel column chromatography (hexane/acetone = 3/1) gave **10** (33 mg, 98% yield, 0.13 mmol scale) as a colorless oil. ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H), 1.92 (m, 2H), 2.25 (s, 6H), 2.64 (m, 2H), 2.77 (m, 1H), 6.76 (s, 1H), 7.16−7.92 (m, 5H). ^{13}C NMR ($CDCl_3$): 28.8, 30.2, 32.8, 42.5, 50.4, 69.9, 125.8, 128.3, 128.4, 142.1, 172.3. IR (KBr): 3340, 2960, 1660, 1510, 1450, 1390, 1360, 1230, 1050 cm^{-1}. HRMS−DART (m/z): Calcd for $C_{16}H_{27}N_2O$ $[M + H]^+$: 263.2123. Found: 263.2122.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Passerini, M. *Gazz. Chem. Ital.* **1921**, *51*, 126−181.

(2) For recent enantioselective Passerini-type reactions, see: (a) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384−8385. (b) Yue, T.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454−9457. (c) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388−391. (d) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667−9676. (e) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231−4233. (f) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021−4024. (g) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825−7827.

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J. Org. Chem. 2015, 80, 3688−3694

(3) (a) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169−4180. (b) El Kaim, L.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2006**, *8*, 5021−5023.
(4) (a) Yanai, H.; Sakiyama, T.; Oguchi, T.; Taguchi, T. *Tetrahedron Lett.* **2012**, *53*, 3161−3164. (b) Yanai, H.; Oguchi, T.; Taguchi, T. *J. Org. Chem.* **2009**, *74*, 3927−3929.
(5) (a) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431−11437. (b) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697−3699.
(6) (a) Soeta, T.; Ukaji, Y. *Chem. Rec.* **2014**, *14*, 101−116. (b) Soeta, T.; Matsuzaki, S.; Ukaji, Y. *Chem.—Eur. J.* **2014**, *20*, 5007−5012. (c) Soeta, T.; Kojima, Y.; Ukaji, Y.; Inomata, K. *Tetrahedron Lett.* **2011**, *52*, 2557−2559. (d) Soeta, T.; Kojima, Y.; Ukaji, Y.; Inomata, K. *Org. Lett.* **2010**, *12*, 4341−4343.
(7) Onomura, O.; Mitsuda, M.; Nguyen, M. T. T.; Demizu, Y. *Tetrahedron Lett.* **2007**, *48*, 9080−9084.
(8) Stensaas, K. L.; McCarty, B. V.; Touchette, N. M.; Brock, J. B. *Tetrahedron* **2006**, *62*, 10683−10687.
(9) Filippo, D. D.; Momicchioli, F. *Tetrahedron* **1969**, *25*, 5733−5744.

DOI: 10.1021/acs.joc.5b00131
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