

# Automated Synthesis: Utilization of MEDLEY in Synthetic Processes

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## Abstract:

A variety of reactions which are commonly used in synthetic chemistry are feasible with the automated synthesizer (MEDLEY). Air-sensitive organolithium and Grignard reagents as well as transition metal catalysts like Ni(0) and Pd(0) species are employable. The precise control of both the reaction temperature and the amount of added reagents enables to examine the dependence of chemical yields on the reaction temperature. Since the order of reagent addition is programmed and the reaction temperature is quickly tunable, sequential reactions can be conducted smoothly. An advanced control system was incorporated which allows a task to start immediately after the preceding one has finished. Owing to this function, the time for completing the multistep process can be minimized.

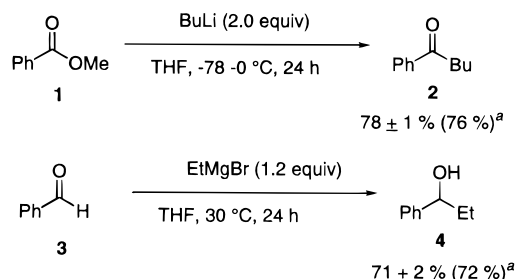
## Introduction

In the preceding contribution, we reported a new type of automated synthesizer (MEDLEY) which allows reactions under the same reaction conditions as those which synthetic chemists employ in normal bench work.<sup>1</sup> One of the purposes of this work is to demonstrate that the synthesizer is actually applicable to various synthetic reactions, in particular, under an inert atmosphere.

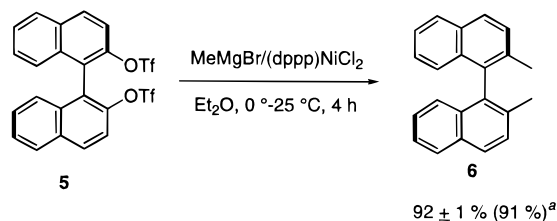
MEDLEY can control the amounts of reagents to be added within a  $\pm 0.01$  mL deviation. The reaction temperature can also be regulated from  $-80$  to  $30$  °C, accurate within  $\pm 0.1$  °C. Such precise control of the reaction conditions allows us to examine the influences of reaction conditions on the carbanion reactions which are heavily affected by reaction parameters. Thus, the next purpose of this work is to show that such influences can be well assessed by the use of MEDLEY.

Of more practical importance is the feasibility of multistep processes to run on MEDLEY. The chemical processes are usually composed of a number of operations. The first reaction transforms a starting material to an intermediate which, after isolation and purification, is subjected to the second reaction leading to the next intermediate. Repetition of these operations drives the process to the final product. The automation of such multistep processes is of great importance from both economical and ecological points of view. We previously advanced a new concept for one-pot reaction, “integrated chemical process”, which enables integration of ordinary reactions under ordinary conditions.<sup>2</sup> It would be of great promise if integrated chemical processes could be operated automatically. Hence, the third purpose

## Scheme 1<sup>a</sup>

<sup>a</sup> Yield obtained by manual operation.

## Scheme 2<sup>a</sup>

<sup>a</sup> Yield obtained by manual operation.

of this work is to demonstrate the successful accommodation of sequential reactions in MEDLEY.

Finally, another characteristics of MEDLEY will be disclosed, the advanced control which allows the next task to start immediately after the previous one has finished. Due to the absence of a dead time between contiguous tasks, the processing time could be minimized. This will be proved to be indeed the case.

## Results and Discussion

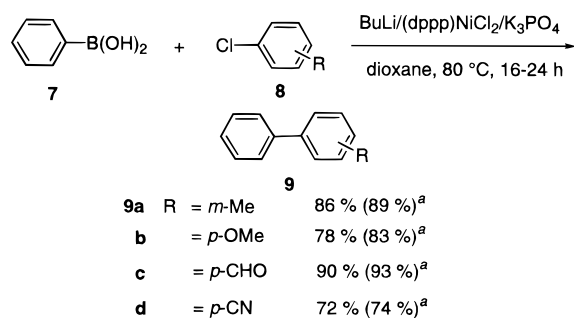
First, employment of air-sensitive organolithium and Grignard reagents were checked. The reaction proceeded smoothly to afford the yields comparable to those obtained by manual operations (Scheme 1).

Then, the utility is further exemplified by the successful use of air-sensitive transition metal catalysts. The Ni(0) catalyst was generated in situ without problem and the two types of coupling reactions proceeded smoothly (Schemes 2<sup>3</sup> and 3<sup>4</sup>). The feasibility of Pd(0)-catalyzed reaction was proved with Suzuki–Miyaura coupling (Scheme 4).<sup>4</sup> As a

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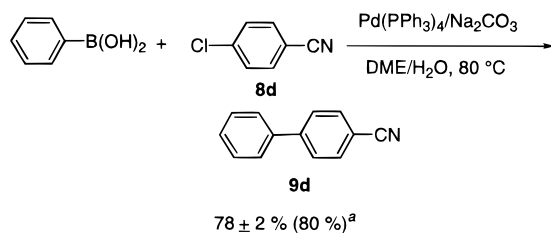
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### Scheme 3<sup>a</sup>



<sup>a</sup> Yield reported.

### Scheme 4<sup>a</sup>



<sup>a</sup> Yield reported.

**Table 1.** Effect of rate of BuLi addition on yields in Peterson elimination<sup>a</sup>

entry	time consumed for adding BuLi, min	temperature during BuLi addition, °C	yield of <b>12</b> , %
1	20	-74.0 to -69.4	97
2	10	-74.0 to -62.4	88
3	5	-74.0 to -61.1	87
4	3	-74.0 to -56.3	84
5	1	-74.0 to -44.1	71

<sup>a</sup> Reaction conditions: **10** (10 mmol), BuLi (12 mmol, 9.25 mL); **11** (12 mmol), THF (20 mL).

result, it is concluded that most of synthetic reactions employing air-sensitive compounds can be performed successfully on MEDLEY.

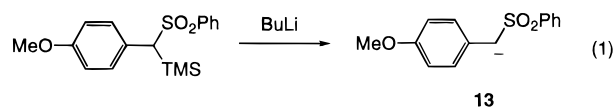
It is well-known that reactions of carbanions are highly dependent on the reaction temperature. Thus, synthetic chemists are forced to regulate the rate of reagent addition to maintain the reaction at a required temperature. However, this is usually done empirically without information about what is actually happening in the flask. Since the real reaction temperature can be measured precisely on MEDLEY, variations in the reaction temperature depending on the addition rate were probed for aldol-type reactions. First, generation of the lithium anion from  $\alpha$ -silyl benzyl sulfone **10** was examined (Table 1).<sup>2c</sup> The time for adding BuLi was altered from 20 to 1 min. The resulting anion was trapped with anisaldehyde **11** to give vinyl sulfone **12** via Peterson elimination. The yield of **12** was straightforwardly decreased

**Table 2.** Effect of rate of aldehyde addition on yields in Aldol reaction<sup>a</sup>

entry	time consumed for adding <b>15</b> , min	temperature during BuLi addition, °C	yield of <b>16</b> , %
1	20	-74.0 to -72.6	95
2	10	-74.0 to -72.4	95
3	5	-74.0 to -69.9	96
4	3	-74.0 to -67.3	92
5	1	-74.0 to -63.5	83

<sup>a</sup> Reaction conditions: **14** (10 mmol), BuLi (11 mmol, 8.46 mL); **15** (12 mmol), THF (20 mL).

with increase in the rate of BuLi addition. This is attributed to the competing cleavage of the trimethylsilyl group to generate the sulfonyl anion **13** (eq 1). The highest temper-

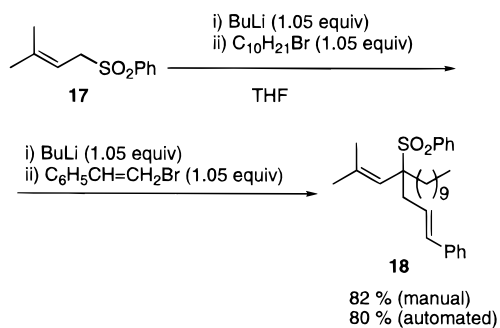


atures reached during the addition are also shown in Table 1 and are totally parallel with the addition rates. The reaction temperature was raised above -70 °C even by very slow addition (9.25 mL/20 min). At the addition rates that we employ in normal synthetic operations (9.25 mL/5–10 min), the reaction temperature jumped to ~-60 °C. These results reveal that the reaction temperature fluctuates more vigorously than we imagine and should be controlled carefully if strict control of the temperature is required.<sup>5</sup> Next the effect of aldehyde addition was examined for simple aldol-type reactions (Table 2). The lithiation of **14** was conducted below -70 °C, and the time for adding aldehyde **15** was changed from 20 to 1 min. The similar variation of the yield was observed although the degree of fluctuation was not so large as that for the former case. The decrease of the yield of **16** at higher temperature may come from the side reactions such as deprotonation of aldehyde **15**, etc.

With these results of elementary reactions in hand, we turned our attention to sequential reactions. The double alkylation of an allylic sulfone was our first choice (Scheme 5).<sup>2c,d</sup> Prenyl sulfone **17** was lithiated, and the resulting anion was treated with decyl bromide. To this reaction mixture was added BuLi followed by cinnamyl bromide. The usual aqueous workup provided the double alkylation product **18** in 82% yield by manual operations. The same reaction was conducted on MEDLEY which executed 14 programmed operations. The reactor was purged with nitrogen, and then the automation process was triggered. After this stage, no further manual operations were needed until the completion

(5) In usual experiments, the temperature of the cooling bath, not the reaction medium itself, is measured. When the same reaction was carried out by using a normal cooling bath, without the use of the reactor for MEDLEY, the temperature of the reaction solution rose similarly.

### Scheme 5



#### Operations Programmed

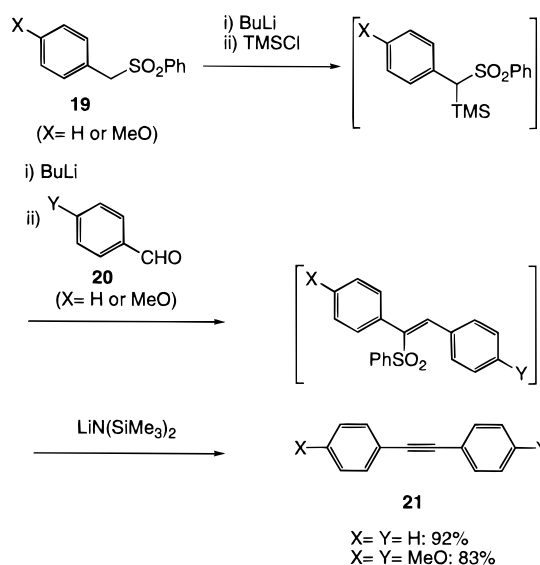
1. addition of sulfone in THF
2. cooling down to -74 °C
3. addition of BuLi (1.05 equiv)/-74 °C
4. stirring/-74 °C/30 min
5. addition of CH<sub>3</sub>(CH<sub>2</sub>)<sub>9</sub>Br (1.05 equiv)/-74 °C
6. warming up to 15 °C
7. stirring/15 °C/2 h
8. cooling down to -74 °C
9. addition of BuLi (1.05 equiv)/-74 °C
10. stirring/-74 °C/30 min
11. addition of PhCH=CHCH<sub>2</sub>Br (1.05 equiv)/-74 °C
12. warming up to 15 °C
13. stirring/15 °C/18 h
14. addition of H<sub>2</sub>O

of the process. The yield of **18** was comparable to that obtained by the manual operations.

Then, we ran the integrated chemical process of the double elimination protocol for the one-pot synthesis of acetylenes (Scheme 6).<sup>2e</sup> Sixteen operations were programmed for this process. After the reaction flask was filled with a THF solution of sulfone under a nitrogen atmosphere, the program was initiated, and all operations proceeded automatically. First, the reactor was cooled by circulating cold MeOH (-85 °C). The solution became -74 °C after 5 min (operation 1). The additions of BuLi, TMSCl, aldehyde **20**, and a base were conducted according to the programme to keep the reaction temperature below -70 °C (operations 2, 4, 8, 10, and 14). All of these operations were completed actually within 5 min. The temperature fluctuated between -74 and 70 °C. As soon as these tasks finished, the next operations started immediately as a result of the advanced control function. After operations 4 and 10, the flow of cold MeOH stopped, and warm MeOH (room temperature) started to circulate. The reaction temperature reached 15 or 0 °C, respectively, within 5 min. On the other hand, in operations 7 and 13, the temperature was cooled to -74 °C within 10 min as described for operation 1. Thus, the ups and downs of the reaction temperature that are frequently encountered in anion chemistry are readily achievable. In the event, 16 operations were done without any manual work. Upon the finish of the programmed tasks, the reaction mixture was subjected to usual aqueous workup to give satisfactory yields of the desired acetylenes **21**. It is apparent from the above results that the computer program effectively enables the maintenance, warming, and cooling of the reaction temperature as well as the addition of the reagents in the required order and amount.

As revealed above, the advanced control system is of great use for minimizing the process time. Moreover, undesired

### Scheme 6



#### Operations Programmed

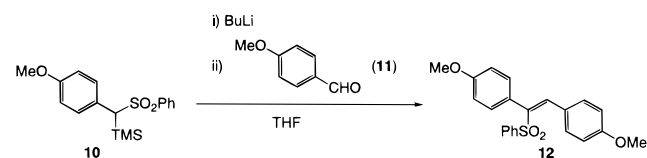
1. cooling down to -74 °C
2. addition of BuLi (1.1 equiv)/-74 °C
3. stirring/-74 °C/30 min
4. addition of TMSCl (1.1 equiv)/-74 °C
5. warming up to 15 °C
6. stirring/15 °C/2 h
7. cooling down to -74 °C
8. addition of BuLi (1.2 equiv)/-74 °C
9. stirring/-74 °C/30 min
10. addition of aldehyde (1.2 equiv)/-74 °C
11. warming up to 0 °C
12. stirring/0 °C/2 h
13. cooling down to -74 °C
14. addition of base (10 equiv)/-74 °C
15. stirring/-74 °C/2 h
16. addition of H<sub>2</sub>O

side reactions or decompositions of the products that may arise upon unnecessarily long reaction can be avoided.<sup>6</sup> The advantage of this system was assessed for the Peterson elimination reaction in detail (Table 3). The reaction temperature was programmed to be kept below -70 °C during the anion generation, and the time required for completing addition of BuLi was measured. In six runs, the times fluctuated extensively from 18' 31" to 23' 58" despite the relatively small reaction scale. Such big fluctuations are rather surprising, considering the precise control of the reaction temperature as well as the amount of the BuLi added. In the time-controlled system, the programming of at least 25 min would be required to secure the completion of the task. Thus, the considerably long dead time (possibly 6' 30" at most) is inevitable, and the accumulation of such intervals in the sequential process should result in wasting a lot of processing time. Of course, the time loss would be greater for reactions in larger scale.

In conclusion, an automated synthesizer has been developed which enables to conduct manifold reactions sequentially under the conditions that are employed in usual synthetic reactions. Through the advanced control, the time required for connecting the successive operations are minimized. "Integrated chemical process" has proved to be, in

(6) For "overnight stirring problem", see ref 5 of ref 1 of this paper.

**Table 3. Variation of the time required for addition of BuLi in Peterson elimination<sup>a</sup>**



entry	time consumed for adding BuLi	temperature during BuLi addition, °C	yield of <b>12</b> /%
1	18' 58''	-73.6 to -69.8	96
2	22' 47''	-73.5 to -69.9	97
3	20' 33''	-73.5 to -69.6	98
4	23' 58''	-73.6 to -70.0	96
5	20' 20''	-73.5 to -69.8	96
6	18' 31''	-73.6 to -69.6	98

<sup>a</sup> Reaction conditions: **10** (10 mmol), BuLi (12 mmol, 9.25 mL); **11** (12 mmol), THF (20 mL).

fact, a useful concept for automation of multistep chemical processes. Of course, it is not always possible to consolidate all reactions needed in a whole synthetic route. Nevertheless, it is highly useful even if only a part of the synthetic sequence is consolidated. As such, we are now in a position to run consecutive reactions with the automated synthesizer without difficulty.

## Experimental Section

**General.** All of the reactions were carried out under nitrogen. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Dioxane and dimethoxyethane (DME) were distilled from calcium hydride. NMR spectra were recorded at 25 °C on JEOL Lambda 300 and JEOL Lambda 500 spectrometers and calibrated with tetramethylsilane (TMS) as an internal reference. Silica gel (Daiso gel IR-60) was used for column chromatography. Sulfones were prepared according to the procedures described in the literature.<sup>7,8</sup> The following compounds are known, and the spectral data of these compounds were consistent with those in the literature: **2**,<sup>9</sup> **4**,<sup>10</sup> **6**,<sup>3</sup> **9**,<sup>4</sup> and 4-methoxy-1-[2-(4-methoxyphenyl)ethynyl]benzene.<sup>11</sup>

**Reaction of Butyl Lithium and Methyl Benzoate.** A reaction flask was evacuated and filled with nitrogen. After THF (6 mL) and methyl benzoate (272 mg, 2.0 mmol) were added, the mixture was cooled in a dry ice/methanol bath. Then, the program was initiated. When the temperature of the reaction mixture reached -78 °C, the addition of a hexane solution of BuLi started. The bath temperature was kept at -78 °C. After completion of BuLi addition (1.52 M, 2.63 mL, 4.0 mmol), the flask was placed in an ice/water bath, and the mixture was stirred for 24 h. After usual aqueous workup, the crude products were subjected to

column chromatography on silica gel (hexane/EtOAc, 9:1) to give pure butyl phenyl ketone (256 mg, 79% yield).

**Reaction of Ethyl Magnesium Bromide and Benzaldehyde.** A flask was evacuated and filled with nitrogen. After THF (6 mL) and benzaldehyde (212 mg, 2.0 mmol) were added, the mixture was kept at 30 °C in the water bath. Then, the program was initiated. When the temperature of the reaction mixture reached 30 °C, the addition of a THF solution of EtMgBr started. The reaction temperature was kept at 30 °C. After completion of the EtMgBr addition (1.0 M, 2.4 mL, 2.4 mmol), the mixture was further stirred at 30 °C for 24 h, and water (30 mL) was added. After usual aqueous workup, the crude products were subjected to column chromatography on silica gel (hexane/EtOAc, 4:1) to give pure 1-phenylpropanol (199 mg, 73% yield).

**Nickel-Catalyzed Methylation of Binaphthyl Triflate (5).** A flask was evacuated and filled with nitrogen. After addition of ether (8 mL), binaphthyl triflate (**5**) (1101 mg, 2 mmol), and NiCl<sub>2</sub>(dppp) (54 mg, 0.1 mmol), the program was initiated. When the temperature of the ether solution reached 0 °C by circulating cold methanol, the addition of an ether solution of MeMgBr started. The reaction temperature was kept at 0 °C. After completion of MeMgBr addition (3.0 M, 2.67 mL, 8.0 mmol), the mixture was stirred at 0 °C for 1 h. The reaction mixture was warmed to 25 °C and stirred at this temperature for 3 h. After addition of water (30 mL) followed by usual aqueous workup, the crude products were subjected to column chromatography on silica gel (hexane/EtOAc, 95:5) to give the pure product (525 mg, 93% yield).

### Nickel-Catalyzed Suzuki–Miyaura Coupling Reaction.

A flask was evacuated and filled with nitrogen. After additions of 1,4-dioxane (7 mL), K<sub>3</sub>PO<sub>4</sub> (1273 mg, 6.0 mmol), and NiCl<sub>2</sub>(dppp) (54 mg, 0.1 mmol), the program was initiated. A hexane solution of BuLi (1.6 M, 0.5 mL, 0.8 mmol) was added at 25 °C, and the mixture was stirred at 25 °C for 10 min. A dioxane solution of 3-chlorotoluene (253 mg, 2.0 mmol) and dihydroxy phenylborane (268 mg, 2.2 mmol) was added, and the mixture was heated at 80 °C for 24 h. After addition of water (30 mL) followed by usual aqueous workup, the crude products were subjected to column chromatography on silica gel (hexane/EtOAc 98:2) to give the pure product (289 mg, 86% yield).

**Palladium-Catalyzed Suzuki–Miyaura Coupling Reaction.** A flask was evacuated and filled with nitrogen. After addition of DME (5 mL), water (1 mL), Na<sub>2</sub>CO<sub>3</sub> (318 mg, 3.0 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (34 mg, 0.03 mmol), the program was initiated. A DME solution (1 mL) of 3-chlorobenzonitrile (138 mg, 1.0 mmol) and dihydroxy phenylborane (134 mg, 1.1 mmol) was added at 25 °C, and the mixture was heated at 80 °C for 24 h. After addition of water (30 mL) followed by usual aqueous workup, the crude products were subjected to a column chromatography on silica gel (hexane/EtOAc, 95:5) to give the pure product (141 mg, 79% yield).

**Peterson Olefination between Silyl Sulfone **10** and Aldehyde **11**.** The reactor having a jacket for circulation of methanol was evacuated and filled with nitrogen. After THF (20 mL) and silyl sulfone **10** (3.34 g, 10 mmol) were added,

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the program was initiated. In this case, the advanced control was not invoked, and the rate of BuLi addition was time-controlled. After the temperature of the reaction mixture reached  $-74\text{ }^{\circ}\text{C}$ , a hexane solution of BuLi (1.3 M, 9.25 mL, 12 mmol) was added over the period required. After the completion of the BuLi addition, the reaction mixture was stirred at the same temperature for 30 min. Then, *p*-anisaldehyde (1.46 mL, 12 mmol) was added. The mixture was warmed to  $0\text{ }^{\circ}\text{C}$  and stirred for 2 h. After addition of saturated  $\text{NH}_4\text{Cl}$  solution (30 mL) followed by usual workup, the yield was determined on the basis of HPLC;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  3.75 (s, 3H), 3.82 (s, 3H), 6.70 (d,  $J = 8.9\text{ Hz}$ , 2H), 6.82 (d,  $J = 8.9\text{ Hz}$ , 2H), 6.94 (d,  $J = 8.9\text{ Hz}$ , 2H), 7.05 (d,  $J = 8.9\text{ Hz}$ , 2H), 7.37–7.42 (m, 2H), 7.49–7.55 (m, 1H), 7.60–7.65 (m, 2H), 7.89 (s, 1H).

**Aldol-type Reaction between Benzyl Sulfone 14 and Aldehyde 15.** The reactor having a jacket for circulation of methanol was evacuated and filled with nitrogen. After THF (20 mL) and benzyl sulfone **14** (2.32 g, 10 mmol) were added, the program was initiated. The reaction mixture was cooled to  $-74\text{ }^{\circ}\text{C}$ , and a hexane solution of BuLi (1.3 M, 8.46 mL, 11 mmol) was added at this temperature. After the completion of the addition, the mixture was stirred at  $-74\text{ }^{\circ}\text{C}$  for 30 min. Then, **15** (1.60 mL, 12 mmol) was added over the period of 20 min at this temperature. The mixture was stirred for 1.5 h, and saturated  $\text{NH}_4\text{Cl}$  solution (30 mL) was added. After usual workup, the yield was determined on the basis of HPLC;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.52–1.60 (m, 1H), 1.62–1.72 (m, 1H), 2.60–2.70 (m, 1H), 2.76–2.83 (m, 1H), 3.25–3.29 (m, 1H), 3.92–4.00 (m, 1H), 4.79–4.84 (m, 1H), 7.08–7.11 (m, 2H), 7.12–7.39 (m, 10H), 7.50–7.60 (m, 3H).

**Double Alkylation Reaction of Sulfone (17).** The reactor having a jacket for circulation of methanol was evacuated and filled with nitrogen. Then, the program was initiated. After addition of THF solution (6 mL) of prenyl phenyl sulfone (420 mg, 2.0 mmol) at ambient temperature, the mixture was cooled to  $-74\text{ }^{\circ}\text{C}$ . A hexane solution of BuLi (1.52 M, 1.38 mL, 2.1 mmol) was added at  $-74\text{ }^{\circ}\text{C}$ , and the mixture was stirred for 30 min. After addition of bromodecane (0.44 mL, 2.1 mmol), the reaction mixture was warmed to  $15\text{ }^{\circ}\text{C}$ , and the mixture was stirred at  $15\text{ }^{\circ}\text{C}$  for 2 h. The

mixture was cooled to  $-74\text{ }^{\circ}\text{C}$  again, and a hexane solution of BuLi (1.52 M, 1.38 mL, 2.1 mmol) was added. After 30 min, cinnamyl bromide (0.31 mL, 2.1 mmol) was added, and the mixture was stirred at  $15\text{ }^{\circ}\text{C}$  for 18 h. After addition of saturated  $\text{NH}_4\text{Cl}$  solution (30 mL) followed by usual aqueous workup, the crude products were subjected to column chromatography on silica gel (hexane/EtOAc, 80:20) to give the pure product (570 mg, 80% yield);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.87 (t,  $J = 6.8\text{ Hz}$ , 3H), 1.1–1.3 (m, 16H), 1.47 (s, 3H), 1.75 (s, 3H), 1.90–2.00 (m, 1H), 2.03–2.10 (m, 1H), 2.73–2.80 (m, 1H), 2.99–3.06 (m, 1H), 4.86 (s, 1H), 6.2–6.4 (m, 1H), 6.46 (d,  $J = 15.7\text{ Hz}$ , 1H), 7.18–7.36 (m, 5H), 7.49–7.57 (m, 2H), 7.59–7.66 (m, 1H), 7.80–7.88 (m, 2H).

#### Synthesis of Diarylacetylenes (21) (Representative).

The reactor having a jacket for circulation of methanol was evacuated and filled with nitrogen. THF (6 mL) and *p*-methoxybenzyl sulfone (524 mg, 2.0 mmol) were added, and then the program was initiated. The mixture was cooled to  $-74\text{ }^{\circ}\text{C}$ , and a hexane solution of BuLi (1.52 M, 1.45 mL, 2.2 mmol) was added. The mixture was stirred for 30 min. After addition of  $\text{Me}_3\text{SiCl}$  (0.28 mL, 2.2 mmol), the mixture was warmed to  $15\text{ }^{\circ}\text{C}$  and stirred for 1 h. The mixture was cooled to  $-74\text{ }^{\circ}\text{C}$  again, and a hexane solution of BuLi (1.52 M, 1.58 mL, 2.4 mmol) was added. After 30 min, *p*-anisaldehyde (0.29 mL, 2.4 mmol) was added. The mixture was warmed to  $0\text{ }^{\circ}\text{C}$  and stirred at this temperature for 2 h. The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$ , and LDA was added. The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 h, and saturated  $\text{NH}_4\text{Cl}$  solution (30 mL) was added. After usual workup, the crude products were subjected to column chromatography on silica gel (hexane/EtOAc, 70:30) to give the pure product (396 mg, 83% yield).

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