ACS Combinatorial Science

Research Article

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Parallel and Combinatorial Liquid-Phase Synthesis of Alkylbiphenyls Using Pentaerythritol Support

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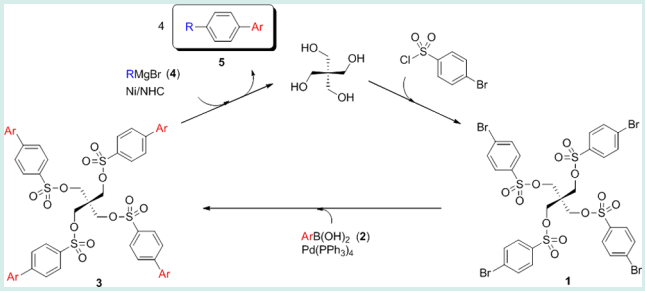
Supporting Information

ABSTRACT: Unfunctionalized alkylbiphenyls were fabricated by a parallel and combinatorial synthesis using pentaerythritol as a tetrapodal soluble support for a sulfonate-based traceless multifunctional linker system. Nickel *N*-heterocyclic carbene-catalyzed reactions of pentaerythritol tetrakis(biphenylsulfonate)s with primary alkylmagnesium bromides generated the alkylbiphenyl derivatives by desulfitative cleavage/cross-coupling of the C−S bond without any "memory" of the attachment on the support. Though the reactions were completed with sufficient yields in 12 h at room temperature, even with only 1.5 equiv of nucleophiles, they still retained the benefits of facile isolation observed in polymer-supported reactions.



KEYWORDS: *pentaerythritol, traceless linker, multifunctional cleavage, combinatorial synthesis*

INTRODUCTION

Combinatorial chemistry affords efficient production of large libraries of structurally analogous compounds, especially for generating lead molecules in drug discovery.[1] The combinatorial approach has also been employed in the field of materials science to discover new functional materials such as electronic, magnetic, sensing, and luminescent materials and catalysts.[2]

Solid-phase organic synthesis (SPOS) using polymer supports has become a powerful tool for combinatorial chemistry and high-throughput screening. The simple isolation and purification of reaction intermediates and products has made polymer-supported SPOS an extremely attractive approach for the rapid production of libraries of structurally similar compounds.[3] However, their heterogeneous characteristics often require large excesses of reagents to overcome their low reactivity. Difficulties in monitoring reaction progress and identifying the reaction intermediates are unavoidable weaknesses in using heterogeneous supports. Accordingly, trials to transform conventional solution reactions to SPOS suffer from limitations, and only a few reactions have been well established using this methodology.

Liquid-phase combinatorial synthesis using soluble supports, which is expected to avoid the drawbacks related to the heterogeneity of SPOS while maintaining its advantages, has recently been considered as an alternative to SPOS.[4] Soluble polymers—typically, polyethylene glycol and non-cross-linked polystyrene—are the most common soluble supports. However, relatively large amounts of supports and reagents are still required owing to their low loading capacities. Therefore, soluble dendrimers[5] and small molecules such as functionalized ionic liquids,[6] polyfunctionalized core molecules,[7] and benzyl alcohol derivatives[8] have continued to be studied as atom-economical supports.[9] We previously reported that a sulfonate-based linker system using a pentaerythritol soluble support had great potential in combining the benefits of both SPOS and conventional solution reaction chemistry.[10] The pentaerythritol system offered an efficient synthetic route to biphenyl and terphenyl derivatives, which are frequently found to be biologically[11] and optically[12] active, via the traceless multifunctional cleavage of carbon−sulfur bonds by arylmagnesium bromides.

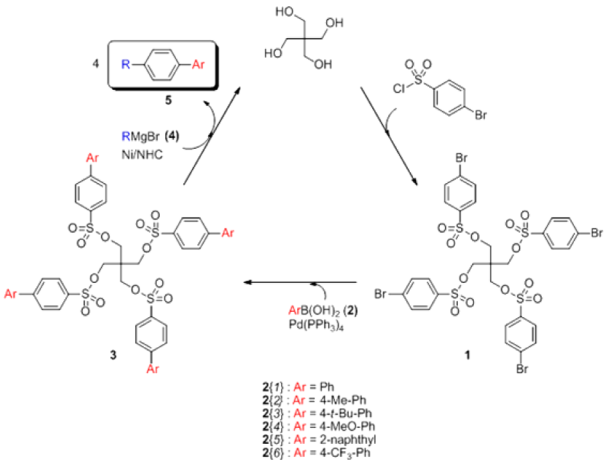
Oligomeric π-conjugated compounds, including *p*-oligophenyls, have recently attracted much attention for potential applications in a wide range of optoelectronic devices such as organic light-emitting diodes, organic field-effect transistors, organic photovoltaic cells, and organic solid-state lasers.[13] Not only have different scaffolds been explored to meet the desired physical and optoelectronic properties, but also variously substituted analogues have been thoroughly investigated to fine-tune the specifications of the compounds. In particular, the introduction of alkyl groups has often been desirable as a means to increase solubility in organic solvents. Therefore, an efficient parallel and combinatorial approach for producing unfunctionalized π-conjugated compounds with various alkyl moieties is quite necessary.

Herein, we present our efforts to develop a traceless and multifunctional sulfonate-based linker system that allows the rapid production of a variety of alkyl-substituted biphenyl compounds. Development of traceless linker strategies that

Received: October 24, 2013
Revised: February 18, 2014
Published: February 25, 2014

enable the release of unfunctionalized compounds from the support has been an important challenge in supported syntheses.[14] The results of the parallel and combinatorial preparations of an unfunctionalized alkybiphenyl library via the desulfitative carbon−carbon cross-coupling of biphenyl moieties attached to a soluble tetrapodal support, pentaerythritol, with primary alkyl Grignard reagents (Scheme 1) are presented and discussed.

Scheme 1. Preparation of Biphenyl Compounds 5



RESULTS AND DISCUSSION

The pentaerythritol-supported biphenylsulfonates **3** were prepared by Suzuki−Miyaura reactions of tetrakis(bromobenzenesulfonate) **1** with arylboronic acids **2** and isolated by facile precipitations from EtOAc or acetone in good purity according to our previous report.[10a] To effect the desulfitative carbon−carbon cross-coupling of the biphenyl moieties of **3** with the primary alkyl Grignard reagents, various conventional phosphinonickel(0) catalysts were initially investigated. However, the slow reaction rate of the unactivated alkyl Grignard reagents required a large excess of the nucleophiles, even at elevated temperatures. The inefficiency of the reagents and the difficulty in isolating the final products from the abundant dimerized byproducts of the alkyl nucleophiles diminished the value of this approach. Therefore, the Ni/NHC catalyst, which was readily generated in situ by the reaction of $Ni(acac)_2$ with 1,3-bis(2,6-diisoprorylphenyl)imidazolium trifluoroborate ($IPr{\cdot}HBF_4$),[15] was explored.

Cross-coupling reactions of **3** with alkylmagnesium bromides **4** were performed in the presence of the catalytic system. Biphenylsulfonate moieties attached to a flexible neopentyl core efficiently underwent the desired traceless multifunctional cleavage reaction at room temperature. From the results of a brief study to optimize the reactant ratios, only 1.5 equiv of the nucleophiles was found to be sufficient. The results are summarized in Table 1. Three alkyl nucleophiles were coupled with the biphenyl moieties via the cleavage of carbon−sulfur bonds to produce the corresponding alkylbiphenyls **5** in competitive yields within 12 h. The neopentyl- and benzylmagnesium bromides **4**{*2*−*3*} showed a slightly lower yield than the methyl nucleophile **4**{*1*}. The relatively higher reactivity of the methyl nucleophile was consistently observed when a 1.0 M solution of methylmagnesium chloride in THF was used.

Application of this strategy to the combinatorial synthesis of an alkylbiphenyl library was demonstrated. Bromobenzenesulfonate **1** was treated with an equimolar mixture of six boronic acids, **2**{*1*−*6*}, 0.17 equiv each, in the presence of $Pd(PPh_3)_4$ for 8 h. After the standard workup, the reaction mixture was passed through a small pad of silica gel to generate the biphenylsulfonate mixture **3** as a yellow powder that was pure enough to be used in the next step.

The relative composition of the biphenyl moieties in mixture **3** was investigated after their cleavage by the reductive coupling reaction with each of **4**{*1*−*3*}. GC and HPLC analyses of the reaction mixture indicated that all **2**{*1*−*6*} successfully underwent the desired coupling reactions, as summarized in Table 2. The averaged relative composition of the biphenyl moieties after the one-pot synthesis of **3** is displayed in Figure 1. 2-Naphthylboronic acids showed relatively higher reactivity, whereas 4-methoxyphenylboronic acid was discovered to be the lowest.

The final cross-coupling reaction of mixture **3** with a mixture of **4**{*1*−*3*} was performed under the standard reaction conditions. To compensate for the higher reactivity of **4**{*1*}, 1.66 equiv each of **4**{*2*} and **4**{*3*} were added with 0.33 equiv of **4**{*1*}. The pentaerythritol-supported combinatorial reaction allowed an efficient preparation of an alkylbiphenyl library in terms of reaction rate and atom economy. After 12 h of reaction and standard workup, all of the expected alkylbiphenyl derivatives **5** could be identified by GC analysis (Figure 2) and HPLC analysis (Figure 3). All **5** were consistently produced and identified from four independent combinatorial reactions started from **1**. The results are summarized in Table 3.

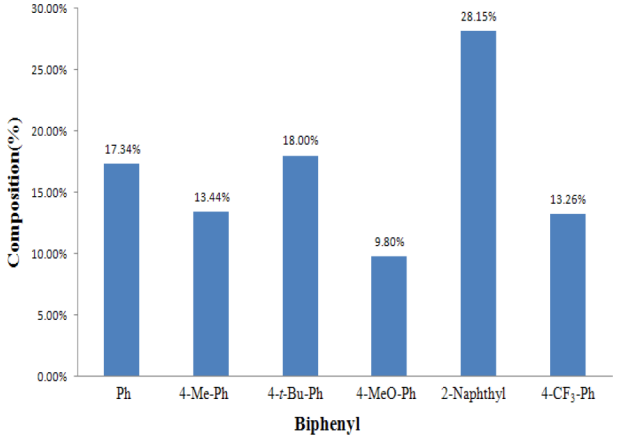


Figure 1. Average composition of biphenyl moieties in **3**.

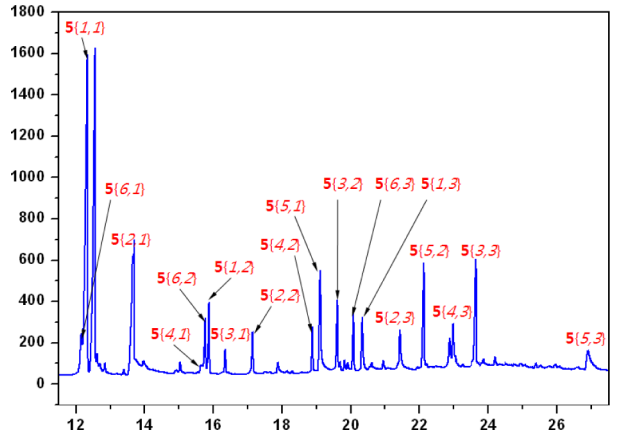
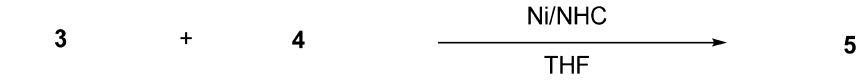
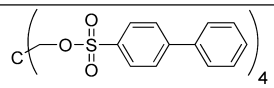
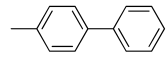
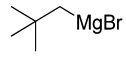
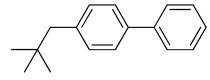
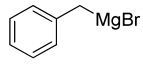
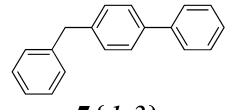
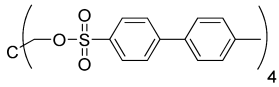
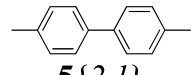
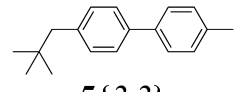
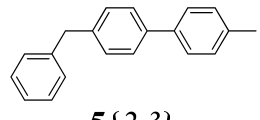
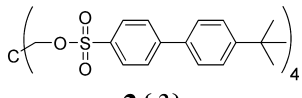
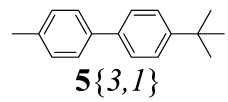
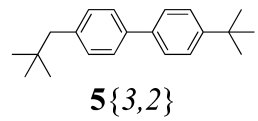
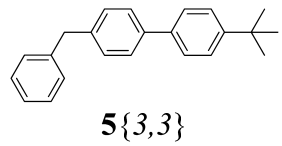
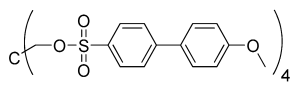
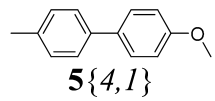
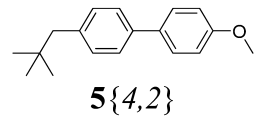
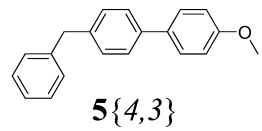


Figure 2. GC Analysis of **5** produced by combinatorial reaction of **3** with **4**.

dx.doi.org/10.1021/co400136k | ACS Comb. Sci. 2014, 16, 225−231

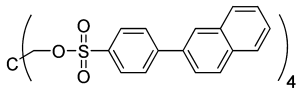
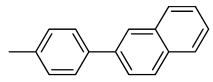
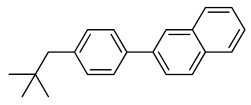
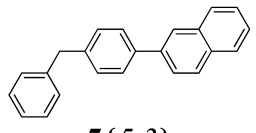
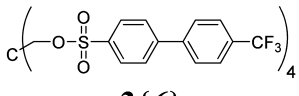
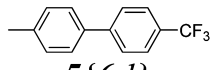
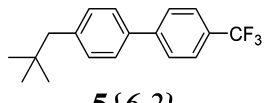
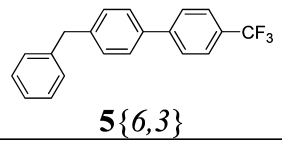
Table 1. Ni/NHC Catalyzed Coupling of 3 with 4 to Produce 5[a]



Entry	Sulfonate **3**	Grignard reagent **4**	Product **5**	Yield (%)[b]
1	 **3**{*1*}	CH_3MgBr **4**{*1*}	 **5**{*1,1*}	85
2	**3**{*1*}	 **4**{*2*}	 **5**{*1,2*}	81
3	**3**{*1*}	 **4**{*3*}	 **5**{*1,3*}	73
4	 **3**{*2*}	**4**{*1*}	 **5**{*2,1*}	86
5	**3**{*2*}	**4**{2}	 **5**{*2,2*}	80
6	**3**{*2*}	**4**{*3*}	 **5**{*2,3*}	72
7	 **3**{*3*}	**4**{*1*}	 **5**{*3,1*}	84
8	**3**{*3*}	**4**{*2*}	 **5**{*3,2*}	78
9	**3**{*3*}	**4**{*3*}	 **5**{*3,3*}	69
10	 **3**{*4*}	**4**{*1*}	 **5**{*4,1*}	85
11	**3**{*4*}	**4**{*2*}	 **5**{*4,2*}	76
12	**3**{*4*}	**4**{*3*}	 **5**{*4,3*}	70

dx.doi.org/10.1021/co400136k | *ACS Comb. Sci.* 2014, 16, 225−231

Table 1. continued

Entry	Sulfonate **3**	Grignard reagent **4**	Product **5**	Yield (%)[b]
13	 **3**{*5*}	**4**{*1*}	 **5**{*5,1*}	83
14	**3**{*5*}	**4**{*2*}	 **5**{*5,2*}	73
15	**3**{*5*}	**4**{*3*}	 **5**{*5,3*}	72
16	 **3**{*6*}	**4**{*1*}	 **5**{*6,1*}	79
17	**3**{*6*}	**4**{*2*}	 **5**{*6,2*}	75
18	**3**{*6*}	**4**{*3*}	 **5**{*6,3*}	70

[a]Reactions between **3** (0.100 mmol) and **4** (0.600 mmol) in THF (3.0 mL) were carried out at 25 °C in the presence of $Ni(acac)_2$ (0.0200 mmol) and IPr·HBF_4 (0.0200 mmol). [b]Isolated yield based on **3**.

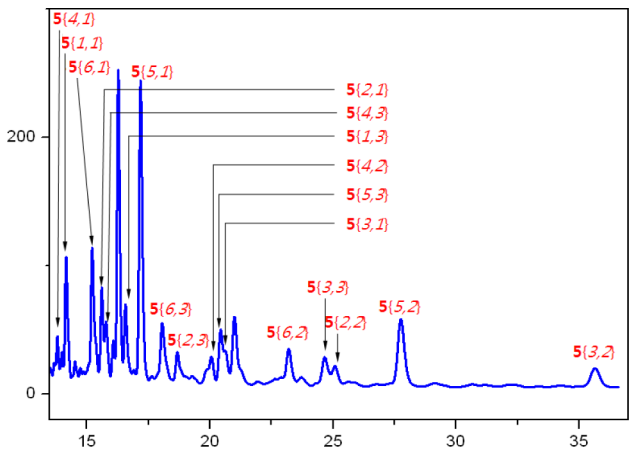


Figure 3. HPLC analysis of **5** produced by combinatorial reaction of **3** with **4**.

CONCLUSION

This study shows that pentaerythritol is an efficient tetrapodal soluble support for the parallel/combinatorial synthesis of various alkylbiphenyl compounds. A neopentyl core possessing four sulfonate linkers allowed the highly efficient traceless multifunctional cleavage of biphenyl moieties without any "memory," typically a polar functional group such as a hydroxyl, carboxyl, or amino group, of their attachment on the support. The reaction rate obtained using only 1.5 equiv of the nucleophiles, even at room temperature, made this approach more attractive. To the best of our knowledge, this is the first general application of sulfonate-based linkers on supports for the traceless preparation of an alkyl-substituted biphenyl library.

The synthetic strategy using pentaerythritol as a soluble support was observed to combine the benefits of both conventional reactions and SPOS. The homogeneous reaction conditions allowed a fast reaction rate and a convenient analysis of reaction progress expected in conventional solution-phase reactions. On the other hand, the facile isolation of intermediates by simple filtration through a small pad of silica gel made this approach as attractive as that with SPOS. In addition, inexpensive pentaerythritol is an atom-economical support that wastes only one equivalent of the small neopentyl core unit while producing four equivalents of alkylbiphenyls.

This small tetrapodal support would be an efficient and economical substitute for common polymer supports in the appropriate combinatorial chemistry. Especially, the traceless multifunctional release is believed to show potential for combinatorial synthesis of larger libraries of π-conjugated hydrocarbons.

dx.doi.org/10.1021/co400136k | *ACS Comb. Sci.* 2014, 16, 225−231

Table 2. Composition of 5 Produced by Reaction of 3 with Each of 4[a]

entry	R	Ar	5	composition (%)[b]	range (%)[b,c]
1	methyl	Ph	5{*1,1*}	13.83	10−29
2	methyl	4-Me-Ph	5{*2,1*}	15.25	11−16
3	methyl	4-*t*-Bu-Ph	5{*3,1*}	16.24	10−20
4	methyl	4-MeO-Ph	5{*4,1*}	8.21	7−10
5	methyl	2-naphthyl	5{*5,1*}	35.68	23−36
6	methyl	4-CF_3-Ph	5{*6,1*}	10.79	11−21
total				100	
7	neopentyl	Ph	5{*1,2*}	15.68	16−27
8	neopentyl	4-Me-Ph	5{*2,2*}	10.50	11−15
9	neopentyl	4-*t*-Bu-Ph	5{*3,2*}	19.00	15−19
10	neopentyl	4-MeO-Ph	5{*4,2*}	9.98	6−10
11	neopentyl	2-naphthyl	5{*5,2*}	36.41	20−36
12	neopentyl	4-CF_3-Ph	5{*6,2*}	8.43	8−16
total				100	
13	benzyl	Ph	5{*1,3*}	22.53	20−30
14	benzyl	4-Me-Ph	5{*2,3*}	14.58	14−19
15	benzyl	4-*t*-Bu-Ph	5{*3,3*}	18.77	18−24
16	benzyl	4-MeO-Ph	5{*4,3*}	11.20	7−11
17	benzyl	2-naphthyl	5{*5,3*}	12.36	12−22
18	benzyl	4-CF_3-Ph	5{*6,3*}	20.57	13−21
total				100	

[a]Reaction of **3** (40.0 mg, approximately 0.0349 mmol) with each of **4** (0.209 mmol, **4**{*1*}: 3.0 M in diethyl ether, 0.069 mL; **4**{*2*} and **4**{*3*}: 1.0 M in THF, 0.209 mL) was carried out in the presence of $Ni(acac)_2$ (1.80 mg, 7.0 μmol) and IPr·HBF_4 (3.33 mg, 7.0 μmol) in THF (3.0 mL) at 25 °C. [b]Relative composition based on GC area. [c]Composition range observed from four independent experiments from **1**.

Table 3. A Library of Alkylbiphenyls 5 Produced by Combinatorial Reaction[a]

entry	R	Ar	5	composition (%)[b]	range (%)[b,c]
1	methyl	Ph	5{*1,1*}	5.56	5−7
2	methyl	4-Me-Ph	5{*2,1*}	11.62	2−15
3	methyl	4-*t*-Bu-Ph	5{*3,1*}	1.71	2−7
4	methyl	4-MeO-Ph	5{*4,1*}	0.83	1−3
5	methyl	2-naphthyl	5{*5,1*}	11.35	4−22
6	methyl	4-CF_3-Ph	5{*6,1*}	4.35	3−14
7	neopentyl	Ph	5{*1,2*}	4.55	2−10
8	neopentyl	4-Me-Ph	5{*2,2*}	3.23	1−4
9	neopentyl	4-*t*-Bu-Ph	5{*3,2*}	5.68	2−6
10	neopentyl	4-MeO-Ph	5{*4,2*}	3.12	1−3
11	neopentyl	2-naphthyl	5{*5,2*}	8.50	3−9
12	neopentyl	4-CF_3-Ph	5{*6,2*}	4.22	2−9
13	benzyl	Ph	5{*1,3*}	5.08	5−14
14	benzyl	4-Me-Ph	5{*2,3*}	4.27	2−11
15	benzyl	4-*t*-Bu-Ph	5{*3,3*}	10.94	5−11
16	benzyl	4-MeO-Ph	5{*4,3*}	5.13	2−5
17	benzyl	2-naphthyl	5{*5,3*}	5.94	3−6
18	benzyl	4-CF_3-Ph	5{*6,3*}	3.91	2−6

[a]Reaction of **3** (240 mg, approximately 0.209 mmol) with **4** (totally 3.07 mmol) was carried out in the presence of $Ni(acac)_2$ (10.8 mg, 0.0418 mmol) and IPr·HBF_4 (19.9 mg, 0.0418 mmol) in THF (6.0 mL) at 25 °C. [b]Relative composition based on GC area. [c]Composition range observed from four independent experiments from **1**.

EXPERIMENTAL PROCEDURES

Solvents were distilled from appropriate drying agents prior to use: THF and DME from sodium-benzophenone ketyl as well as Et_2O and toluene from CaH_2. ^1H NMR (300, 500, or 600 MHz) and ^{13}C NMR (75 or 150 MHz) were acquired using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ units (ppm) by assigning the TMS resonance in the ^1H NMR spectrum as 0.00 ppm and the $CDCl_3$ resonance in the ^{13}C NMR spectrum as 77.2 ppm. All coupling constants (J) are reported in hertz (Hz). GC analyses were performed on a bonded 5% phenylpolysiloxane BPX 5 capillary column (SGE, 30 m, 0.32 mm i.d.). Electron impact (EI, 70 eV) was used as the ionization method for mass spectrometry.

General Procedure for Cross-Coupling Reactions of 3 with 4. To a stirred solution of **3** (0.100 mmol), $Ni(acac)_2$ (0.0200 mmol), and IPr·HBF_4 (0.0200 mmol) in THF (3.0 mL) under an argon atmosphere was slowly added the alkyl Grignard reagent **4** (0.600 mmol). The reaction mixture was stirred at room temperature for 12 h and diluted with Et_2O. The organic layer was washed with 1% aqueous HCl, water, and brine; dried over $MgSO_4$; and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel.

4-*t*-Butyl-4′-neopentylbiphenyl, 5{*3,2*}. 4-*t*-Butyl-4′-neopentylbiphenyl **5**{*3,2*} was prepared by the reaction of **3**{*3*} (122.6 mg, 0.100 mmol) with **4**{*2*} (1.0 M in THF, 0.600 mL, 0.600 mmol) in the presence of $Ni(acac)_2$ (5.10 mg, 0.0200 mmol) and IPr·HBF_4 (9.50 mg, 0.0200 mmol). The crude product was purified by column chromatography on silica gel to afford **5**{*3,2*} (87.5 mg, 78%) as a yellow solid: TLC R_f 0.88 (Et_2O/*n*-hexane = 1:4). mp 92−93 °C (uncorrected). ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 9H), 1.36 (s, 9H), 2.52 (s, 2H), 7.18 (d, J = 7.98 Hz, 2H), 7.45 (d, J = 8.32 Hz, 2H), 7.49 (d, J = 7.98 Hz, 2H), 7.53 (d, J = 8.32 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.4 (× 3), 31.4 (× 3), 31.8, 34.5, 49.9, 125.6 (× 2), 126.2 (× 2), 126.6 (× 2), 130.8 (× 2), 138.2, 138.4, 138.6, 149.9. HRMS (EI, 70 eV) calcd for $C_{21}H_{28}$ (M^+): 280.2191. Found: 280.2195.

2-(4-Neopentylphenyl)naphthalene, 5{*5,2*}. 2-(4-Neopentylphenyl)naphthalene **5**{*5,2*} was prepared by the reaction of **3**{*5*} (120.1 mg, 0.100 mmol) with **4**{*2*} (1.0 M in THF, 0.600 mL, 0.600 mmol) in the presence of $Ni(acac)_2$ (5.10 mg, 0.0200 mmol) and IPr·HBF_4 (9.50 mg, 0.0200 mmol). The crude product was purified by column chromatography on silica gel to afford **5**{*5,2*} (80.1 mg, 73%) as a white solid: TLC R_f 0.66 (Et_2O/*n*-hexane = 1:4). mp 87−88 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.56 (s, 2H), 7.24 (d, J = 8.19 Hz, 2H), 7.45−7.51 (m, 2H), 7.63 (d, J = 8.19 Hz, 2H), 7.76 (dd, J = 8.48, 1.72 Hz, 1H), 7.86 (d, J = 7.79 Hz, 1H), 7.89 (d, J = 7.17 Hz, 1H), 7.90 (d, J = 8.48 Hz, 1H), 8.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5 (× 3), 32.0, 50.0, 125.7, 125.8, 126.0, 126.5, 126.9 (× 2), 127.9, 128.4, 128.6, 131.3 (× 2), 132.8, 134.0, 138.7, 138.8, 139.3. HRMS (EI, 70 eV) calcd for $C_{21}H_{22}$ (M^+): 274.1722. Found: 274.1727.

4-Neopentyl-4′-trifluoromethylbiphenyl, 5{*6,2*}. 4-Neopentyl-4′-trifluoromethylbiphenyl **5**{*6,2*} was prepared by the reaction of **3**{*6*} (127.3 mg, 0.100 mmol) with **4**{*2*} (1.0 M in THF, 0.600 mL, 0.600 mmol) in the presence of $Ni(acac)_2$ (5.10 mg, 0.0200 mmol) and IPr·HBF_4 (9.50 mg, 0.0200 mmol). The crude product was purified by column chromatography on silica gel to afford **5**{*6,2*} (87.7 mg, 75%) as a white solid: TLC R_f 0.78 (Et_2O/*n*-hexane = 1:4). mp 71−72 °C (uncorrected). ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.55 (s, 2H), 7.23 (d, J = 7.89 Hz, 2H), 7.50 (d, J = 7.89 Hz, 2H), 7.68 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.4 (× 3), 31.9, 49.9, 124.3 (q, J = 271.85 Hz, 1C), 125.6 (q, J = 3.78 Hz, 2C), 126.4 (× 2), 127.2 (× 2), 129.0 (q, J = 32.49 Hz, 1C), 131.1 (× 2), 137.1, 140.0, 144.6. HRMS (EI, 70 eV) calcd for $C_{18}H_{19}F_3$ (M^+): 292.1439. Found: 292.1444.

dx.doi.org/10.1021/co400136k | ACS Comb. Sci. 2014, 16, 225−231

2-(4-Benzylphenyl)naphthalene, 5{*5,3*}. 2-(4-Benzylphenyl)naphthalene **5**{*5,3*} was prepared by the reaction of **3**{*5*} (120.1 mg, 0.100 mmol) with **4**{*3*} (1.0 M in THF, 0.600 mL, 0.600 mmol) in the presence of $Ni(acac)_2$ (5.10 mg, 0.0200 mmol) and IPr·HBF_4 (9.50 mg, 0.0200 mmol). The crude product was purified by column chromatography on silica gel to afford **5**{*5,3*} (84.8 mg, 72%) as a white solid: TLC R_f 0.76 (Et_2O/*n*-hexane = 1:4). mp 101−102 °C (uncorrected). ^1H NMR (600 MHz, $CDCl_3$): δ 4.05 (s, 2H), 7.20−7.26 (m, 3H), 7.31 (d, J = 8.01 Hz, 2H), 7.32 (t, J = 5.97, 7.41 Hz, 2H), 7.45−7.51 (m, 2H), 7.65 (d, J = 8.01, 2H), 7.73 (dd, J = 8.58, 1.85 Hz, 1H), 7.86 (d, J = 7.82 Hz, 1H), 7.88 (d, J = 9.43 Hz, 1H), 7.90 (d, J = 8.58 Hz, 1H), 8.02 (d, J = 0.40 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 41.6, 125.50, 125.52, 125.8, 126.1, 126.2, 127.5 (× 2), 127.6, 128.1, 128.3, 128.5 (× 2), 128.9 (× 2), 129.4 (× 2), 132.5, 133.7, 138.3, 138.9, 140.4, 141. HRMS (EI, 70 eV) calcd for $C_{23}H_{18}$ (M^+): 294.1409. Found, 294.1414.

4-Benzyl-4′-trifluoromethylbiphenyl, 5{*6,3*}. 4-Benzyl-4′-trifluoromethylbiphenyl **5**{*6,3*} was prepared by the reaction of **3**{*6*} (127.3 mg, 0.100 mmol) with **4**{*3*} (1.0 M in THF, 0.600 mL, 0.600 mmol) in the presence of $Ni(acac)_2$ (5.10 mg, 0.0200 mmol) and IPr·HBF_4 (9.50 mg, 0.0200 mmol). The crude product was purified by column chromatography on silica gel to afford **5**{*6,3*} (87.5 mg, 70%) as a white solid: TLC R_f 0.86 (Et_2O/*n*-hexane = 1:4). mp 64−65 °C (uncorrected). ^1H NMR (600 MHz, $CDCl_3$): δ 4.03 (s, 2H), 7.21−7.24 (m, 3H), 7.30 (d, J = 8.28 Hz, 2H), 7.32 (t, J = 7.40, 7.46 Hz, 2H), 7.53 (d, J = 8.24 Hz, 2H), 7.67 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 41.6, 124.3 (q, J = 271.84 Hz, 1C), 125.7 (q, J = 3.79 Hz, 2C), 126.2, 127.2 (× 2), 127.3 (× 2), 128.6 (× 2), 128.9 (× 2), 129.4 (q, J = 42.55 Hz, 1C), 129.7 (× 2), 137.5, 140.7, 141.4, 144.5. HRMS (EI, 70 eV) calcd for $C_{20}H_{15}F_3$ (M^+): 312.1128. Found: 312.1133.

Procedure for Combinatorial Reaction of 1 with 2. To a solution of **1** (400 mg, 0.396 mmol) and $Pd(PPh_3)_4$ (9.13 mg, 0.0792 mmol) in toluene (16 mL) was added 2.0 M aq. Na_2CO_3 (1.58 mL, 3.16 mmol). To the resulting mixture was added **2**{*1*−*6*} (**2**{*1*}, 32.2 mg; **2**{*2*}, 35.9 mg; **2**{*3*}, 47.0 mg; **2**{*4*}, 40.1 mg; **2**{*5*}, 45.4 mg; and **2**{*6*}, 50.1 mg; 0.264 mmol each) dissolved in EtOH (4.0 mL). The reaction mixture was refluxed for 8 h with vigorous stirring and then cooled to room temperature. The residue was diluted with CH_2Cl_2. The organic layer was washed with 1% aqueous HCl, water, and brine; dried over $MgSO_4$; and concentrated in vacuo. The resulting crude product was dissolved in ether and passed through a small pad of silica gel to generate **3** as a yellow powder, which did not show a noticeable amount of impurity by TLC analysis.

Procedure for Combinatorial Cross-Coupling Reaction of 3 with 4. To a stirred solution of **3** (240 mg, approximately 0.209 mmol), $Ni(acac)_2$ (10.8 mg, 0.0418 mmol), and IPr·HBF_4 (19.9 mg, 0.0418 mmol) in THF (6.0 mL) under an argon atmosphere were slowly added the alkyl Grignard reagents **4**{*1*} (3.0 M in diethyl ether, 0.093 mL, 0.279 mmol), **4**{*2*} (1.0 M in THF, 1.395 mL, 1.395 mmol), and **4**{*3*} (1.0 M in THF, 1.395 mL, 1.395 mmol). The reaction mixture was stirred at room temperature for 12 h and diluted with CH_2Cl_2. The organic layer was washed with 1% aqueous HCl, water, and brine; dried over $MgSO_4$; and concentrated in vacuo.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Further details on the experimental procedures and spectra are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Chung-Ang University Excellent Student Scholarship in 2014 and the National Research Foundation of Korea Grant funded by the Korean Goverment (MEST). (NRF-2012R1A1A2043846).

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