Title
Phosphine-Mediated Multi-Component γ-Umpolung/Aldol/Wittig Cascade Reaction for the Synthesis of Functionalized Naphthalenes

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Publication Date
2013

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Phosphine-Mediated Multi-Component γ-Umpolung/Aldol/Wittig Cascade Reaction for the Synthesis of Functionalized Naphthalenes

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Chemistry

by

Kui Zhang

2013

Abstract

Phosphine-Mediated Multi-Component γ-Umpolung/Aldol/Wittig Cascade Reaction for the Synthesis of Functionalized Naphthalenes

by

Kui Zhang

Master of Science in Chemistry

University of California, Los Angeles, 2013

Professor Ohyun Kwon, Chair

This study describes an efficient and convenient triphenylphosphine-mediated γ-umpolung/aldol/Wittig cascade reaction. This is the first time that phosphines have been used to mediate a multi-component coupling reaction involving allenoates, nucleophiles, and substituted *o*-phthalaldehydes to synthesize naphthalenes. The reaction conditions have been optimized and employed in the synthesis of eight functionalized naphthalenes. This reaction proceeds under mild conditions and produces good to excellent yields.

The thesis of Kui Zhang is approved.

Paula L. Diaconescu

Yves Rubin

Ohyun Kwon, Committee Chair

University of California, Los Angeles

2013

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Acknowledgements

I gratefully acknowledge the help of my supervisor, Professor Ohyun Kwon, who has offered me valuable suggestions in my academic endeavors. Without her patient instruction, insightful criticism, and expert guidance, the completion of this thesis would not have been possible. I would also like to thank Professor Diaconescu and Professor Rubin for serving on my thesis committee.

My thanks also go to Dr. Qihai Xu, who, despite having practically no spare time, still managed to provide me with ample help and advice.

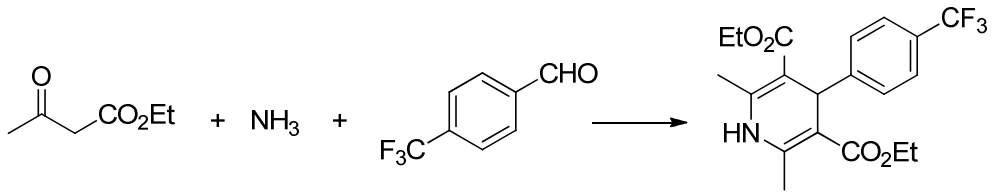
I would finally like to express my gratitude to my husband and my parents, who helped me out in difficulties and supported me without a word of complaint.

Introduction

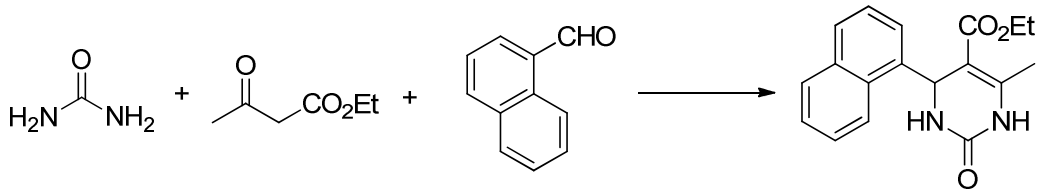
The "optimized synthesis" of a desired product involves a simple one pot procedure that is environmental friendly and employs commercially available starting materials. In that vein, multi-component reactions (MCRs) represent excellent examples of optimized syntheses, because structurally complex molecules are formed in one pot from a multitude of starting materials.[1] By reducing the number of reaction steps and starting from simple, inexpensive starting materials, the cost of constructing highly diverse and complex small molecules is reduced to a minimum. In addition, both waste production and human labor costs are significantly reduced. MCRs also allow systematic variations in reaction components and offer possibilities for automation because of their experimental simplicity. Well-known MCRs include the Strecker,[2] Hantzsch,[3] Biginelli,[4] Mannich,[5] Passerini,[6] and Ugi[7] reactions (Schemes 1–6).

Scheme 1. Strecker reaction.

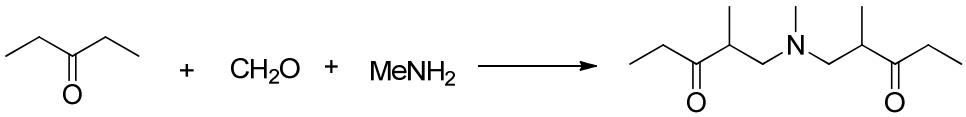
Scheme 2. Hantzsch reaction.



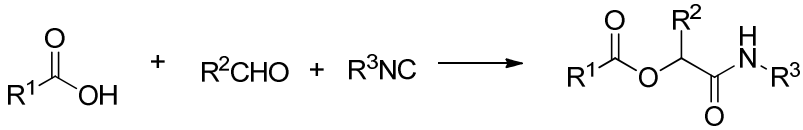
Scheme 3. Biginelli reaction.



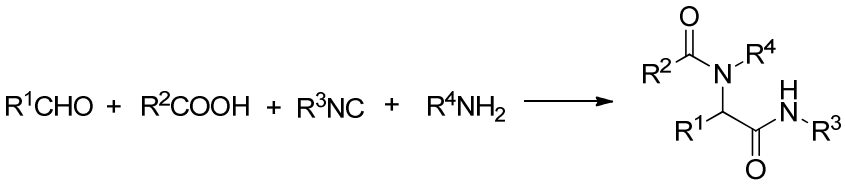
Scheme 4. Mannich reaction.



Scheme 5. Passerini reaction.



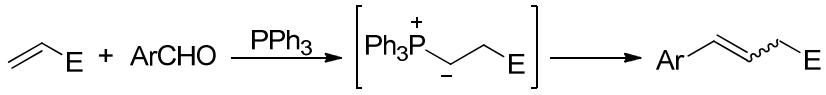
Scheme 6. Ugi reaction.



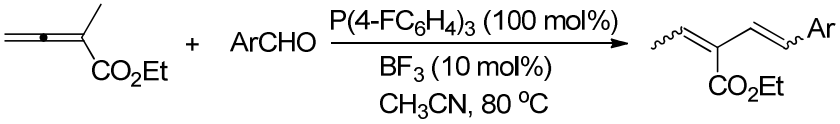
The phosphine-mediated Wittig olefination was originally reported by Oda and co workers in 1964. This also marked the first phosphine-mediated reaction between an olefin and an aldehyde (Scheme 7).[8] In recent years, our group[9] and He[10] reported phosphine-mediated vinylogous Wittig reactions of α-methyl allenoates with aldehydes (Schemes 8 and 9). During the same time, intramolecular Wittig reactions of in situ-generated ylides from activated olefins have been developed for the synthesis of pyrroles,[11] furans,[12] and dienones (Scheme 10–12).[13] However, intramolecular Wittig

reactions involving an allenoate have rarely been reported. Only Virieux reported the formation of a pyrrolizine as a minor product (6%) from the annulation of an allenoate and pyrrole-2-carboxaldehyde (Scheme 13).[14]

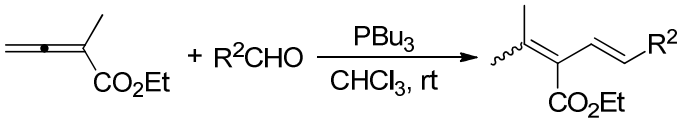
Scheme 7. Phosphine-mediated Wittig olefination.



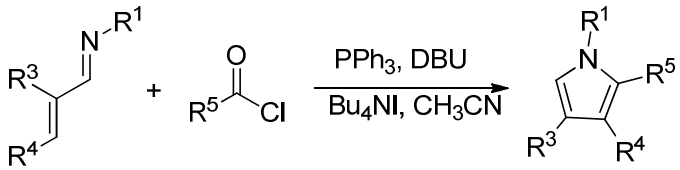
Scheme 8. Phosphine-mediated vinylogous Wittig reaction.



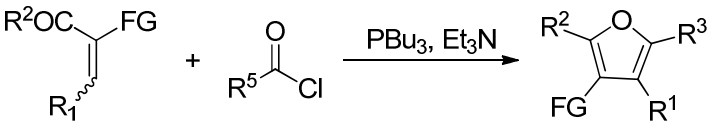
Scheme 9. Phosphine-mediated vinylogous Wittig reaction.



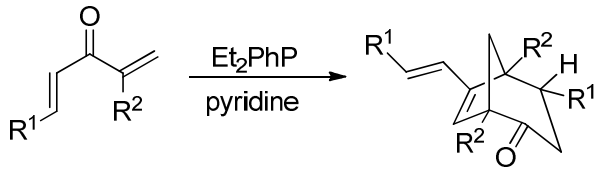
Scheme 10. Intramolecular Wittig reactions for the synthesis of pyrroles.



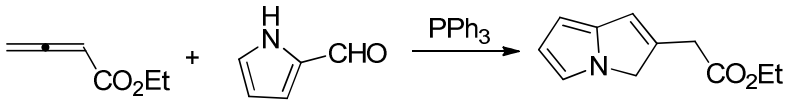
Scheme 11. Intramolecular Wittig reactions for the synthesis of furans.



Scheme 12. Intramolecular Wittig reactions for the synthesis of dienones.

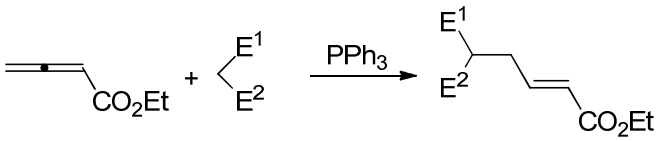


Scheme 13. Intramolecular Wittig reactions involving an allenoate.

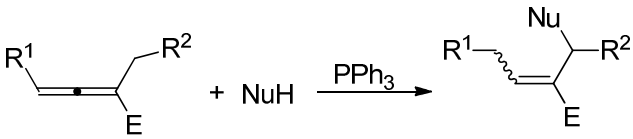


Phosphine catalysts have been used in reactions between electron-deficient allenes and nucleophiles, electrophiles, electrophile-nucleophiles, or dinucleophiles. Selective examples of phosphine catalysis reactions include the *γ*-umpolung addition,[15] the *β'*-umpolung addition,[16] the *γ*-umpolung-Michael [n + 2] annulation,[17] the double-Michael [4 + 1] annulation,[18] and the *γ*-umpolung-S_N2' [4 + n] annulation (Schemes 14–18).[19]

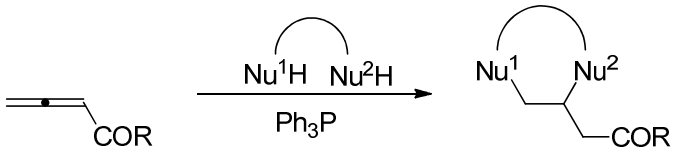
Scheme 14. *γ*-Umpolung addition.



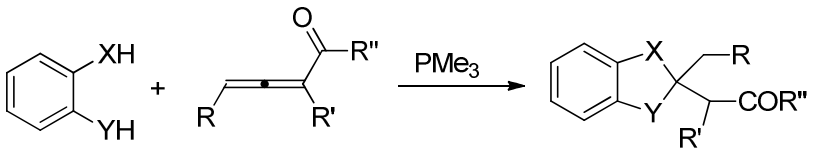
Scheme 15. *β'*-Umpolung addition.



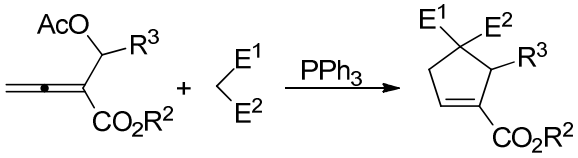
Scheme 16. γ-Umpolung-Michael [n + 2] annulation.



Scheme 17. Double-Michael [4 + 1] annulation.

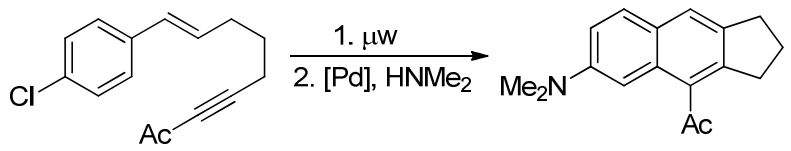


Scheme 18. γ-Umpolung-S_N2' [4 + n] annulation.

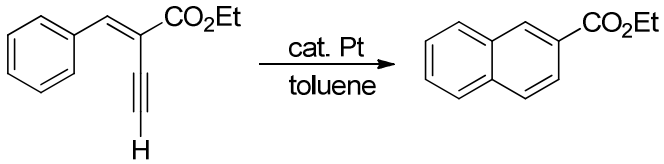


Functionalized naphthalene compounds can serve as valuable building blocks for the synthesis of small molecules in many important areas, such as pharmaceuticals, chiral reagents, liquid crystals, and organic dyes.[20] Recent syntheses functionalized naphthalenes have been realized through Diels-Alder reaction,[21] platinum-catalyzed hydroarylation,[22] and palladium-catalyzed bisolefination (Schemes 19–21).[23] However, these methods need to use expensive transition metals or need several steps to make the starting materials. Herein, we report our study on a γ-umpolung/aldol/Wittig reaction cascade employing an easily available allenoate, a nucleophilic reagent, and a substituted *o*-phthalaldehyde, to synthesize naphthalenes. To the best of our knowledge, there have been no previous reports of phosphine-mediated multi-component reactions involving an allenoate for the synthesis of naphthalenes.

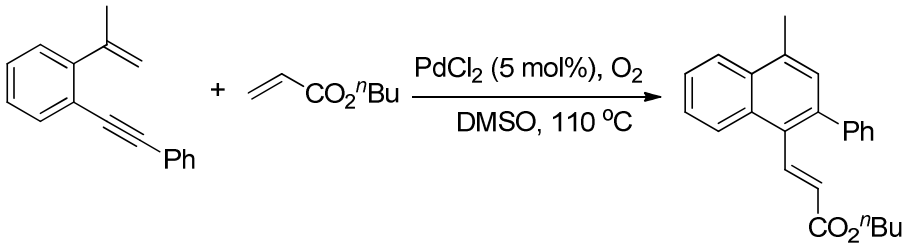
Scheme 19. Synthesis of functionalized naphthalenes through Diels-Alder reaction.



Scheme 20. Synthesis of functionalized naphthalenes through platinum-catalyzed hydroarylation.



Scheme 21. Synthesis of functionalized naphthalenes through palladium-catalyzed bisolefination.



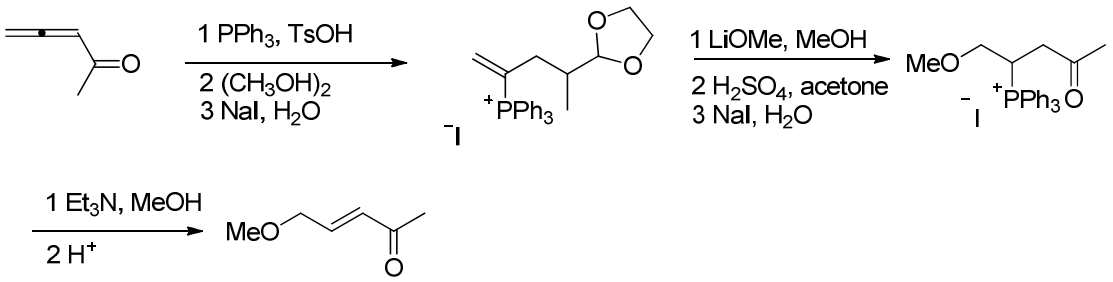
Results

Unlike phosphine catalyzed Michael additions of electron-deficient olefins with nucleophiles, γ-umpolung reaction take place when electron-deficient allenes are reacted with nucleophiles in the presence of a phosphine catalyst. The concept of γ-umpolung addition to activated allenoates was first exercised by Cristau in 1982,[24] not under catalytic conditions, but rather by treating the isolated vinyl phosphonium iodide with methanol in the presence of lithium methoxide. About a decade later (1994), a catalytic variant of the γ-umpolung reaction of activated allenonates was

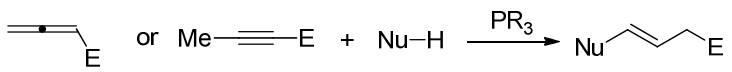
developed by Trost.[25] According to the proposed mechanism, both 2,3-butadienoate ester and 2-butynoate are suitable for the reaction and proceed through a common phosphonium dienolate intermediate. In our work, we thought that the γ-umpolung addition between an allenoate and *p*-toluenesulfonamide should proceed first and a plausible reaction mechanism is depicted in Scheme 24.

The reaction is initiated by the nucleophilic addition of triphenylphosphine to the electron-deficient allenoate ester **3a** to produce the zwitterionic intermediate **5**. The enolate **5** deprotonates *p*-toluenesulfonamide (**2a**) to generate nucleophilic species **7** and the vinylphosphonium cation **6**. Next, nucleophilic addition of **7** to the vinylphosphonium **6** yields the ylide **8**. Then, intermediate **9** is obtained through proton transfer, which is intercepted by *o*-phthalaldehyde (**1**) through an aldol reaction to obtain alkoxide **10**. After further proton transfer, compound **11** undergoes intramolecular Wittig reaction to form compound **12**, which aromatizes spontaneously to produce **4a** by elimination of water.

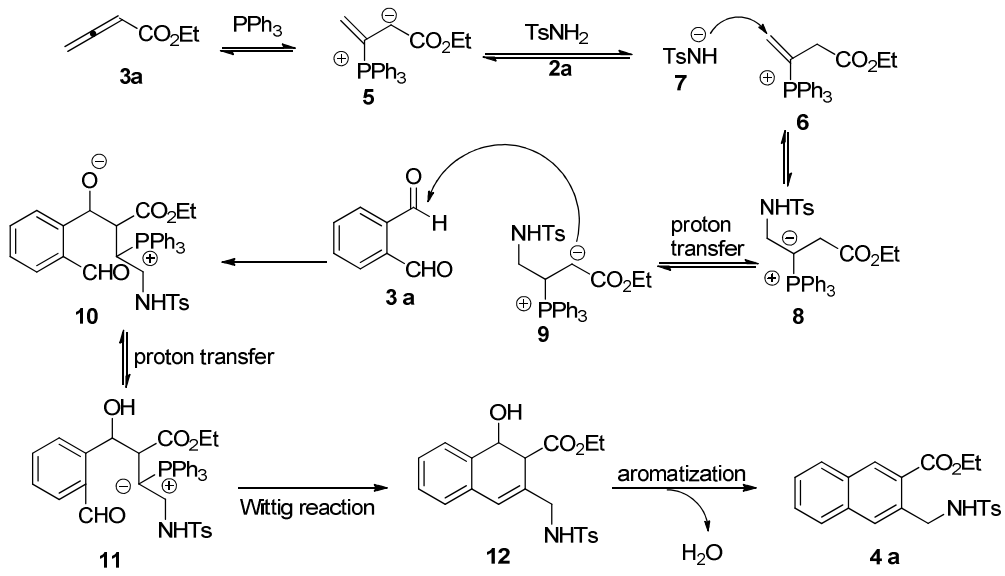
Scheme 22. The first reported umpolung addition to activated allenoates mediated by triphenylphosphine.



Scheme 23. The first umpolung addition to activated allenoates catalyzed by triphenylphosphine.

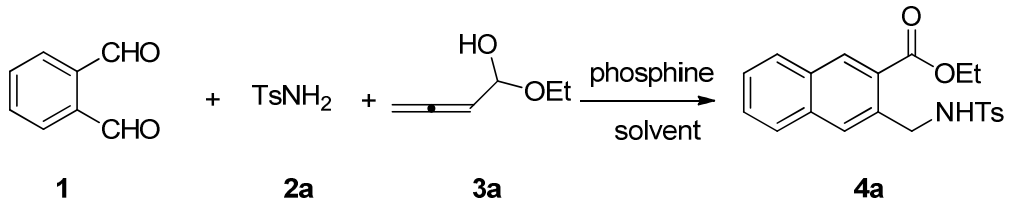


Scheme 24. Proposed mechanism for the γ-umpolung/aldol/Wittig reaction.



In order to determine optimal reaction conditions, we tested several reaction variables including solvents, phosphines, ratios of the starting materials, reaction time, and reaction temperature. We initiated our investigation by using *o*-phthalaldehyde (**1**), *p*-toluenesulfonamide (**2a**) and ethyl buta-2,3-dienoate (**3a**) to establish the reaction conditions (Table 1). First, we screened several nucleophilic phosphines and found that triphenylphosphine gave the best yield (33%) (Table 1, Entry 1). Several other phosphines were examined. Tris(4-chlorophenyl)phosphine, tris(3-fluorophenyl)phos -phine, and tris(3,5-bis(trifluoromethyl)phenyl)phosphine also gave the desired product, but the yields were lower compared to the use of triphenylphosphine as the phosphine source (entries 2–4). Tributylphosphine, ethyldiphenylphosphine, and tri-(*o*-tolyl) -phosphine failed to facilitate this reaction (entries 5–7). Having selected triphenylphosphine as the optimum source of phosphine, solvents were then screened. We found that toluene, benzene, THF, DCM, and dioxane failed to improve the yields of the reactions (entries 8–12).

Table 1. Optimization of solvents and phosphines for the γ-umpolung/aldol/Wittig reaction.[a]



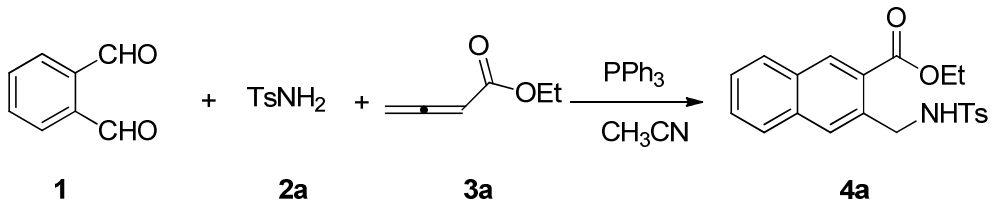
Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]
1	CH_3CN	PPh_3	18	33
2	CH_3CN	$P(p\text{-}ClC_6H_4)_3$	18	26
3	CH_3CN	$P(m\text{-}FC_6H_4)_3$	18	22
4	CH_3CN	$P[m,m\text{-}(CF_3)_2C_6H_3]_3$	18	14
5	CH_3CN	$P(n\text{-}Bu)_3$	18	no reaction
6	CH_3CN	$PEtPh_2$	18	no reaction
7	CH_3CN	$P(o\text{-}CH_3C_6H_4)_3$	18	no reaction
8	PhH	PPh_3	18	26
9	$PhCH_3$	PPh_3	18	25
10	THF	PPh_3	18	6
11	CH_2Cl_2	PPh_3	18	28
12	1,4-dioxane	PPh_3	18	-

[a] Conditions: **1** (0.5 mmol), **2a** (1 equiv) and phosphine (1 equiv) were dissolved in the above solvent (3 mL), followed by the addition of **3a** (1 equiv) at room temperature. [b] Based on ^{1}H NMR analysis of the crude product.

After screening the phosphines and solvents, the reaction was still producing low yields. We thought that the yields could be improved by changing the concentration of the reaction mixture (as we had experienced before)[26] and the ratio of the substrates, as

well as by slowing the addition of the allenoate **3a**. First, we tried different ratios of substrates: the yields increased to 52% when we used the ratio **1**:**2a**:**3a**:PPh_3 = 1:2:2:1 (Table 2, entries 1–3). Then, we tried a substrate ratio of **1**:**2a**:**3a**:PPh_3 = 1:2:3:1 and in more dilute solutions, found that the yield improved to 73% (Table 2, entry 4). Next, we optimized the reaction temperature and time, and obtained naphthalene **4a** in 84% yield when the reaction was run at 0 ^{o}C for 18 h (Table 2, entries 5–8). However, the yields did not improve when we changed the concentration of the reaction system to be either more dilute or concentrated (Table 2, entries 9 and 10). Thus, the optimized reaction condition was established: this was a ratio of **1**:**2a**:**3a**:PPh_3 = 1:2:3:1 with triphenylphosphine as the mediator in CH_3CN as solvent at 0 ^{o}C.

Table 2. Optimization of the ratio of the substrates, reaction time and temperature for the γ-umpolung/aldol/Wittig reaction.



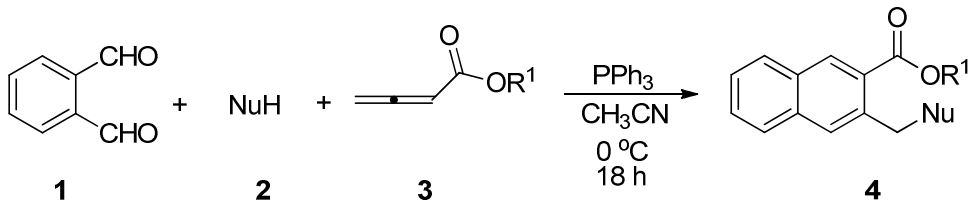
Entry	Ratio (1:2a:3a:PPh_3)	Concentration (M)[a]	Time (h)	Temp (^{o}C)	Yield (%)
1	1:1:1:1	0.080	18	rt	33
2	1:2:2:2	0.080	18	rt	50
3	1:2:2:1	0.080	18	rt	52
4	1:2:3:1	0.042	18	rt	73
5	1:2:3:1	0.042	18	50	53
6	1:2:3:1	0.042	18	0	84

7	1:2:3:1	0.042	2	0	38
8	1:2:3:1	0.042	13	0	55
9	1:2:3:1	0.036	18	0	78
10	1:2:3:1	0.050	18	0	65

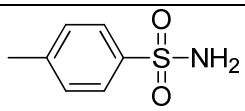
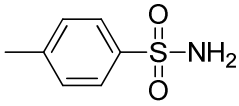
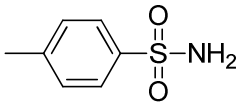
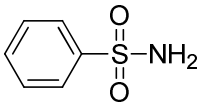
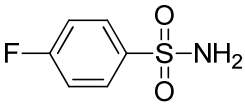
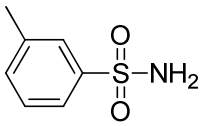
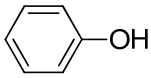
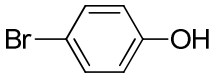
[a] Concentration of the *o*-phthalaldehyde.

Employing this satisfactory reaction condition for the phosphine-mediated *γ*-umpolung/aldol/Wittig reaction, we explored the scope of this cascade reaction with *o*-phthalaldehyde **1**, nucleophiles **2a-c**, and allenoates **3a-c**. The results are summarized in Table 3. We found that ethyl (**3a**), benzyl (**3b**), and (trimethylsilyl)ethyl (**3c**) allenoates reacted well (Table 3, entries 1–3). In particular, product **4b** could be obtained in quantitative yield when benzyl allenoate was used (Table 3, entries 2). With substituted benzenesulfonamides **2b-e**, the highest yield was obtained when electron-rich *p*-toluenesulfonamide (**2a**) was used (Table 3, entries 1 and 4–6). When we used phenol and *p*-bromophenol as nucleophilic reagents, we also obtain the desired naphthalenes in excellent yields (Table 3, entries 7 and 8).

Table 3. Triphenylphosphine-mediated *γ*-umpolung/aldol/Wittig reaction involving allenoates **3a-c** to offered naphthalene derivetives **4a-h**.



Entry	NuH	R^1	Yield (%)[a]

1	 **(2a)**	Et **(3a)**	**4a**, 84
2	 **(2a)**	Bn **(3b)**	**4b**, 99
3	 **(2a)**	$(CH_2)_2TMS$ **(3c)**	**4c,** 87
4	 **(2b)**	Et **(3a)**	**4d**, 88
5	 **(2c)**	Et **(3a)**	**4e**, 78
6	 **(2d)**	Et **(3a)**	**4f,** 70
7	 **(2e)**	Et **(3a)**	**4g**, 99
8	 **(2f)**	Et **(3a)**	**4h,** 95

[a] Isolated yield.

Conclusion

We have developed a highly efficient triphenylphosphine-mediated multicomponent *γ*-umpolung/aldol/Wittig cascade reaction. This reaction incorporates allenoates **3a-c**, *o*-phthalaldehyde (**1**), and nucleophilic reagents **2a-f** to synthesize naphthalene derivatives **4a-h** in one pot. We have optimized the reaction conditions and synthesized eight naphthalene derivatives in good to excellent yields. In the future, we plan to continue our investigation on the substrate scope, including changing the nucleophilic

reagents and using substituted *o*-phthalaldehydes, as well as the potential applications of this methodology.

Supporting Information

All reactions were performed in dry solvents under an Ar atmosphere and anhydrous conditions. DCM, THF, and MeCN were freshly distilled over CaH_2 prior to use. All other reagents were used as received from commercial sources. Reactions were monitored through thin layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates and visualized under UV light. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60-Å pore size, 40–63 μm). IR spectra were recorded using a Jasco FT-IR 4100 spectrometer. NMR spectra of the naphthalenes **4** were recorded using Bruker Avance-300, Bruker Avance-400 and Bruker Avance-500 instruments, calibrated to $CD(H)Cl_3$ as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C NMR spectra, respectively). ^{1}H NMR spectral data are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectral data are reported in terms of chemical shift (δ, ppm) and multiplicity, with the coupling constant (Hz) in the case of $J_{C–F}$ coupling. The following abbreviations indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectra were recorded using a Waters LCT Premier XE time-of-flight instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the multi-mode ionization source. The lock mass standard for accurate mass determination was leucine enkephalin (Sigma L9133

Experimental Procedures

General Procedure for the Synthesis of Naphthalene Derivatives 4a-h.

o-Phthalaldehyde **1** (0.5 mmol, 67 mg), nucleophilic reagents **2a-e** (2 equiv), Ph_3P (1 equiv, 131 mg) and MeCN (4 mL) were added sequentially to a flame-dried flask (25 mL) and then cooled to 0 ^oC. The allenoates **3a-c** (3 equiv) in MeCN (8 mL) were added dropwise over 4 h, and then the reaction mixture was stirred under Ar at 0 ^oC for 18 h. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure and the product was purified by flash column chromatography of silica gel [EtOAc/hexanes, 1:6] to yield the desired naphthalene product **4a-h**.

Ethyl 3-((4-methylphenylsulfonamido)methyl)-2-naphthoate (**4a**). Following the general procedure, *o*-phthalaldehyde **1** (0.5 mmol, 67 mg), *p*-toluenesulfonamide **2a** (2 equiv, 171 mg), Ph_3P (1 equiv, 131 mg), and ethyl buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4a** (160 mg, 84% yield) as a pale yellow oil; IR (film) ν_{max} 3252, 2927, 1710, 1321, 1282, 1157, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.43 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.61–7.58 (m, 3H), 7.54–7.50 (m, 1H), 7.01 (d, J = 8.0 Hz, 2H), 6.00 (t, J = 7.2 Hz, 1H), 4.51 (d, J = 6.8 Hz, 2H), 4.40 (q, J = 7.2, 6.8 Hz, 2H), 2.21 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 142.7, 138.0, 134.8, 133.2, 132.9, 131.8, 130.9, 129.2, 128.8, 128.7, 127.6, 127.0, 126.9, 126.3, 61.5, 47.4, 21.3, 14.3; HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{21}H_{21}NO_4S$ 384.1270, found 384.1256.

Benzyl 3-((4-methylphenylsulfonamido)methyl)-2-naphthoate (**4b**). Following the general procedure, *o*-phthalaldehyde **1** (0.5 mmol, 67 mg), *p*-toluenesulfonamide **2a** (2

equiv, 171 mg), Ph_3P (1 equiv, 131 mg), and benzyl buta-2,3-dienoate **3b** (3 equiv, 261 mg) were employed to give **4b** (222 mg, 99% yield) as a pale yellow oil; IR (film) ν_{max} 3277, 3031, 2944, 1707, 1278, 1150, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.60–7.56 (m, 1H), 7.54–7.44 (m, 7 H), 7.39–7.36 (m, 3H), 6.95 (d, J = 8.0 Hz, 2H), 5.99 (t, J = 6.8 Hz, 1H), 4.53 (d, J = 6.8 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 142.7, 138.0, 135.7, 134.8, 133.2, 133.2, 131.8, 130.9, 129.2, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 127.7, 127.1, 126.9, 67.2, 47.4, 21.3; HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{26}H_{24}NO_4S$ 446.1426, found 446.1430.

2-(Trimethylsilyl)ethyl 3-((4-methylphenylsulfonamido)methyl)-2-naphthoate (**4c**). Following the general procedure, *o*-phthalaldehyde **1** (0.5 mmol, 67 mg), *p*-toluenesulfonamide **2a** (2 equiv, 171 mg), Ph_3P (1 equiv, 131 mg), and ethyl 2-(trimethylsilyl)ethyl buta-2,3-dienoate **3c** (3 equiv, 276 mg) were employed to give **4c** (198 mg, 87% yield) as a colorless oil; IR (film) ν_{max} 3300, 3058, 2953, 1701, 1280, 1157, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.85–7.82 (m, 1H), 7.75–7.72 (m, 1H), 7.64 (s, 1H), 7.61–7.56 (m, 3H), 7.54–7.49 (m, 1H), 7.01–6.98 (m, 2H), 6.03 (t, J = 6.9 Hz, 1H), 4.51 (d, J = 6.9 Hz, 2H), 4.46–4.40 (m, 2 H), 2.20 (s, 3H), 1.20–1.15 (m, 2H), 012 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 142.7, 138.1, 134.7, 133.2, 133.0, 131.9, 130.9, 129.2, 128.7, 128.7, 127.7, 127.0, 126.9, 126.5, 63.9, 47.5, 21.3, 17.6, –1.4; HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{24}H_{30}NO_4SSi$ 456.1665, found 456.1674.

Ethyl 3-(phenylsulfonamidomethyl)-2-naphthoate (**4d**). Following the general procedure, *o*-phthalaldehyde **1** (0.5 mmol, 67 mg), phenylsulfonamide **2b** (2 equiv,

157 mg), Ph_3P (1 equiv, 131 mg), and ethyl buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4d** (163 mg, 88% yield) as a pale yellow oil; IR (film) ν_{max} 3271, 3058, 2980, 1705, 1283, 1160, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.72–7.70 (m, 3H), 7.59–7.50 (m, 3H), 7.34–7.29 (m, 1H), 7.25–7.21 (m, 1H), 6.08 (t, J = 7.2 Hz, 1H), 4.52 (d, J = 7.2 Hz, 2H), 4.38 (q, J = 7.2, 6.8 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 141.0, 134.8, 133.2, 133.0, 132.0, 131.9, 130.9, 128.8, 128.7, 128.7, 127.7, 127.1, 126.8, 126.3, 61.5, 47.4, 14.3; HRMS (ESI-TOF) m/z $[M–H]^+$ Calcd for $C_{20}H_{18}NO_4S$ 368.0956, found 368.0971.

Ethyl 3-((4-fluorophenylsulfonamido)methyl)-2-naphthoate (**4e**). Following the general procedure, the *o*-Phthalaldehyde **1** (0.5 mmol, 67 mg), 4-fluoro -benzenesulfonamide **2c** (2 equiv, 175 mg), Ph_3P (1 equiv, 131 mg), and ethyl buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4d** (150 mg, 78% yield) as a pale yellow oil; IR (film) ν_{max} 3206, 3067, 2982, 1708, 1281, 1134, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.87–7.85 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.70–7.67 (m, 3H), 7.62–7.58 (m, 1H), 7.56–7.52 (m, 2H), 7.48–7.44 (m, 1H), 6.12 (t, J = 6.8 Hz, 1H), 4.53 (d, J = 6.8 Hz, 2H), 4.39 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.5 (d, $J_{C–F}$ = 252.5 Hz, 1C), 137.2 (d, $J_{C–F}$ = 3.2 Hz, 1C), 134.7, 133.1, 133.0, 131.9, 130.9, 129.5 (d, $J_{C–F}$ = 9.2 Hz, 1C), 129.0, 128.8, 128.6, 128.5, 127.6, 127.2, 126.2, 115.7 (d, $J_{C–F}$ = 22.4 Hz, 1C), 61.6, 47.5, 14.3 ; HRMS (ESI-TOF) m/z $[M–H]^+$ Calcd for $C_{20}H_{17}FNO_4S$ 386.0862, found 386.0878.

Ethyl 3-((3-methylphenylsulfonamido)methyl)-2-naphthoate (**4f**). Following the general procedure, the *o*-Phthalaldehyde **1** (0.5 mmol, 67 mg), 3-methylbenzene -sulfonamide **2d** (2 equiv, 171 mg), Ph_3P (1 equiv, 131 mg), and ethyl

buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4d** (134 mg, 70% yield) as a pale yellow oil; IR (film) ν_{max} 3284, 2981, 1708, 1218, 1154, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 8.39 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.59–7.53 (m, 2H), 7.52–7.48 (m, 1H), 7.37 (s, 1H), 7.12–7.06 (m, 2H), 6.07 (t, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 2.06 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 140.9, 138.8, 134.7, 133.1, 132.9, 132.6, 131.9, 131.0, 128.8, 128.7, 128.5, 127.7, 127.2, 127.1, 126.1, 123.8, 61.5, 47.6, 20.9, 14.3; HRMS (ESI-TOF) m/z $[M–H]^+$ Calcd for $C_{21}H_{20}NO_4S$ 382.1113, found 382.1111.

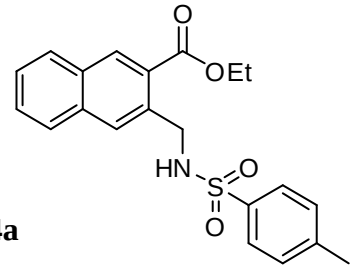
Ethyl 3-(phenoxymethyl)-2-naphthoate (**4g**). Following the general procedure, the *o*-Phthalaldehyde **1** (0.5 mmol, 67 mg), phenol **2e** (2 equiv, 94 mg), Ph_3P (1 equiv, 131 mg), and ethyl buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4d** (190 mg, 99% yield) as a colorless oil; IR (film) ν_{max} 3020, 2978, 1700, 1279, 1173, 1014 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.16 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.62–7.51 (m, 2H), 7.37–7.32 (m, 2H), 7.11–7.08 (m, 2H), 7.03–6.98 (m, 1H), 5.62 (d, *J* = 0.9 Hz, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 157.9, 134.9, 134.0, 132.5, 132.3, 131.7, 128.8, 128.6, 127.8, 126.9, 126.8, 126.2, 116.8, 113.1, 68.9, 61.3, 14.4; HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{20}H_{19}O_3$ 307.1334, found 307.1342.

Ethyl 3-((4-bromophenoxy)methyl)-2-naphthoate (**4h**). Following the general procedure, the *o*-Phthalaldehyde **1** (0.5 mmol, 67 mg), 3-bromophenol **2f** (2 equiv, 172 mg), Ph_3P (1 equiv, 131 mg), and ethyl buta-2,3-dienoate **3a** (3 equiv, 168 mg) were employed to give **4h** (182 mg, 95% yield) as a colorless oil; IR (film) ν_{max} 3057, 2979,

1707, 1486, 1278, 1199, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.08 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.61–7.53 (m, 2H), 7.40 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 5.57 (s, 2H), 4.41 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 158.9, 134.9, 134.6, 132.4, 131.7, 129.6, 128.8, 128.7, 127.9, 126.9, 126.7, 126.4, 121.0, 115.0, 68.7, 61.3, 14.4; HRMS (ESI-TOF) m/z $[M+H]^+$ Calcd for $C_{20}H_{18}BrO_3$ 387.0421, found 387.0406.

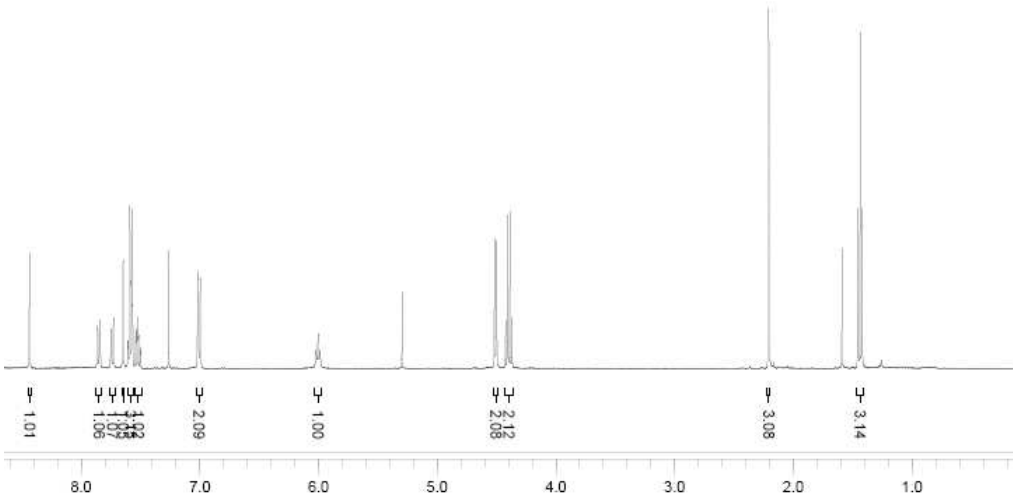
Appendix

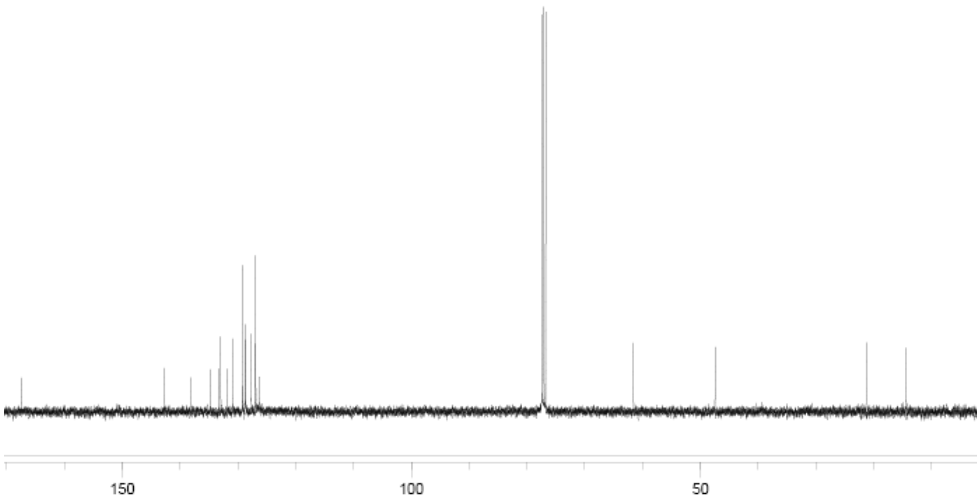
^{1}H and ^{13}C NMR Spectra

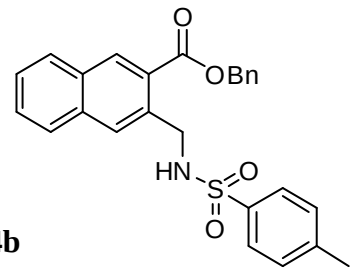


4a

Figure 1. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4a.**

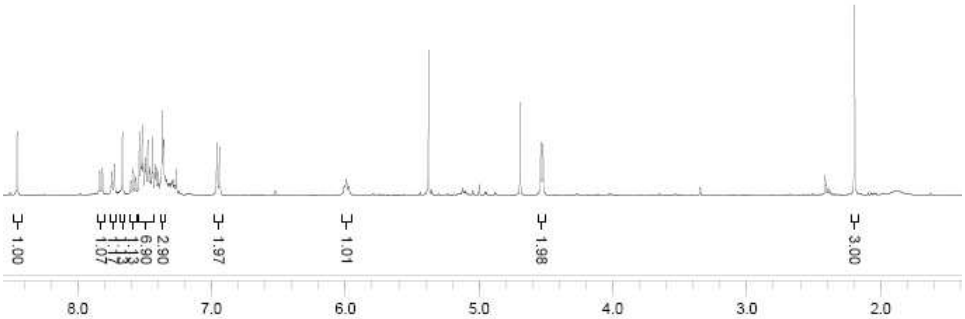


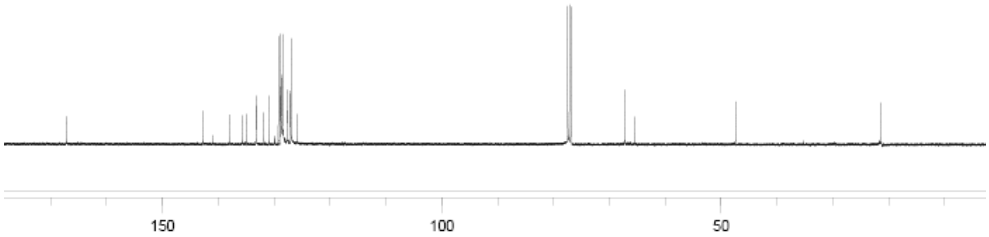


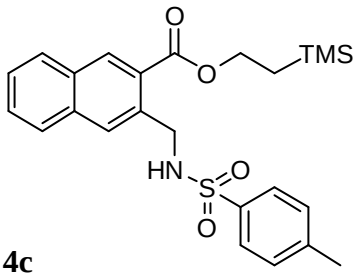


4b

Figure 2. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4b.**

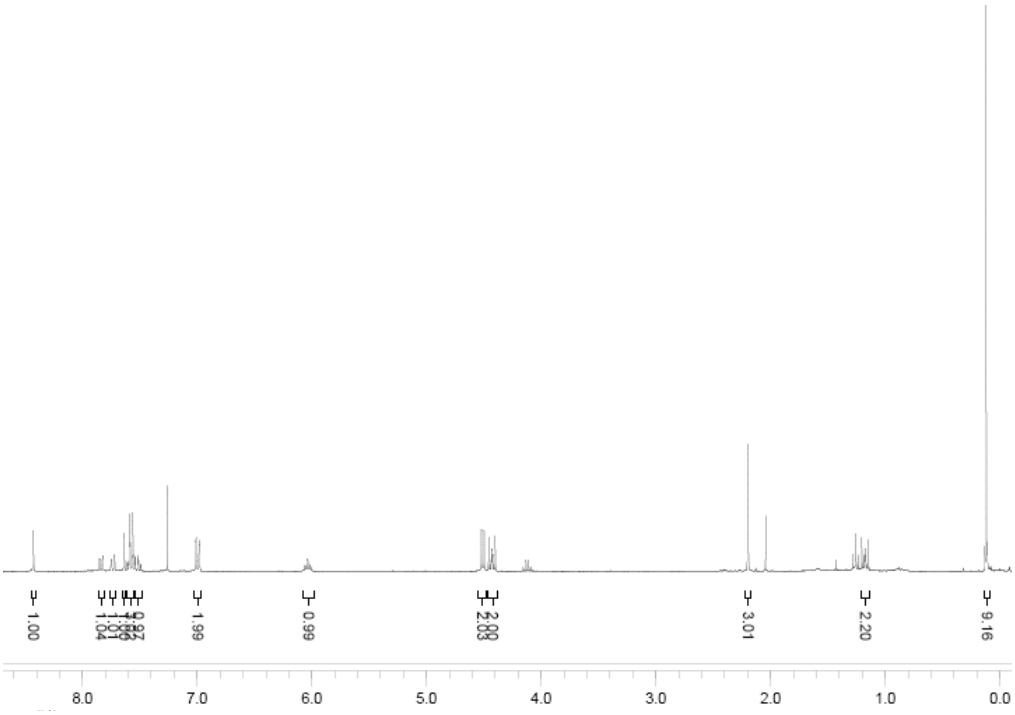


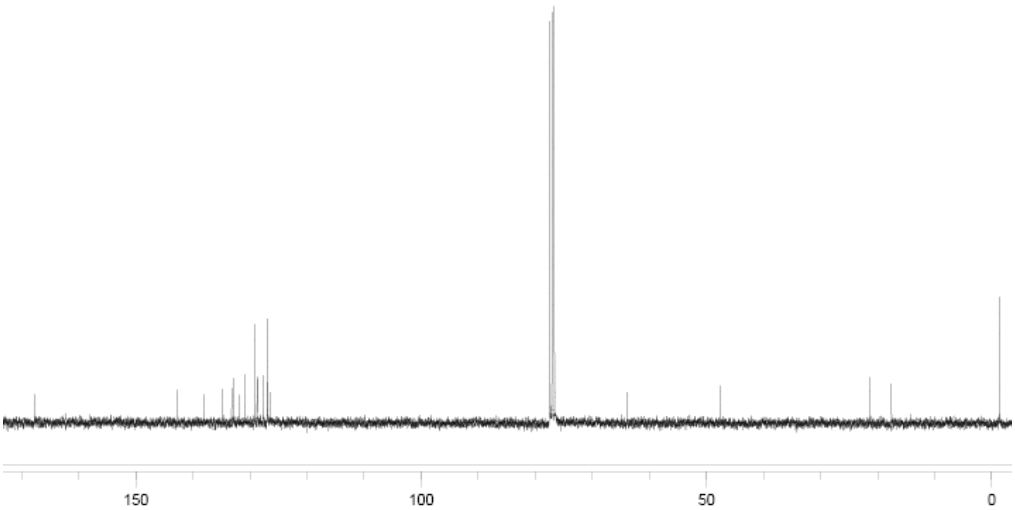


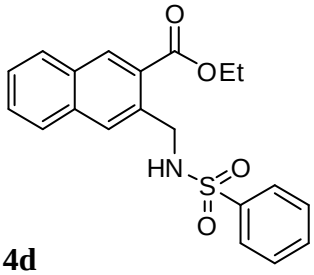


4c

Figure 3. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4c.**

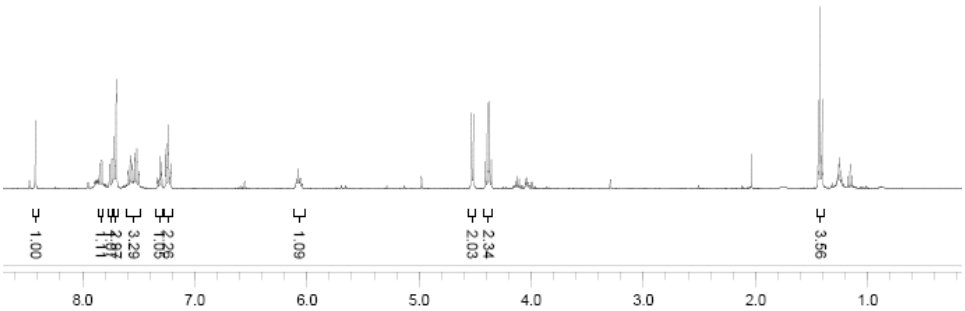


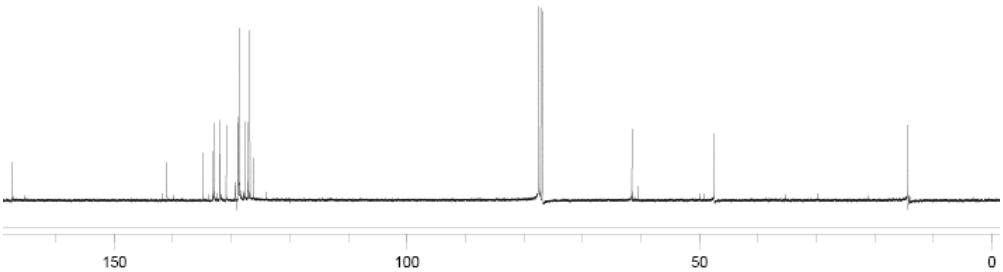


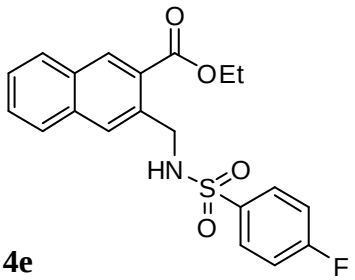


4d

Figure 4. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4d.**

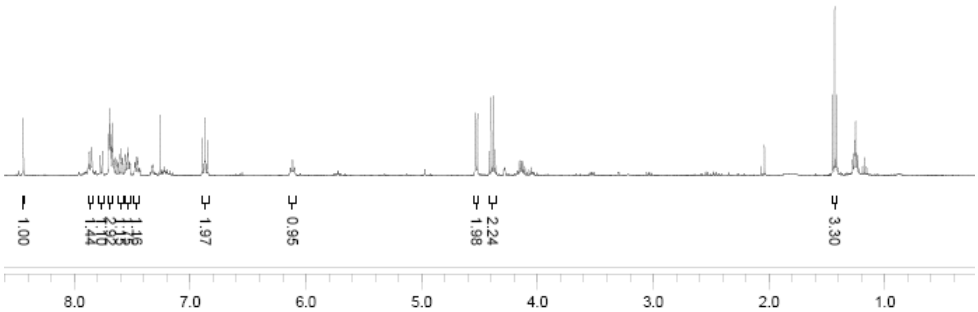


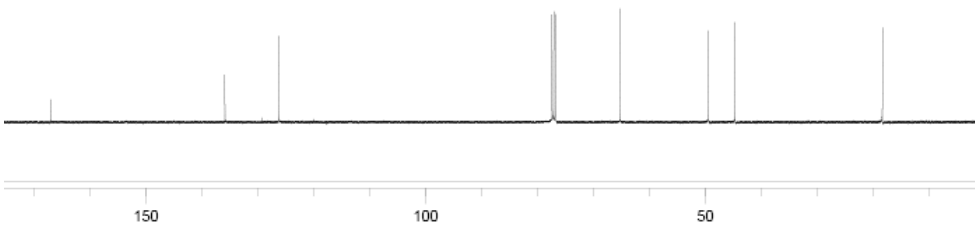


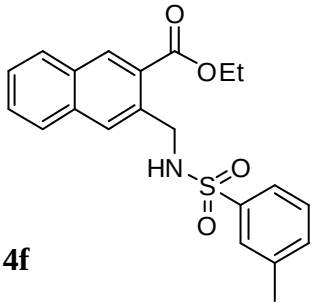


4e

Figure 5. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4e.**

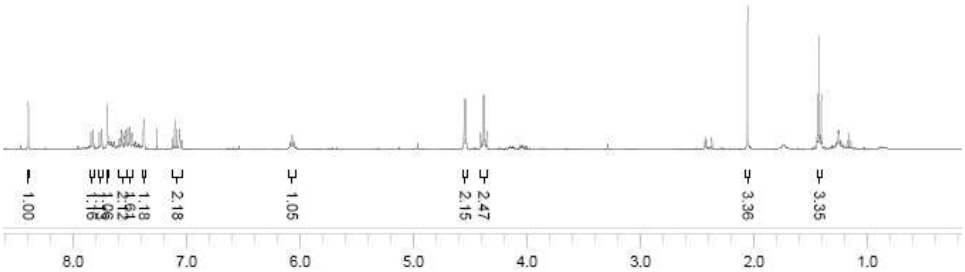


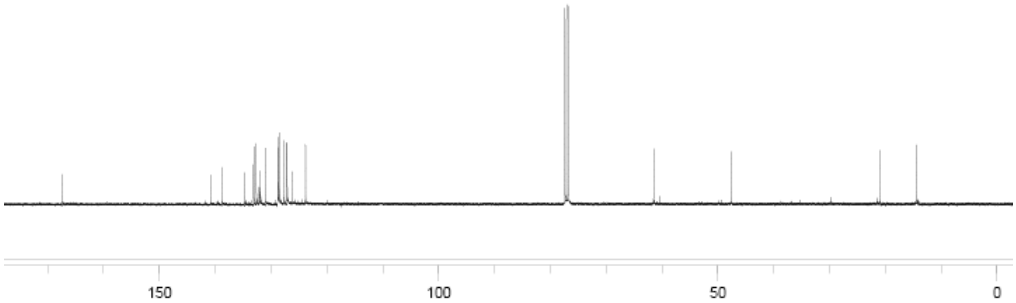


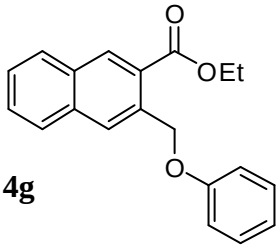


4f

Figure 6. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4f.**

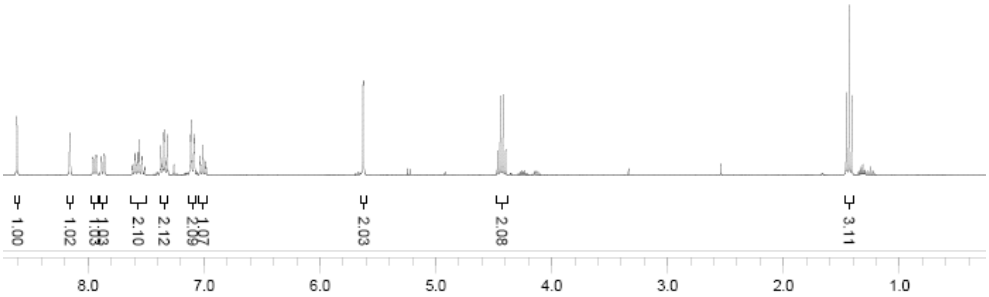


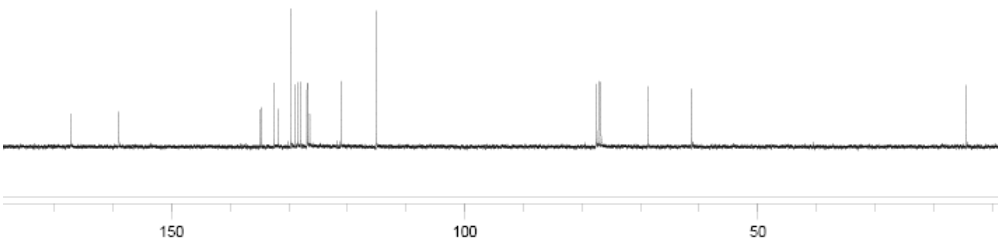


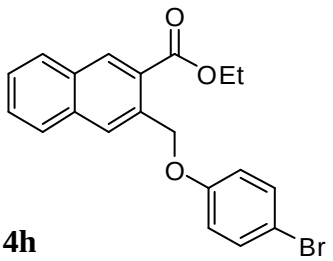


4g

Figure 7. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4g.**

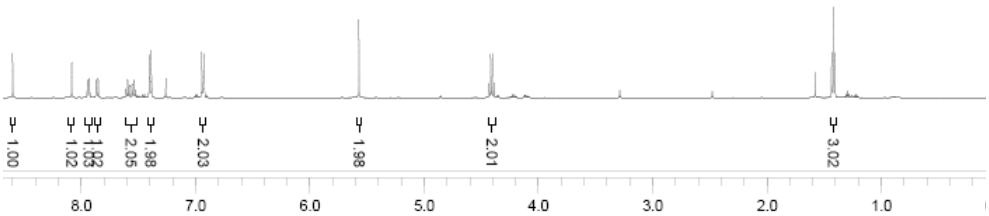


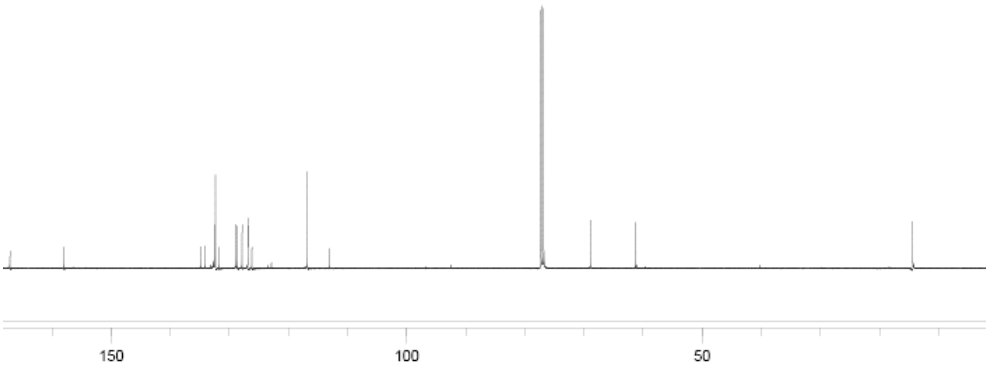




4h

Figure 8. ^{1}H NMR and ^{13}C NMR Spectra of naphthalene derivative **4h.**





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