JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

ortho-Lithium/Magnesium Carboxylate-Driven Aromatic Nucleophilic Substitution Reactions on Unprotected Naphthoic Acids

Regadia Aissaoui,[†,‡] Arnaud Nourry,[†] Ariane Coquel,[†,§] Thi Thanh Hà Dao,[§] Aicha Derdour,[‡] Jean-Jacques Helesbeux,[§] Olivier Duval,[§] Anne-Sophie Castanet,[†] and Jacques Mortier*[,†]

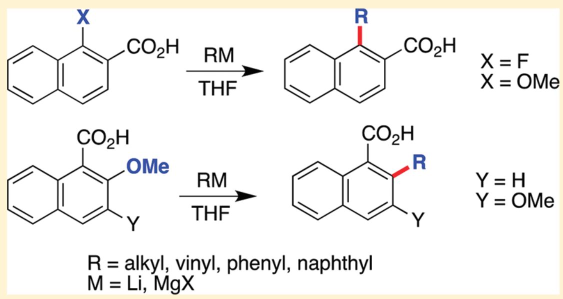
[†]Unité de Chimie Organique Moléculaire et Macromoléculaire (UMR 6011), Faculté des Sciences, Université du Maine and CNRS, avenue Olivier Messiaen, 72085 Le Mans Cedex 9, France

[‡]Laboratoire de Synthèse Organique Appliquée, Université d'Oran Es-Senia, Oran 31000, Algeria

[§]Laboratoire SONAS, Faculté de Pharmacie, Université d'Angers, 49100 Angers, France

Supporting Information

ABSTRACT: Substitution of an *ortho*-fluoro or methoxy group in 1- and 2-naphthoic acids furnishing substituted naphthoic acids occurs in good to excellent yields upon reaction with alkyl/vinyl/aryl organolithium and Grignard reagents, in the absence of a metal catalyst without the need to protect the carboxyl (CO_2H) group. This novel nucleophilic aromatic substitution is presumed to proceed via a precoordination of the organometallic with the substrate, followed by an addition/elimination.



Functionalization of naphthalenes has become a prominent route by which many important organic compounds are accessed.[1] The 1,1′-binaphthyl unit has enjoyed extensive use in the design and syntheses of chiral catalysts for carbon−carbon or carbon−hydrogen bond-making reactions and of chiral reagents for reducing ketones to optically active alcohols.[1] Gossypol, which is based on the 2,2′-binaphthalene system, is a major constituent of cottonseed pigment which displays multiple pharmacological applications.[2] *ortho*-Phenylnaphthalene carboxylic acid is the core unit of more complex bioactive compounds such as gilvocarcin antibiotics.[3,4]

Because of the significance and prevalence of these classes of compounds, considerable efforts have been undertaken to develop efficient methods for their synthesis. The approaches are characterized by their conceptual diversity and can be divided into two major classes:

(1) Catalytic aryl−aryl couplings such as the Suzuki, Stille, and Negishi coupling[5,6] and the transition-metal-catalyzed direct arylation of aromatic C−H bonds[7] are hampered by several restrictions. Metallic impurities used in the manufacturing processes can either be present in active pharmaceutical ingredients (API) in the original form of the metal catalyst or as the form of the metallic element changed by downstream chemical processing. The guideline set by the European Medicines Agency recommends maximum acceptable concentration limits for metal residues arising from the use of metal catalysts or metal reagents in the synthesis of pharmaceutical substances.[8] On a practical level, when a synthetic scheme requires the use of a metal of significant safety concern, such as Pd,[9] and that the standards of metal content permitted in the API are exceeded, it is necessary to find empirically a disposal method, which is costly in time and money.[10]

(2) Conventional wisdom indicates that the nucleophilic aromatic substitution (S_NAr) reaction of fluoro and alkoxy naphthoic acids requires steps of protection and deprotection of the carboxyl group (CO_2H) which acts as an essential carbon anchor group for subsequent chemical transformations.[11] Among a variety of methods for effecting this construction, the carboxyl group was converted into an oxazoline,[12] a bulky ester group,[13] or an imino group[14] for activation of the *ortho*-fluoro/methoxy group for S_NAr reaction with aryl Grignard and aryllithium reagents as well as for protection of the carbonyl group from the nucleophilic attack by the aryl carbanion species. These methods have suffered from several limitations, the most severe being most certainly the difficulty removing the protecting group to restore the carboxyl moiety, especially in the case of 2,6-disubstituted benzoates which are inert to hydrolysis.[12,15]

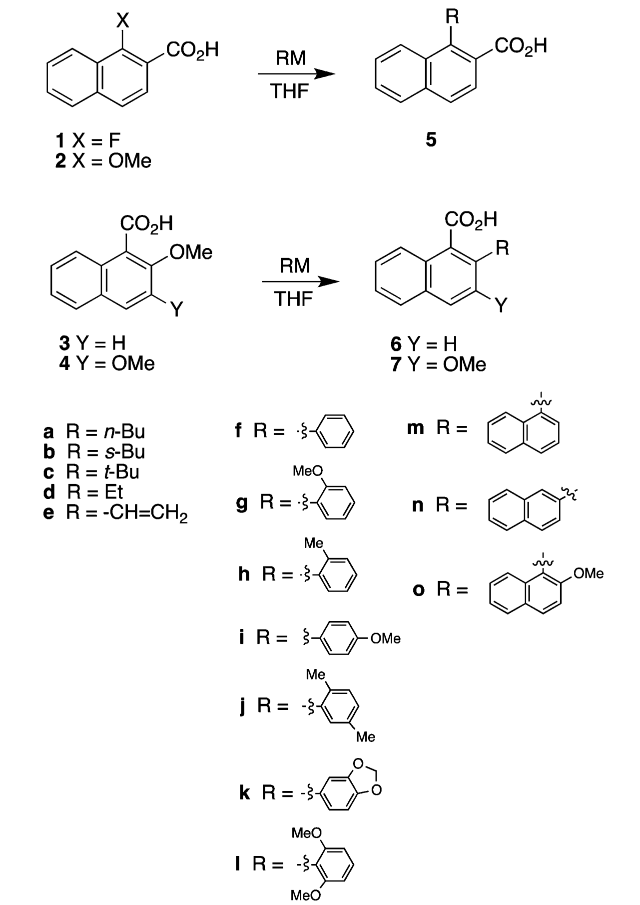
In pursuit of our contributions to the development of polar organometallic chemistry centered around the versatile *unprotected* carboxylic acid moiety,[16] we report that alkyl as well as aryl substitution can be readily accomplished in generally excellent yields via a nucleophilic mode by displacement of an *ortho*-fluoro or methoxy group in unprotected naphthoic acids with lithium and Grignard reagents in the absence of a metal catalyst.

1-Fluoro-2-naphthoic acid (**1**), 1-methoxy-2-naphthoic acid (**2**), 2-methoxy-1-naphthoic acid (**3**), and 2,3-dimethoxy-1-

Received: October 5, 2011
Published: November 22, 2011

naphthoic acid (**4**) served as suitable starting material for various organometallic reactions (Scheme 1).[17] Alkyllithium

Scheme 1. Nucleophilic Aromatic Substitution of Unprotected 1- and 2-Naphthoic Acids 1−4 with RM (M = Li, MgX)



reagents typically gave good to excellent yields, whether primary, secondary, or tertiary at −78 °C (entries 1−8, Table 1). Displacement of a fluoro or a methoxy group occurs with equal efficacy. The methoxide displacement is described more frequently in the literature most certainly due to the greater availability of the appropriate substrates, whereas the fluoride group often allows coupling at more sterically congested sites.[11]

Table 1. Reactions of Alkyllithium and Grignard Reagents[a]

entry	cpd	RM (2−4 equiv), −78 °C	R	yield (%)
1	1	*n*-BuLi	*n*-Bu-	87 [**5a**]
2	1	*s*-BuLi	*s*-Bu-	86 [**5b**]
3	1	*t*-BuLi	*t*-Bu-	92 [**5c**]
4	2	*n*-BuLi	*n*-Bu-	86 [**5a**]
5	2	*s*-BuLi	*s*-Bu-	92 [**5b**]
6	2	*t*-BuLi	*t*-Bu-	87 [**5c**]
7	3	*s*-BuLi	*s*-Bu-	95 [**6b**]
8	3	*t*-BuLi	*t*-Bu-	87 [**6c**]
9	1	*n*-BuMgBr	*n*-Bu-	81 [**5a**]
10	2	EtMgBr	Et-	93 [**5d**]
11	2	$H_2C{=}CHMgBr$, Δ[b]	$H_2C{=}CH-$	85 [**5e**]

[a]See Supporting Information. Yields refer to purified product by column chromatography. [b]Refluxing in THF.

The absence of *ortho*-lithiation was confirmed by quenching the reaction product with MeI after addition of *n*-BuLi, *s*-BuLi, and *t*-BuLi.

It is noteworthy that the use of C(sp^3) organometallics in Pd-catalyzed cross-coupling reactions normally suffers from spontaneous decomposition by LiM (*β*-) elimination or slow transmetalation.[18] Thereby, it is usually required to identify complex combinations of ligands, metals, and conditions to promote effectively the cross-coupling reaction. Alkyl Grignard reagents EtMgBr and *n*-BuMgBr proved to be very reactive at −78 °C, while vinyl magnesium bromide required refluxing in THF (entries 9−11).[19]

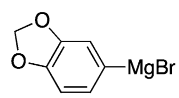
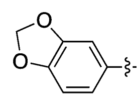
The method provides excellent latitude with respect to the synthesis of 1- and 2-phenylnaphthalenes, 1,1′-binaphthalenes, and 2,2′-binaphthalenes. The versatility of the process can be appreciated by examining the large variation in organometallic structures present in Tables 2 and 3. Naphthoic acids **1** and **2** were subjected to *ortho*-fluoro/methoxy displacement by phenyllithium and phenylmagnesium bromide affording 1-phenyl-2-naphthoic acid (**5f**) in good yields (Table 2, entries 1−3). Reaction of **3** with PhLi followed by quench with iodomethane provided as the sole product the ortho substitution compound **8** (Figure 1), whereas PhMgBr gave exclusive biaryl formation (entries 4 and 5). The reaction also proceeds efficiently when a vicinal methoxy group is present (entry 6).

It is interesting to note that, in those instances where the aryllithium reagents gave poor yields of coupling products, the corresponding Grignard reagents proved to be much more effective (compare entries 7,8 and 9,10). *o*-Tolyllithium, *o*-tolylmagnesium bromide, (4-methoxyphenyl)magnesium bromide, (2,5-dimethylphenyl)magnesium bromide, and benzo-[*d*][1,3]dioxol-5-ylmagnesium bromide smoothly displaced the fluoro/methoxy group ortho to the CO_2M group to give **5h−j** and **7k** (entries 11−16), while reaction of (2,6-dimethoxyphenyl)magnesium bromide proceeded with less efficiency presumably due to steric effects imparted by the two *ortho*-methoxy groups (entries 17−19). Above 0 °C, the only other major products observed are the ketones **9** and **10**,[20] which were readily separated by column chromatography. Particularly useful is the phenylnaphthalene **5g** which allows for further elaboration after the coupling is performed. Deprotection of the methoxy group in **5g** followed by cyclization was realized with BBr_3 to afford 6*H*-naphtho[2,1-*c*]chromen-6-one (**11**) which was isolated in 97% yield (Figure 1). This lactone is the starting building block for the preparation of optically active atropisomers by enantioselective ring opening.[4]

An interesting facet of this reaction arose when it was found that 1,1′-binaphthyl derivative **5m** can be readily prepared from 1-naphthyllithium and 1-naphthylmagnesium bromide (entries 1−3, Table 3). 2-Naphthylmagnesium bromide reacted as well with **3** to afford 2,2′-binaphthalene **6n** (entry 4). Reaction of 2-methoxy-1-naphthylmagnesium bromide with **1** leading to **5o** proceeded in low yield (22%, entry 5), thus indicating the slowness of the process. This is not surprising in view of the large ortho substituents present in **5o**. Better results were obtained with a methoxy leaving group (40%, entry 6).

Other metal derivatives also appear to behave similarly in this substitution process. Thus, reaction of $PhCH_2MgBr$ with **1** and **2** gave 1-benzyl-2-naphthoic acid **12** in 75 and 85% yield, respectively, while a variety of lithioamines smoothly displaced the methoxy group, affording anthranilic acid derivatives **13** and **14**.[21]

Table 2. Reactions of Phenyllithium/Grignard Reagents[a]

entries	cpd	RM (2-4 equiv)	R	yield (%)
1	**1**	PhLi, −30 °C	Ph-	75 [**5f**]
2	**2**	PhLi, −30 °C	Ph-	80 [**5f**]
3	**2**	PhMgBr, 0 °C	Ph-	84 [**5f**]
4	**3**	1) PhLi, −30 °C. 2) MeI[c]	Ph-	86 [**8**]
5	**3**	PhMgBr, Δ[b]	Ph-	67 [**6f**]
6	**4**	PhMgBr, Δ	Ph-	81 [**7f**]
7	**1**	2-$MeOC_6H_4Li$, −30 °C	2-$MeOC_6H_4$-	53 [**5g**]
8	**2**	2-$MeOC_6H_4Li$, −30 °C	2-$MeOC_6H_4$-	20 [**5g**]
9	**1**	2-$MeOC_6H_4MgBr$, Δ	2-$MeOC_6H_4$-	60 [**5g**]
10	**2**	2-$MeOC_6H_4MgBr$, Δ	2-$MeOC_6H_4$-	64 [**5g**]
11	**1**	2-MeC_6H_4Li, −30 °C	2-MeC_6H_4-	85 [**5h**]
12	**2**	2-MeC_6H_4Li, −30 °C	2-MeC_6H_4-	84 [**5h**]
13	**2**	2-MeC_6H_4MgBr, Δ	2-MeC_6H_4-	81 [**5h**]
14	**2**	4-$MeOC_6H_4MgBr$, rt	4-$MeOC_6H_4$-	83 [**5i**]
15	**2**	2,5-diMeC_6H_4MgBr, Δ	2,5-diMeC_6H_4-	72 [**5j**]
16	**4**	 , Δ		70 [**7k**]
17	**1**	2,6-di$MeOC_6H_4Li$, Δ	2,6-di$MeOC_6H_4$	37[c] [**5l**]
18	**1**	2,6-di$MeOC_6H_4MgBr$, Δ	2,6-di$MeOC_6H_4$	13 [**5l**]
19	**2**	2,6-di$MeOC_6H_4MgBr$, Δ	2,6-di$MeOC_6H_4$	29 [**5l**]

[a]See Supporting Information. Yields refer to purified product by column chromatography. [b]Refluxing in THF. [c]NMR yield.

In all previous observations involving F/OMe group displacement by organometallics, a mechanism has been invoked which involved complexation of the metal to both the F/OMe group and the "activating" group followed by 1,4-addition.[11,12] If it is assumed that these reactions proceed via an addition−elimination sequence,[22,23] then the σ complex **B** allows the carboxylate to orientate itself in a coplanar fashion with the aromatic ring while the metal (Li^+ or Mg^{2+}) forms a strong complex with the F/OMe group (complex-induced proximity effect, CIPE)[24] (Figure 2) similar to those proposed for the *ortho*-lithiation of benzoic acids.[16] The transition state leading to **B** may be envisioned as forming from **A**, where the R group enters from the side almost perpendicular to the aromatic ring (to the π cloud). This is consistent with the lack of steric inhibition to addition by large groups such as *t*-Bu.

Understanding the factors governing regioselectivity is a long-standing challenge and essential for further development of this process.[25] The 1,2-(ketone formation) versus 1,4-(conjugate) selectivity has been shown to be dependent on the type of organometallic reagents[26] and the ion-pair structure of organometallic reagents.[27] It is apparent that the relative magnitude of the LUMO coefficient might be one of the major factors governing the substituent-dependent regioselectivity of the ambident naphthoic acids.[25]

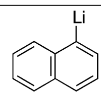
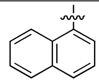
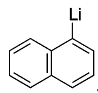
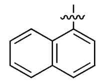
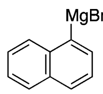
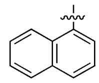
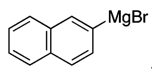
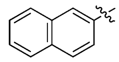
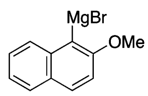
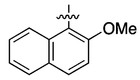
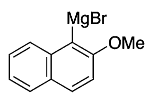
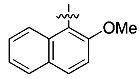
Studies are continuing to determine the scope of this novel nucleophilic substitution which also promises to provide a versatile approach to 1- and 2-arylnaphthalenes in a chiral form.[28]

■ EXPERIMENTAL SECTION

Grignard reagents were prepared according to standard working practice.[29] For the preparation of aryllithiums, the following procedure was followed: *t*-BuLi (1 equiv) was added dropwise to a solution of aryl bromide (1 equiv) in dry THF (1 mL/mmol of aryl bromide) at −78 °C. The reaction mixture was stirred at this temperature for 30 min before use.

1-*n*-Butyl-2-naphthoic acid (5a): General Procedures. Table 1, entries 1 and 4 (**1**,**2** + *n*-BuLi). To a solution of 1-fluoro-2-naphthoic acid (**1**) (570 mg, 3.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) in THF (20 mL) at −78 °C was added dropwise *n*-BuLi (1.1 M in hexane, 6.0 mL, 6.6 mmol). After 2 h stirring at this temperature, the reaction mixture was quenched with water (20 mL) and allowed to warm to rt. The aqueous layer was acidified to pH 1 (2 M HCl) and extracted with ethylacetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Recrystallization (*n*-hexane/ethylacetate 9:1) afforded **5a** as a white solid (600 mg, 87% from **1**; 590 mg, 86% from **2**): mp 98−99 °C (lit.[30] 97.0−97.7 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.24 (m, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.86 (m, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.59−7.55 (m, 2H), 3.49 (t, *J* = 7.5 Hz, 2H),

Table 3. Reactions of 1- and 2-Naphthyllithium/Grignard Reagents

entries	cpd	RM (2-4 equiv)	R	yield (%)[a]
1	**1**	 , −30 °C		87[**5m**]
2	**2**	 , −30 °C		91 [**5m**]
3	**2**	 , Δ[b]		70 [**5m**]
4	**3**	 , Δ		94 [**6n**]
5	**1**	 , Δ		22 [**5o**]
6	**2**	 , Δ		40 [**5o**]

[a]See Supporting Information. Yields refer to purified product by column chromatography. [b]Refluxing in THF.

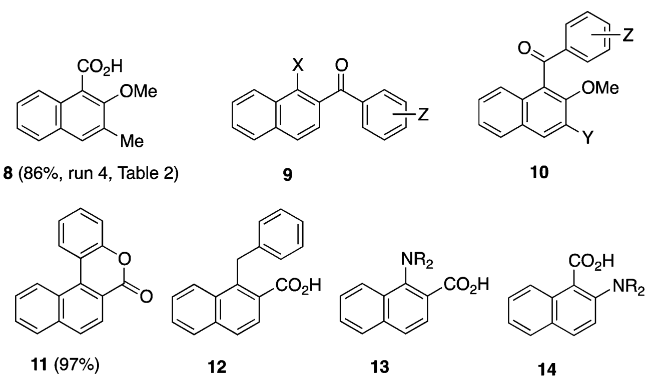


Figure 1. Substituted naphthoic acids **8** and **12**−**14**, ketones **9** and **10**, and naphthochromenone **11**.

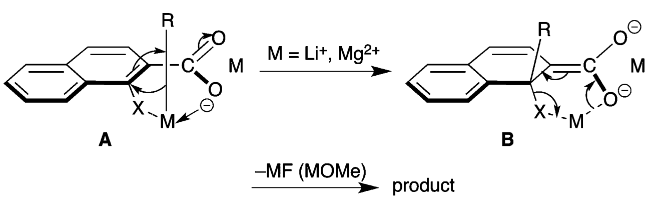


Figure 2. Aromatic nucleophilic substitution reactions on unprotected naphthoic acids. Proposed mechanism.

1.81−1.72 (m, 2H), 1.62−1.53 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 144.2, 135.7, 132.3, 128.8, 127.7, 126.7 (2), 126.4, 125.9, 125.6, 33.8, 29.3, 23.4, 14.0; IR (KBr, cm^{-1}) 1736, 1685, 1235, 1221, 1168, 1136, 1028, 937, 1069, 982, 768; HRMS calcd for $C_{15}H_{16}O_2$ ([M]$^+$) 228.1150, found 228.1159. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.75; H, 6.99.

1-*sec*-Butyl-2-naphthoic acid (5b). Table 1, entries 2 and 5 (**1**,**2** + *s*-BuLi). According to the general procedure, 1-fluoro-2-naphthoic acid (**1**) (570 mg, 3.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) was allowed to react with *s*-BuLi (1.3 M in hexane, 5.1 mL, 6.6 mmol). Stirring was maintained at −78 °C for 2 h. Standard workup followed by recrystallization (cyclohexane/ethylacetate 1:3) gave **5b** as a white solid (590 mg, 86% from **1**, 630 mg, 92% from **2**): mp 113−114 °C (lit.[31] 117−118 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.7 (s, 1H), 8.40 (m, 1H), 7.85 (m, 1H), 7.75−7.71 (m, 2H), 7.55−7.48 (m, 2H), 3.89 (m, 1H), 2.09 (m, 2H), 1.65 (d, *J* = 7.2 Hz, 3H), 0.9 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 144.5, 135.6, 131.8, 129.2 (2), 127.0, 126.9, 125.8, 125.4, 38.5, 29.8, 20.6, 13.4; IR (KBr, cm^{-1}) 2963, 1682, 1279, 1170, 886, 767; HRMS calcd for $C_{15}H_{16}O_2$ ([M]$^+$) 228.1150, found 228.1153.

1-*tert*-Butyl-2-naphthoic acid (5c). Table 1, entries 3 and 6 (**1**,**2** + *t*-BuLi). According to the general procedure, 1-fluoro-2-naphthoic acid (**1**) (570 mg, 3.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) was allowed to react with *t*-BuLi (1.7 M in pentane, 3.9 mL, 6.6 mmol) at −78 °C. Stirring was maintained at −78 °C for 2 h. Standard workup and recrystallization (cyclohexane/ethylacetate 1:3) afforded **5c** as a white solid (630 mg, 92% from **1**, 600 mg, 87% from **2**): mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 8.52 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.1 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.52−7.45 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 1.76 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 143.7, 135.3, 132.3, 130.2, 129.4, 128.3, 127.4, 125.9, 125.0, 124.8, 38.1, 32.7 (3); IR (KBr, cm^{-1}) 3000, 1684, 1415, 1037, 938, 774; HRMS calcd for $C_{15}H_{16}O_2$ ([M]$^+$) 228.1150, found 228.1163.

1-Ethyl-2-naphthoic acid (5d). Table 1, entry 10 (**2** + EtMgBr). According to the general procedure, 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) was treated with ethyl magnesium bromide (1.1 M in ether, 6.0 mL, 6.6 mmol). Standard workup followed by recrystallization (cyclohexane/ethylacetate 1:3) afforded **5d** as a white solid (560 mg, 93%): mp 147−149 °C (lit.[32] 150 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 11.71 (s, 1H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.93−7.90 (m, 2H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.62−7.55 (m, 2H), 3.49 (q, *J* = 7.4 Hz, 2H), 1.37 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.0, 143.7, 136.0, 132.6, 129.5, 128.5, 128.0, 127.5, 127.1, 127.0, 125.9, 23.0, 16.1; IR (KBr, cm^{-1}) 3000, 1629, 1450, 1244, 869, 793; HRMS calcd for $C_{13}H_{12}O_2$ ([M]$^+$) 200.0837, found 200.0843.

1-Vinyl-2-naphthoic acid (5e). Table 1, entry 11 (**2** + H_2C=CHMgBr). According to the general procedure, vinyl magnesium bromide (0.75 M in THF, 8.8 mL, 6.6 mmol) was added dropwise to a solution of 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) at rt. The mixture was then refluxed for 2 h. Standard workup followed by recrystallization (cyclohexane/ether 1:3) afforded **5e** as a white solid (505 mg, 85%): mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.61−7.52 (m, 2H), 7.46 (dd, *J* = 17.8 Hz, *J* = 11.5 Hz, 1H), 5.78 (dd, *J* = 11.5 Hz, *J* = 1.8 Hz, 1H), 5.41 (dd, *J* = 17.8 Hz, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 141.1, 135.7, 134.3, 131.6, 128.1, 128.0, 127.7, 127.3, 126.5, 125.9, 125.1, 120.8; IR (ATR, cm^{-1}) 2798, 2510, 1687, 1558, 1459, 1409, 1277, 1248, 1165, 914, 831, 794, 756; HRMS calcd for $C_{13}H_{10}O_2$ ([M]$^+$) 198.0681, found 198.0680.

1-Phenyl-2-naphthoic acid (5f). Table 2, entries 1 and 2 (**1**,**2** + PhLi). According to the general procedure, phenyllithium (1.0 M in dibutylether, 6.6 mL, 6.6 mmol) was added dropwise to a solution of 1-fluoro-2-naphthoic acid (**1**) (570 mg, 3.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) in THF at −30 °C. Stirring was maintained at this temperature for 2 h. Standard workup followed by recrystallization (*n*-hexane/ethylacetate 1:3) afforded **5f** as a pale yellow solid (560 mg, 75% from **1**, 597 mg, 80% from **2**): mp 145−147 °C (lit.[33] 147−148.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (br s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.56−7.48 (m, 2H), 7.43−7.37 (m, 4H), 7.29−7.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 142.8, 138.7, 135.3, 132.8, 129.6 (2), 128.1, 128.0 (2), 127.9 (2), 127.8, 127.5, 126.7 (2), 125.9; IR (KBr, cm^{-1}) 3000, 1692, 1408, 1284, 873, 757; HRMS calcd for $C_{17}H_{12}O_2$ ([M]$^+$) 248.0837, found 248.0869. Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.03; H, 4.85.

Table 2, entry 3 (**2** + PhMgBr). According to the general procedure, phenylmagnesium bromide (2.16 M in THF, 3.1 mL, 6.6 mmol) was added dropwise to a solution of 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) in THF at 0 °C. Stirring was maintained this temperature for 2 h. Standard workup followed by recrystallization (*n*-hexane/ethylacetate 1:3) gave **5f** as a pale yellow solid (630 mg, 84%).

1-(2-Methoxyphenyl)-2-naphthoic acid (5g). Table 2, entries 7 and 8 (**1**,**2** + 2-MeOC_6H_4Li). According to the general procedure, (2-methoxyphenyl)lithium (8.0 mmol) was added dropwise to a solution of 1-fluoro-2-naphthoic acid (**1**) (380 mg, 2.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (404 mg, 2.0 mmol) in THF at −30 °C. The reaction mixture was stirred at −30 °C for 2 h. Standard workup followed by chromatography on silica gel (cyclohexane/DCM 30:70 → 0:1 and DCM/ethylacetate 95:5 → 0:1) afforded **5g** as a white solid (293 mg, 53% from **1**; 109 mg, 20% from **2**): mp 182−184 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.00−7.94 (m, 3H), 7.54 (m, 1H), 7.46−7.37 (m, 3H), 7.10−7.08 (m, 2H), 7.02 (m, 1H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 169.0, 158.3, 139.3, 135.8, 133.6, 131.7, 129.8 (2), 129.0, 128.8, 128.3, 128.2, 128.1, 127.3, 126.8, 121.0, 111.9, 55.8; IR (ATR, cm^{-1}) 2835, 1687, 1492, 1284, 910, 787, 756; HRMS calcd for $C_{18}H_{14}O_3$ ([M]$^+$) 278.0943, found 278.0956.

1-(2-Methylphenyl)-2-naphthoic acid (5h). Table 2, entries 11 and 12 (**1**,**2** + 2-MeC_6H_4Li). According to the general procedure, *o*-tolyllithium (4.4 mmol) was added dropwise to a solution of 1-fluoro-2-naphthoic acid (**1**) (380 mg, 2.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (404 mg, 2.0 mmol) in THF at −30 °C. The reaction mixture was then stirred at this temperature for 2 h. Standard workup followed by chromatography on silica gel (cyclohexane/DCM 20:80 → 0:1 then DCM/ethylacetate 1:0 → 1:1) afforded **5h** as a white solid (446 mg, 85% from **1**, 437 mg, 84% from **2**): mp 136−138 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.90 (br, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.51 (m, 1H), 7.36−7.30 (m, 3H), 7.29−7.21 (m, 2H), 7.06 (d, *J* = 7.4 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 142.8, 138.4, 136.7, 135.4, 132.6, 129.7, 129.3, 128.1, 127.8, 127.7, 126.9, 126.4, 126.2, 125.6, 20.0; IR (KBr, cm^{-1}) 2859, 1693, 1464, 1253, 942, 770, 755; HRMS calcd for $C_{18}H_{14}O_2$ ([M]$^+$) 262.0994, found 262.0997.

1-(4-Methoxyphenyl)-2-naphthoic acid (5i). Table 2, entry 14 (**2** + 4-MeOC_6H_4MgBr). According to the general procedure, 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) was allowed to react with (4-methoxyphenyl)magnesium bromide (0.85 M in THF, 7.8 mL, 6.6 mmol) for 2 h at rt. Standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 9:1 → 0:1) afforded **5i** as a white solid (691 mg, 83%): mp 177.5−180.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.54 (m, 1H), 7.41 (m, 1H), 7.25−7.21 (m, 2H), 7.02−6.99 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.5, 159.1, 142.4, 135.2, 133.1, 130.8 (2), 130.7, 128.1, 127.9, 127.8, 127.7, 127.0, 126.7, 125.9, 113.6 (2), 55.3; IR (ATR, cm^{-1}) 1698, 1675, 1504, 1463, 1329, 1285, 1238, 1175, 1034, 827, 769; HRMS calcd for $C_{18}H_{14}O_3$ ([M]$^+$) 278.0943, found 278.0940.

1-(2,5-Dimethylphenyl)-2-naphthoic acid (5j). Table 2, entry 15 (**2** + 2,5-diMeC_6H_4MgBr). According to the general procedure, (2,5-dimethylphenyl)magnesium bromide (0.50 M in THF, 13.2 mL, 6.6 mmol) was allowed to react with 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) in THF at rt. The reaction mixture was refluxed for 2 h. Standard workup followed by recrystallization (cyclohexane) afforded **5j** as a white solid (600 mg, 72%): mp 165- °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 1H), 7.88−7.86 (m, 2H), 7.53 (m, 1H), 7.37−7.36 (m, 2H), 7.22−7.13 (m, 2H), 6.89 (s, 1H), 2.32 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 142.9, 138.1, 135.3, 134.8, 133.6, 132.5, 129.9, 129.5, 128.5, 128.0, 127.9, 127.6, 126.8, 126.3, 126.1, 21.0, 19.4; IR (KBr, cm^{-1}) 2916, 1673, 1410, 1279, 913, 771, 758; HRMS calcd for $C_{19}H_{17}O_2$ ([M + H]$^+$) 277.1229, found 277.1234.

1-(2,6-Dimethoxyphenyl)-2-naphthoic acid (5l). Table 2, entries 18 and 19 (**1**,**2** + 2,6-diMeOC_6H_3MgBr). According to the general procedure, (2,6-dimethoxyphenyl)magnesium bromide (0.43 M in THF, 5.1 mL, 2.2 mmol) was added dropwise at rt to a solution of 1-fluoro-2-naphthoic acid (**1**) (190 mg, 1.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (202 mg, 1.0 mmol) in THF. After 2 h refluxing, standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 9:1 → 0:1) gave **5l** as a pale yellow solid (40 mg, 13% from **1**, 90 mg, 29% from **2**): mp 242−244 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.92−7.87 (m, 2H), 7.58−7.33 (m, 4H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.61 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 168.5, 157.4 (2), 134.5, 134.3, 132.1, 129.5, 129.1, 127.9, 127.1, 127.0, 126.6, 126.4, 126.0, 115.8, 104.2 (2), 55.5 (2); IR (ATR, cm^{-1}) 2940, 1665, 1587, 1470, 1430, 1286, 1248, 1105, 910, 759, 724; HRMS calcd for $C_{19}H_{16}O_4$ ([M]$^+$) 308.1049, found 308.1064.

[1,1′-Binaphthalene]-2-carboxylic acid (5m). Table 3, entries 1 and 2 (**1**,**2** + 1-naphthyllithium). According to the general procedure, naphthalen-1-yllithium (4.4 mmol) was allowed to react with 1-fluoro-2-naphthoic acid (**1**) (380 mg, 2.0 mmol) or 1-methoxy-2-naphthoic acid (**2**) (404 mg, 2.0 mmol) in THF at −30 °C for 2 h for **1** and for 16 h for **2**. Standard workup and chromatography on silica gel (cyclohexane/ethylacetate 95:5 → 0:1) afforded **5m** as a white solid (516 mg, 87% from **1**, 544 mg, 91% from **2**): mp 180−182 °C (lit.[34] 177−184 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 1H), 7.95−7.89 (m, 4H), 7.54−7.49 (m, 2H), 7.43 (m, 1H), 7.30−7.20 (m, 4H), 7.12 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 141.4, 136.6, 135.2, 133.3, 133.2, 132.9, 128.3, 128.2 (2), 128.0 (2), 127.9, 127.3, 127.0, 126.8, 126.2, 126.1, 126.0, 125.7, 125.3; IR (ATR, cm^{-1}) 2922, 1691, 1461, 1251, 913, 795, 768; HRMS calcd for $C_{21}H_{15}O_2$ ([M + H]$^+$) 299.1072, found 299.1077.

Table 3, entry 3 (**2** + naphthalen-1-ylmagnesium bromide). According to the general procedure, naphthalen-1-ylmagnesium bromide (0.66 M in THF, 10.0 mL, 6.6 mmol) was added dropwise to a solution of 1-methoxy-2-naphthoic acid (**2**) (606 mg, 3.0 mmol) in THF at −30 °C. The mixture was then refluxed for 2 h. Standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 3:2) afforded **5m** as a white solid (630 mg, 70%).

2′-Methoxy-[1,1′-binaphthalene]-2-carboxylic acid (5o). Table 3, entry 6 (**2** + (2-methoxynaphthalen-1-yl)magnesium bromide). According to the general procedure, (2-methoxynaphthalen-1-yl)magnesium bromide (0.25 M in THF, 17.5 mL, 4.4 mmol) was added dropwise to a solution of 1-methoxy-2-naphthoic acid (**2**) (404 mg, 2.0 mmol) in THF at rt. The mixture was then refluxed for 2 h. Standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 9:1 → 0:1) afforded **5o** as a white solid (265 mg, 40%): mp 258−261 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 1H), 7.99 (m, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.53 (ddd, *J* = 1.6 Hz, *J* = 6.4 Hz, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 9.1 Hz, 1H), 7.32−7.19 (m, 3H), 7.17 (ddd, *J* = 1.3 Hz, *J* = 6.8 Hz, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2, 153.9, 135.7, 134.5, 133.3, 132.3, 130.1, 129.3, 128.5, 128.1, 127.9, 127.7, 127.5, 126.8, 126.7, 126.3, 126.1, 124.3, 123.2, 121.2, 113.9, 56.1; IR (ATR, cm^{-1}) 1688, 1669, 1464, 1248, 1082, 1053, 913, 797, 765, 756, 737; HRMS calcd for $C_{22}H_{20}NO_3$ ([M + NH_4]$^+$) 346.1443, found 346.1425.

2-*sec*-Butyl-1-naphthoic acid (6b). Table 1, entry 7 (**3** + *s*-BuLi). According to the general procedure, 2-methoxy-1-naphthoic acid (**3**) (606 mg, 3.0 mmol) was allowed to react with *s*-BuLi (0.90 *M* in hexane, 7.3 mL, 6.6 mmol) at −78 °C. Standard workup followed by recrystallization (cyclohexane/ethylacetate 1:3) afforded **6b** as a white solid (650 mg, 95%): mp 168−170 °C (lit.[31] 166−168 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.93 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.56 (m, 1H), 7.50−7.43 (m, 2H), 3.12 (m, 1H), 1.83−1.69 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 142.5, 131.8, 130.4, 129.5, 129.1, 128.1, 127.2, 125.8, 124.8, 123.5, 35.1, 30.7, 22.1, 12.3; IR (KBr, cm^{-1}) 2850, 1695, 1400, 1253, 900, 780, 751; HRMS calcd for $C_{15}H_{16}O_2$ ([M]$^+$) 228.1150, found 228.1170. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.67; H, 7.14.

2-*tert*-Butyl-1-naphthoic acid (6c). Table 1, entry 8 (**3** + *t*-BuLi). According to the general procedure, 2-methoxy-1-naphthoic acid (**3**) (606 mg, 3.0 mmol) was reacted with *t*-BuLi (1.70 M in pentane, 3.9 mL, 6.6 mmol) at −78 °C. Standard workup followed by recrystallization (cyclohexane/ethylacetate 1:3) afforded **6c** as a white solid (600 mg, 87%): mp 120−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 7.93 (d, *J* = 8.4 Hz 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.83

(d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.57 (m, 1H), 7.49 (m, 1H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 144.0, 131.4, 130.0, 129.5, 128.1, 127.9, 127.2, 126.1, 125.6, 124.6, 36.8, 31.8 (3); IR (KBr, cm^{-1}) 2950, 1685, 1464, 1103, 933, 770, 741; HRMS calcd for $C_{15}H_{16}O_2$ ([M]$^+$) 228.1150, found 228.1166. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.73; H, 6.99.

2-Phenyl-1-naphthoic acid (6f). Table 2, entry 5 (**3** + PhMgBr). According to the general procedure, 2-methoxy-1-naphthoic acid (**3**) (606 mg, 3.0 mmol) was allowed to react with phenyl magnesium bromide (0.20 M in THF, 33 mL, 6.6 mmol). The reaction mixture was then refluxed for 2 h. Standard workup followed recrystallization (cyclohexane/ethylacetate 1:3) afforded **6f** as a white solid (540 mg, 67%): mp 118−120 °C (lit.[35] 114 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 8.1 Hz, 1H), 7.86 (t, J = 9.3 Hz, 2H), 7.73 (d, J = 6.8 Hz, 2H), 7.48−7.42 (m, 2H), 7.36−7.24 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.2, 141.4, 138.8, 132.4, 131.9, 129.8, 128.0 (2), 127.7 (2), 126.6, 126.3, 125.6; IR (ATR, cm^{-1}) 3049, 1693, 1463, 1333, 861, 759; HRMS m/z calc. for $C_{17}H_{13}O_2$ ([M + H]$^+$) 249.0916, found 249.0940.

[2,2′-Binaphthalene]-1-carboxylic acid (6n). Table 4, entry 4 (**3** + 2-naphthylmagnesium bromide). According to the general procedure, naphthalen-2-ylmagnesium bromide (0.94 M in THF, 7.5 mL, 7 mmol) was added dropwise to a solution of 2-methoxy-1-naphthoic acid (**3**) (602 mg, 3.0 mmol) in THF. The reaction mixture was refluxed for 2 h. Standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 1:0 → 0:1) afforded **6n** as a white solid (720 mg, 94%): mp 178−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−7.95 (m, 7H), 7.75−7.54 (m, 6H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.6, 139.3, 137.7, 134.3, 133.7, 133.3, 132.4, 130.6, 130.4, 129.1, 129.0, 128.9, 128.6 (2), 128.5, 128.3, 127.8, 127.3 (2), 127.2, 126.1; IR (ATR, cm^{-1}) 2925, 1681, 1415, 1249, 809, 747; HRMS calcd for $C_{21}H_{15}O_2$ ([M + H]$^+$) 299.1072, found 299.1068.

3-Methoxy-2-phenyl-1-naphthoic acid (7f). Table 2, entry 6 (**4** + PhMgBr). According to the general procedure, 2,3-dimethoxy-1-naphthoic acid (**4**) (150 mg, 0.64 mmol) in THF (4.5 mL) was treated with phenyl magnesium bromide (3 M in THF, 0.47 mL, 1.41 mmol) at rt for 2 h. Standard workup followed by chromatography on silica gel (DCM/MeOH/AcOH 10:0.2:0.05) afforded **7f** as a beige solid (145 mg, 81%): mp 196−197 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.89 (d, J = 8 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 7.54−7.43 (m, 7H), 7.30 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.5, 154.6, 135.8, 134.0, 131.9, 131.1, 129.9, 127.8, 127.7, 126.8, 125.0, 124.9, 107.8, 107.7, 55.9; IR (KBr, cm^{-1}) 3449, 3025, 1692, 1412, 1248, 1058, 699; HRMS calcd for $C_{18}H_{15}O_3$ ([M + H]$^+$) 279.1021, found 279.1021.

3-Methoxy-2-(3′,4′-methylenedioxyphenyl)-1-naphthoic acid (7k). Table 2, entry 16 (**4** + 3,4-(OCH_2O)C_6H_4MgBr). According to the general procedure, 2,3-dimethoxy-1-naphthoic acid (**4**) (155 mg, 0.67 mmol) in THF (4.5 mL) was allowed to react with benzo[*d*][1,3]dioxol-5-ylmagnesium bromide (0.37 M in THF, 4 mL, 2.2 equiv) at rt for 2 h. Standard workup and chromatography on silica gel (CH_2Cl_2/MeOH/AcOH 10:0.2:0.05) afforded **7k** as a beige solid (150 mg, 70%): mp 227−229 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.90 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 7.54−7.42 (m, 2H), 7.29 (s, 1H), 6.94 (bs, 1H), 6.90−6.88 (m, 2H), 6.00 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.0, 154.7, 147.4, 147.3, 134.0, 131.9, 130.7, 129.4, 126.8, 125.0, 124.9, 123.5, 110.8, 108.0, 107.8, 101.1, 56.0; IR (KBr, cm^{-1}) 3447, 2902, 1691, 1459, 1251, 1039; HRMS calcd for $C_{19}H_{15}O_5$ ([M + H]$^+$) 323.0919, found 323.0911.

2-Methoxy-3-methyl-1-naphthoic acid (8). Table 2, entry 4 (**3** + PhLi/MeI). According to the general procedure with 2-methoxy-1-naphthoic acid (**3**) (606 mg, 3.0 mmol) and phenyllithium (1.80 M in dibutylether, 3.7 mL, 6.6 mmol) in THF at −30 °C. Stirring was maintained at at −30 °C for 2 h after which iodomethane (1.0 mL, 16.1 mmol) was added. Stirring was then maintained for 30 min. Standard workup followed by recrystallization (cyclohexane/ethylacetate 1:3) gave **8** as a yellow solid (897 mg, 86%): mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.74−7.70 (m, 2H), 7.49 (t, J = 8.4 Hz, 1H), 7.42 (t, J = 8.1 Hz, 1H), 3.99 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 155.7, 132.8, 130.9, 130.7, 129.8, 127.5, 126.9, 125.6, 124.5, 121.6, 62.3, 16.7; IR (ATR, cm^{-1}) 2948, 1689, 1448, 1244, 884, 748, 458; HRMS calcd for $C_{13}H_{12}O_3$ ([M]$^+$) 216.0786, found 216.0788. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.32; H, 5.63.

***6H*-Naphtho[2,1-c]chromen-6-one (11).** To a solution of 1-(2-methoxyphenyl)-2-naphthoic acid (**5g**) (838 mg, 3.01 mmol) in dry DCM (30 mL) at −78 °C was added dropwise tribromoborane (1.0 M in DCM, 9.0 mL, 9.03 mmol). The reaction mixture was successively stirred overnight at −78 °C then 1 h at rt, quenched with water (30 mL), and extracted with DCM (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel (cyclohexane/ethylacetate 9:1 → 6:4) afforded **11** as a pink solid (722 mg, 97%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.89 (m, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.04−7.94 (m, 2H), 7.75−7.70 (m, 2H), 7.56−7.37 (m, 3H);[36] ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5, 151.4, 136.9, 134.1, 130.0, 129.5, 129.1, 128.9, 128.1, 127.8, 127.5, 127.0, 124.3, 124.1, 119.9, 118.6, 117.8; IR (ATR, cm^{-1}) 2924, 1721, 1596, 1465, 1287, 1244, 1217, 1086, 748; HRMS calcd for $C_{17}H_{11}O_2$ ([M + H]$^+$) 247.0759, found 247.0752.

1-Benzyl-2-naphthoic acid (12). According to the general procedure, 1-fluoro-2-naphthoic acid (**1**) (285 mg, 1.5 mmol) or 1-methoxy-2-naphthoic acid (**2**) (324 mg, 1.5 mmol) was allowed to react with benzylmagnesium bromide (0.54 M in ether, 6.1 mL, 3.3 mmol). The mixture was refluxed for 1 day. Standard workup followed by chromatography on silica gel (cyclohexane/ethylacetate 95:5 → 0:1) afforded **12** as a white solid (295 mg, 75% from **1**; 335 mg, 85% from **2**): mp 191−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.54 (m, 1H), 7.46 (m, 1H), 7.23−7.19 (m, 2H), 7.15−7.10 (m, 3H), 4.97 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 140.9, 137.1, 134.5, 131.8, 130.0, 128.5, 128.2 (2), 128.1 (2), 127.2, 127.0, 126.8, 125.8, 125.7, 125.6, 33.8; IR (ATR, cm^{-1}) 2926, 2853, 1687, 1405, 1282, 1253, 769, 756, 740; HRMS calcd for $C_{18}H_{15}O_2$ ([M + H]$^+$) 263.1072, found 263.1076.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details of compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jacques.mortier@univ-lemans.fr. Fax: +33 (0) 243 83 39 02.

■ ACKNOWLEDGMENTS

We thank Région Pays-dela-Loire (A.N. and A.C), the Algerian Ministry of Research (R.A.), and Agence Universitaire de la Francophonie (T.T.H.D.) for doctoral and postdoctoral fellowships. We also express appreciation to Patricia Gangnery and Frédéric Legros (Université du Maine) for technical assistance.

■ REFERENCES

(1) Pu, L., Ed. *1,1′-Binaphthyl-Based Chiral Materials*; Imperial College Press: London, 2010.

(2) Le, T. T.; Chau, N. T. T.; Nguyen, T. T.; Brien, J.; Thai, T. T.; Nourry, A.; Castanet, A.-C.; Nguyen, K. P. P; Mortier, J. *J. Org. Chem.* **2011**, *76*, 601−608.

(3) Kharel, M. K.; Zhu, L.; Liu, T.; Rohr, J. *J. Am. Chem. Soc.* **2007**, *129*, 3780−3781.

(4) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563−639.

(5) (a) Cepanec, I., Ed. *Synthesis of Biaryls*; Elsevier Ltd.: Oxford, 2004. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469.

(6) On large-scale applications of transition-metal-catalyzed couplings for the synthesis of pharmaceuticals, see: (a) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651−2710. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177−2250.

(7) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238.

(8) EMEA/CHMP/SWP/4446/2000 (final), Guideline on the specification limits for residues of metal catalysts or metal reagents. Committee for Medicinal Products for Human Use (CHMP), London, 21 February 2008, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003586.pdf, accessed on September 29, 2011.

(9) The pharmaceutical industry generally needs to achieve less than 10 and 1 ppm for the permitted daily exposure of patients to palladium for oral and parenteral drug substances, respectively: see ref 8.

(10) Techniques to purge product streams and effluents from metal contamination have been divided into (1) extraction and precipitation treatments and (2) solid phase treatments: (a) Mendonca, A. *Power of Functional Resins in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2008. (b) Pink, C. J.; Wong, H. T.; Ferreira, F. C.; Livingston, A. G. *Org. Process Res. Dev.* **2008**, *12*, 589−595.

(11) Crampton, M. R. Nucleophilic Aromatic Substitution. In *Organic Reaction Mechanisms*; Knipe, A. C., Ed.; John Wiley & Sons: New York, 2008; pp 189−198.

(12) Review: Mortier, J. *Curr. Org. Chem.* **2011**, *15*, 2413−2437. See also: (a) Fuson, R. C.; Wassmundt, F. W. *J. Am. Chem. Soc.* **1956**, *78*, 5409−5413. (b) Carini, D. J.; et al. *J. Med. Chem.* **1991**, *34*, 2525−2547.

(13) Hattori, T.; Shimazumi, Y.; Goto, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099−2108.

(14) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732−8733.

(15) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(16) (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, *5*, 1919−1922. (b) Nguyen, T. H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765−768. (c) Tilly, D.; Fu, J.-m.; Zhao, B.-p.; Alessi, M.; Castanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68−71.

(17) The requisite naphthoic acids **1** and **2** were prepared by lithiation of 1-fluoronaphthalene using *s*-BuLi in THF at −75 °C followed by quench with CO_2 (Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 3351−3358) and by metalation of 1-methoxynaphthalene with *n*-BuLi/*t*-BuOK followed by carboxylation (Castagnetti, E.; Schlosser, M. *Chem. Eur. J.* **2002**, 799−804). 2-Methoxy-1-naphthoic acid (**3**) and 2,3-dimethoxy-1-naphthoic acid (**4**) were synthesized from 2-methoxynaphthalene and 2,3-dimethoxynaphthalene, respectively, by bromination followed by Br-Li permutation and CO_2 quench (Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010−1015).

(18) Jane, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417−1492.

(19) *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2008; p 321.

(20) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1−97.

(21) Belaud-Rotureau, M.; Le, T. T.; Phan, T. H. T.; Nguyen, T. H.; Aissaoui, R.; Gohier, F.; Derdour, A.; Nourry, A.; Castanet, A.-S.; Nguyen, K. P. P; Mortier, J. *Org. Lett.* **2010**, *12*, 2406−2409.

(22) In earlier studies, we described a stereospecific route to 1,1,2- and 1,2,2-trisubstituted 1,2-dihydronaphthalenes that involves the nucleophilic conjugate addition of organolithium reagents to unprotected 1- and 2-naphthalenecarboxylic acids followed by trapping of the intermediate carboxylic acid dilithium enolates with several electrophiles: (a) Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206−5207. See also: (b) Tilly, D.; Castanet, A.-S.; Mortier, J. *Chem. Lett.* **2005**, *34*, 446−447.

(23) The S_RN_1 mechanism seems less plausible because the addition of radical scavengers (tetraphenylhydrazine or 2-methyl-2-nitrosopropane dimer) to a mixture of 2-fluorobenzoic acid and NEt_2 gave only a slight lowering of the yield of the substitution product. See ref 21.

(24) Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.

(25) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K.-i. *J. Org. Chem.* **2001**, *66*, 7051−7054.

(26) Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5279−5282.

(27) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14−15.

(28) (a) Mortier, J.; Castanet, A.-S.; Nourry, A.; Belaud-Rotureau, M. WO2011101604A1, 2011. (b) Mortier, J.; Castanet, A.-S.; Belaud-Rotureau, M. WO2011101599A1, 2011.

(29) (a) Schlosser, M. *Organometallics in Synthesis. A Manual*, 2nd ed.; Wiley: Chichester, UK, 2002. (b) See also: *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2008.

(30) Huisgen, R.; Zirngibl, L. *Chem. Ber.* **1958**, *91*, 1438−1452.

(31) Mortier, J.; Vaultier, M.; Plunian, B.; Sinbandhit, S. *Can. J. Chem.* **1999**, *77*, 98−112.

(32) Gabard, J.; Dvolaitzky, M.; Jacques, J. *Bull. Soc. Chim. Fr.* **1964**, 27−30.

(33) Meyers, A. I.; Lutomski, K. A. *Synthesis* **1983**, 105−107.

(34) Shindo, M.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *Chem. Pharm. Bull.* **2009**, *57*, 752−754.

(35) Rao, R. A.; Rao, R. R. *Indian J. Chem.* **1967**, *5*, 610−612.

(36) Vishnumurthy, K.; Makriyannis, A. *J. Comb. Chem.* **2010**, *12*, 664−669.