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Direct Displacement of Alkoxy Groups of Vinylogous Esters by Grignard Reagents

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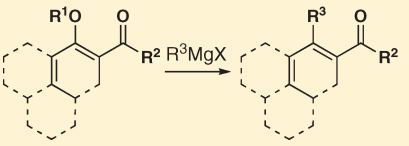
Supporting Information

ABSTRACT: The direct displacement of alkoxy groups from the β position of aromatic and unsaturated esters and ketones is described. The reaction is chemo- and regioselective, displaying wide substrate scope.



- R^1=various alkyl
- R^2=OCH_3, *n*-alkyl (unhindered esters & ketones)
- non-aromatic susbtrates

The creation of carbon−carbon bonds at sp^2-hybridized carbon centers is dominated by transition metal-catalyzed cross-coupling reactions. In most cases, an organometallic coupling partner reacts with an aryl or vinyl halide or triflate in the presence of a palladium or nickel catalyst.[1] Although these transformations are a mainstay of organic synthesis, complementary reactivity in the form of direct displacement reactions are useful in cases where orthogonal reactivity enables selective functionalization of a synthetic intermediate.

The direct, i.e. catalyst-free, displacement of aryl alkoxy groups has been used in the synthesis of substituted aromatic rings. An early example is found in the displacement of an *o*-methoxy group from a hindered naphthophenone (Figure 1).[2] This reaction was later applied to aromatic esters[3] and to the auxiliary-controlled synthesis of biaryl bonds using a naphthyl ether derived from menthol.[4] One dramatic example of displacement of a methoxy group on an unhindered ester has been reported to proceed in high yield, which was tentatively attributed to the presence of an activating *o*-cyano group.[5] Displacement of *o*-methoxy groups from extremely hindered benzoate esters was also demonstrated.[6] A more general synthetic strategy was realized by replacing carbonyl groups with oxazolines to serve as carboxylic acid equivalents that avoided any potential carbonyl addition.[7] This reaction was subsequently extended to naphthalenes,[8] rendered asymmetric with chiral oxazolines,[9] and used as a key bond construction in the assembly of natural products.[10]

We recently observed that iodinated naphthopyranone **1** (Scheme 1) exhibited remarkably selective reactions with *i*-PrMgCl. Almost exclusive displacement of the methoxy group at the 10-position was observed, with no observable addition to the lactone ring. On the basis of this result, we initiated a systematic study of this displacement reaction. Herein we report the capabilities of this reaction using a variety of substrates, including nonaromatic vinylogous esters and unhindered ketones.

A series of 1-alkoxy-2-naphthoic methyl esters was examined in displacement reactions with a variety of Grignard reagents. As

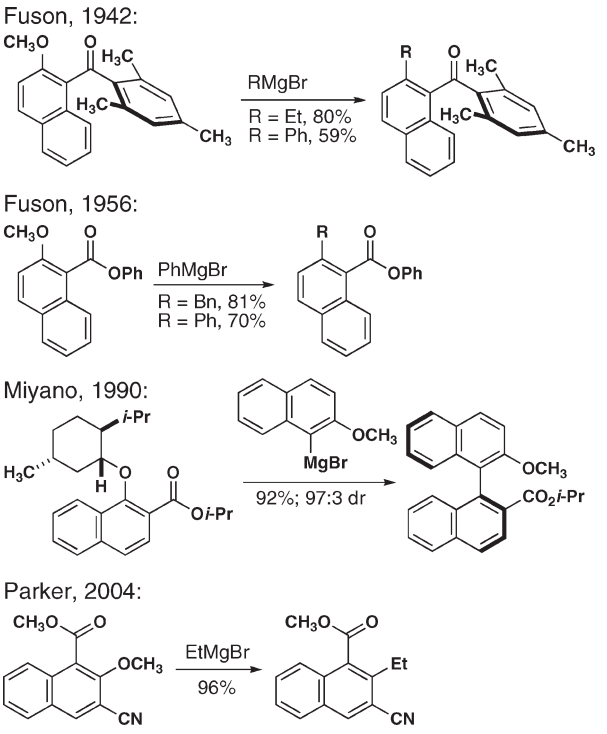


Figure 1. Displacement of methoxy groups from naphthyl ketones and esters.

seen in Table 1, the displacement of alkoxy groups adjacent to esters in naphthyl esters is affected by the steric demand of both the Grignard reagent and the alkyl group of the ether. Although displacement of methoxy groups is efficient for aryl as well as primary and secondary organomagnesium compounds, this reaction fails completely for *t*-BuMgCl. A similar trend was

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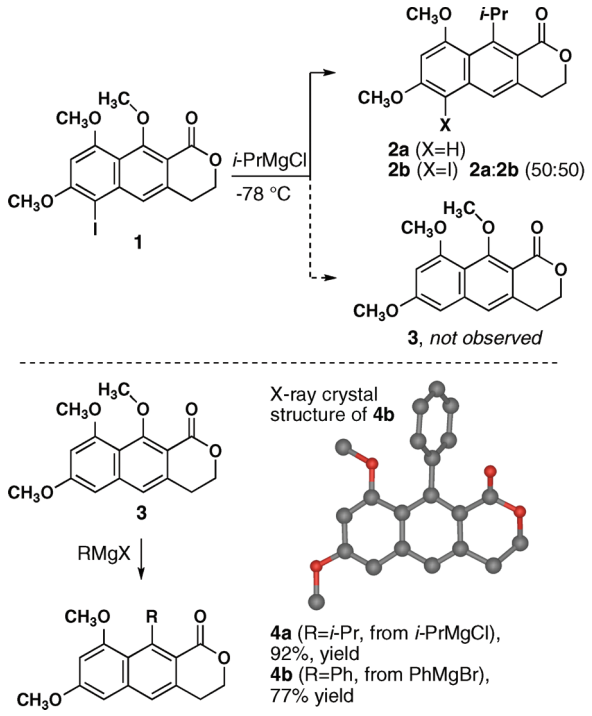
Scheme 1. Displacement of a Methoxy Group in the Presence of a Lactone and an Aryl Iodide



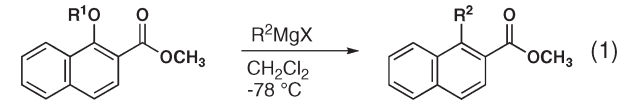
observed for *n*-butyl ethers and the efficiency of displacement drops off for benzyl ethers. Finally, isopropyl ethers are not displaced under temperatures ranging from −78 °C to room temperature but can be displaced in modest yields upon refluxing in dichloromethane (DCM).

The displacement reaction is unique to organomagnesium compounds, possibly due to the activating effect of a transiently formed magnesium chelate. Addition of *n*-butyllithium to **5a** or *n*-butylzinc chloride provided the displacement product in poor yields (20% and 15% respectively). In addition, competition between displacement of a methoxy group and a toluenesulfonate favored displacement of the methoxy group completely (Scheme 2). A one-to-one mixture of propyl ester **7** and allyl ester **8** was treated with 1 equiv of *n*-butyl magnesium chloride. Although a tosylate is ostensibly a much better leaving group, the reduced Lewis basicity of this group would be expected to form a much less stable chelate complex with magnesium, resulting in less activation of the sp^2 carbon center toward nucleophilic attack. A subsequent experiment revealed complete selectivity pairing between Grignard reagents and alkoxy groups and a similar relationship between organomagnesium cuprates and naphthyl tosylates.

High yields of displacement product are observed in the reaction of methyl 3-methoxy-2-naphthoate **12**. This reaction requires the disruption of all of the naphthalene aromaticity to proceed. In contrast, no reaction is observed with methyl 2-methoxybenzoate (not shown), demonstrating that the activation energy for this process is prohibitively high. The analogous reaction of the corresponding oxazoline requires high temperature and long reaction times.[7a]

The displacement reaction is regioselective (Scheme 3). A competition experiment between **5a** and **12** indicated that attack at the 1 position was favored. This trend is also observed in the

Table 1. Influence of Steric Demand of the Alkoxy Substituent (R^1) and Grignard Reagent (R^2) on the Yield of Displacement Product



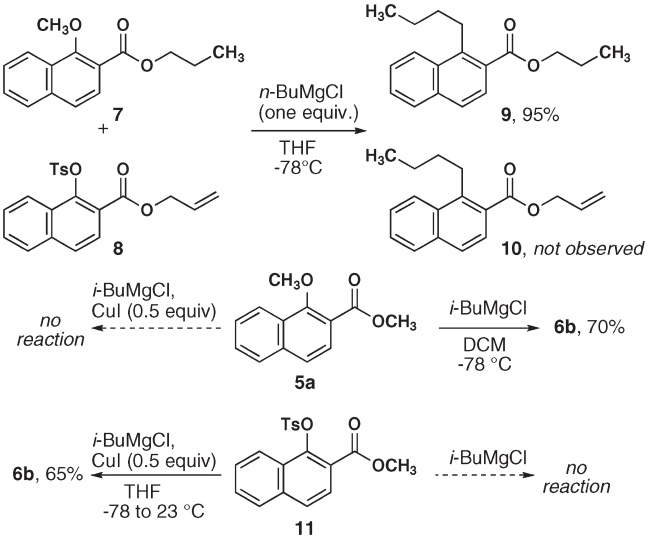
5a, R^1=CH_3; **5b**, R^1=*n*-Bu; **5c**, R^1=Bn; **5d**, R^1=*i*-Pr

6a, R^2=*n*-Bu; **6b**, R^2=*i*-Bu; **6c**, R^2=Ph; **6d**, R^2=*i*-Pr

entry	substrate (R^1)	R^2 MgX	product	yield, %
1	**5a** (CH_3)	*n*-BuMgCl	**6a**	90
2	**5b** (*n*-Bu)	*n*-BuMgCl	**6a**	80
3	**5c** (Bn)	*n*-BuMgCl	**6a**	58
4	**5d** (*i*-Pr)[a]	*n*-BuMgCl	**6a**	35
5	**5a** (CH_3)	*i*-BuMgCl	**6b**	70
6	**5b** (*n*-Bu)	*i*-BuMgCl	**6b**	63
7	**5c** (Bn)	*i*-BuMgCl	**6b**	53
8	**5d** (*i*-Pr)[a]	*i*-BuMgCl	**6b**	33
9	**5a** (CH_3)	PhMgBr	**6c**	70
10	**5b** (*n*-Bu)	PhMgBr	**6c**	66
11	**5c** (Bn)	PhMgBr	**6c**	49
12	**5d** (i-Pr)[a]	PhMgBr	**6c**	25
13	**5a** (CH_3)	*i*-PrMgCl	**6d**	78
14	**5b** (*n*-Bu)	*i*-PrMgCl	**6d**	71
15	**5c** (Bn)	*i*-PrMgCl	**6d**	50
16	**5d**(i-Pr)[a]	*i*-PrMgCl	**6d**	30

[a] Heated to reflux for 3 h.

Scheme 2. Comparison of Alkyl Ether and Tosylate Reactivity toward Displacement



reaction of substrate **14**, in which methoxy groups at both positions can be displaced. Although no reaction is observed in THF, the reaction in dichloromethane proceeded readily at −78 °C with preferential attack at the 1 position. As expected, higher reactivity was observed in DCM, when compared to THF, due to the decreased solvation of the Grignard reagent.

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Scheme 3. Regioselectivity in the Displacement of Alkoxides with Grignard Reagents

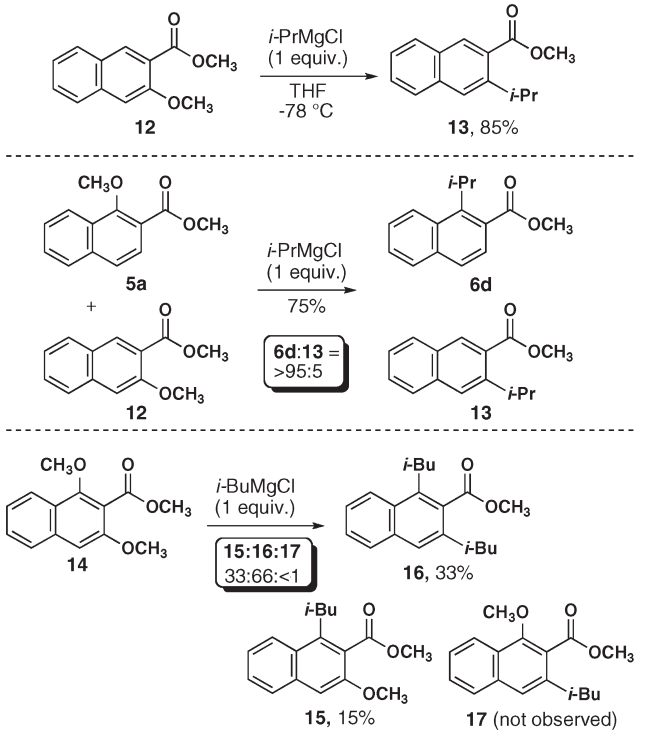
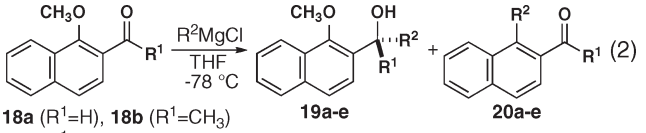


Table 2. Comparison of Carbonyl Reactivity toward Alkoxide Displacement



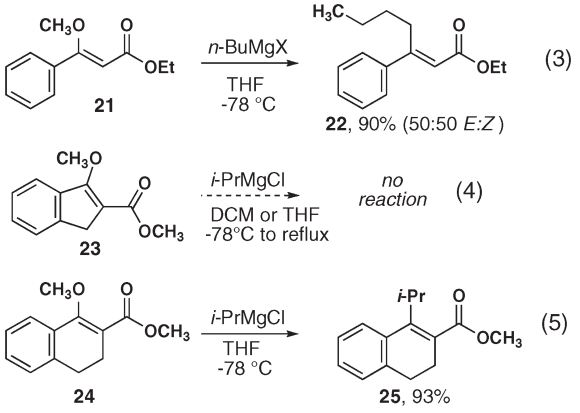
18a (R^1=H), **18b** (R^1=CH_3)
18c (R^1=*n*-Bu)

entry	substrate (R^1)	R^2	ratio of **19**:**20**	isolated yield, % (product)
1	**18a**	*n*-Bu	>95:<5	85 (**19a**)
2	**18b**	*n*-Bu	27:73	66 (**20b**)
3	**18c**	*n*-Bu	<5:>95	85 (**20c**)
4	**18b**	*i*-Pr	<5:>95	61 (**20d**)[a]
5	**18c**	*i*-Pr	<5:>95	90 (**20e**)

[a] The corresponding secondary alcohol, resulting from carbonyl reduction, was isolated in 20% yield.

The displacement reaction works well with alkyl ketones (Table 2). Methyl ketone **18b** reacts with a significant preference for methoxy group displacement when treated with either *i*-PrMgCl or *n*-BuMgCl. *n*-Butyl ketone **18c** reacts with *complete* selectivity for methoxy group displacement and none of the alcohol product **20c** can be observed by GCMS. Although related reactions of hindered aromatic ketones have been observed, this is the first example of an *n*-alkyl ketone undergoing alkoxy group displacement.

Nonaromatic carbonyl compounds are also substrates for displacement. *Z*-Ethyl 3-methoxycinnamate **21** reacts with *n*-BuMgCl with high yield to give a 50:50 mixture of alkene isomers (eq 3). This result indicates that the collapse of the presumed β-alkoxy enolate intermediate proceeds with little preference for placement of the alkyl or aryl group cis to the ester. Analogous cyclic substrates react with a range of efficiency. A fused 5-membered-ring ester **23** is totally unreactive



toward *n*-BuMgCl, even in refluxing THF or CH_2Cl_2 (eq 4). 6-Membered-ring ester **24** undergoes smooth displacement (eq 5). These results are consistent with the increased bond angle and the weaker chelate structure that can be formed between magnesium and the β-alkoxy carbonyl.

In summary, we have demonstrated that direct displacement of alkoxy groups from aromatic and α,β-unsaturated esters and ketones is an efficient C−C bond-forming process. Although ketones are generally viewed as incompatible with the high nucleophilicity of Grignard reagents, we have shown that the displacement reaction is facile at temperatures below which the ester or ketone products will undergo addition. This process enables the C−C bond formation with normally unreactive alkoxy groups and minimal use of protecting groups.

EXPERIMENTAL SECTION

General Procedure 1: Displacement of Alkyl Ethers by Grignard Reagents. To a cooled solution (−78 °C) of alkyl ether (1.00 mmol) in THF or DCM (5 mL) was added a solution of *i*-PrMgCl in THF (2.0 M, 0.5 mL). The reaction was monitored until complete by TLC and quenched with saturated ammonium chloride (5 mL). The resulting layers were separated, and the aqueous layer was extracted with 2 × 10 mL of EtOAc. The combined organic layers were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude displacement product. The product was purified by flash chromatography to afford pure displacement product.

General Procedure 2: Displacement of Alkyl Ethers by Grignard Reagents. To a cooled solution (−78 °C) of alkyl ether (1.00 mmol) in THF or DCM (5 mL) was added a solution of *i*-PrMgCl in THF (2.0 M, 0.5 mL). The solution was allowed to warm to rt and then heated at reflux for 3 h. The reaction was monitored until complete by TLC and quenched with saturated ammonium chloride (5 mL). The resulting layers were separated, and the aqueous layer was extracted with 2 × 10 mL of EtOAc. The combined organic layers were washed with 20 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude displacement product. The product was purified by flash chromatography to afford pure displacement product.

4b: According to general procedure 1, **3** (0.030 g 0.104 mmol) was reacted with a solution of PhMgBr in THF (1.0 M, 0.10 mL) to afford a crude yellow solid. The solid was purified by flash chromatography (10:90 EtOAc/hexanes) to yield the product **4b** as a white solid (0.027 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.33 (d, J = 7.2 Hz, 3H), 7.19 (dd, J = 2.0, 7.4 Hz, 2H), 6.72 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 4.48 − 4.43

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(m, 2H), 3.93 (s, 3H), 3.32 (s, 3H), 3.15 (t, J = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 160.7, 159.9, 144.9, 142.9, 138.5, 136.5, 128.2, 126.7, 126.2, 124.5, 120.9, 120.3, 99.8, 98.4, 66.7, 55.7, 55.6, 30.2; HRMS (ESI) m/z calcd for $C_{21}H_{18}O_4Na$ $(M + Na)^+$ 357.1103, found 357.1111; IR (thin film) 3095, 2910, 1715, 1595 cm^{-1}; mp 185−186 °C.

9: Double Labeling Experiment. An equimolar amount of **7** (0.030 g, 0.079 mmol) and **8** (0.019 g, 0.079 mmol) was dissolved in 0.5 mL of THF and the solution was cooled to −78 °C. To this solution was added a 1.5 M solution of *n*-BuMgCl in THF (0.052 mL, 0.079 mmol). The reaction was stirred for 10 min and was then quenched with saturated ammonium chloride (5 mL). The resulting layers were separated, and the aqueous layer was extracted with 2 × 10 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford a crude oil. GCMS and NMR analysis showed only methoxy displacement and no observable evidence of tosylate displacement. The crude product was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **9** (0.020 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.09 (m, 1H), 7.80−7.43 (m, 5H), 4.25 (t, J = 6.7 Hz, 2H), 3.36−3.2 (m, 2H), 1.81−1.60 (m, 2H), 1.53−1.40 (m, 4H), 0.99 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 141.985, 135.2, 132.3, 128.9, 128.1, 127.3, 126.7, 126.4, 126.2, 125.5, 67.0 33.9, 29.6, 23.6, 22.4, 14.2, 10.9; HRMS (ESI) m/z calcd for $C_{18}H_{23}O_2$ $(M + H)^+$ 271.1693, found 271.1690; IR (thin film) 3070, 2937, 2880, 1715, 1595 cm^{-1}.

Competition Experiment. An equimolar amount of **5a** (0.10 g, 0.462 mmol) and **11** (0.10 g, 0.462 mmol) was dissolved in 2 mL of THF and the solution was cooled to −78 °C. To this solution was added a 2.0 M solution of *i*-PrMgCl in THF (0.23 mL, 0.462 mmol). The reaction was stirred for 10 min and was then quenched with saturated ammonium chloride (5 mL). The resulting layers were separated, and the aqueous layer was extracted with 2 × 10 mL of EtOAc. The combined organic layers were washed with 10 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford a crude oil. NMR analysis showed only displacement at the 1-position. The crude product was purified by flash chromatography (20:80 EtOAc/hexanes) to afford **6d** (0.079 g, 75%) as the only product.

20e: According to general procedure 1, **18c** (0.035 g, 0.1457 mmol) was reacted with a solution of *i*-PrMgCl in THF (2.0 M, 0.073 mL) to afford a crude oil. The oil was purified by flash chromatography (10:90 EtOAc/hexanes) to yield the product **20e** as a colorless oil (0.033 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.53−7.34 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 3.60−3.42 (m, 1H), 2.81 (t, J = 7.4 Hz, 2H), 1.71−1.59 (m, 2H), 1.50 (d, J = 7.2 Hz, 6H), 1.35 (dd, J = 7.4, 14.8 Hz, 2H), 0.88 (t, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 140.9, 139.3, 134.9, 131.8, 129.4, 127.1, 126.4, 126.3, 126.1, 123.0, 44.4, 31.6, 26.5, 22.9, 22.6, 14.2; HRMS (ESI) m/z calcd for $C_{18}H_{23}O$ $(M + H)^+$ 255.1743, found 255.1742; IR (thin film) 3095, 2959, 2865, 1687 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectra (^{1}H NMR, ^{13}C NMR, NMR) for all new compounds, and a CIF file for **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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