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Bromoetherification of Alkenyl Alcohols by Aerobic Oxidation of Bromide: Asymmetric Synthesis of 2-Bromomethyl 5-Substituted Tetrahydrofurans

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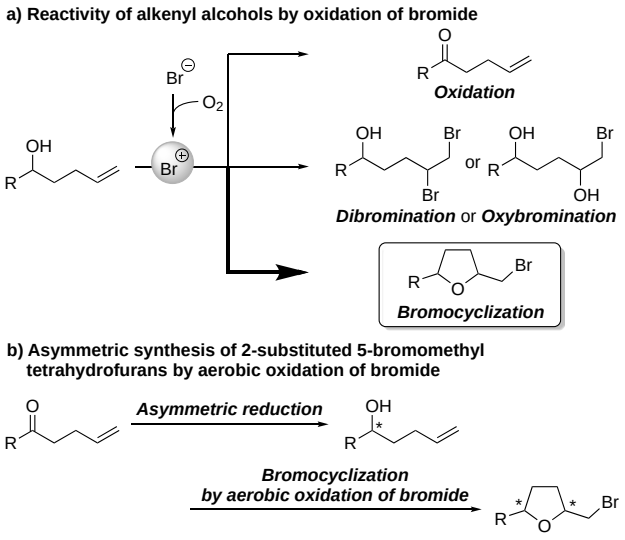
Abstract. An asymmetric synthesis of 2-bromomethyl-5-substituted tetrahydrofurans via a chiral-ruthenium-catalyzed transfer hydrogenation of 3-butenyl ketones and bromoetherification of chiral pentenyl alcohols was developed. The inhibition of some side reactions furnished the desired products in high yields with high enantioselectivities. In addition, chiral pentenyl alcohols bearing electron-donating groups triggered substrate racemization in the aerobic bromoetherification.

Keywords: Aerobic Oxidation; Bromoetherification; Enantioselective reduction; Catalytic reaction; Tetrahydrofuran

The functional group selective transformation of organic compounds is an important strategy to provide desired products efficiently for fine organic synthesis. Although the transformation by bromide oxidation has attracted considerable attention as an environmentally friendly and practical methodology, the oxidized bromine causes some reactions in organic molecules because it has both cationic and radical characters that promote electrophilic addition reaction, radical reaction, and so on.[1] For example, the oxidation of alcohols using bromide and an oxidant has been reported (Scheme 1a, top).[2] In addition, dibromination and oxybromination by the addition of oxygen nucleophiles as in the electrophilic addition reaction of alkenes, easily proceed with molecular bromine (Scheme 1a, middle).[3] As shown above, the acceleration of the intramolecular bromocyclization in these side reactions is a challenging task for the transformation via the oxidation of bromide (Scheme 1a, bottom). On the other hand, chiral 2,5-disubstituted tetrahydrofuran derivatives are important structures in natural products and biologically active products.[4] Although the intramolecular bromoetherification of substituted pentenyl alcohols is an extremely useful way to construct the 2,5-disubstituted tetrahydrofuran skeleton,[5] no asymmetric intramolecular bromoetherification that furnishes products with high optical purity has been established. We envisioned that the enantioselective reduction of butenyl ketones, followed by the intramolecular bromoetherification of chiral pentenyl alcohols by the aerobic oxidation[6] of bromide, would provide chiral substituted tetrahydrofurans efficiently (Scheme 1b). To the best of our knowledge, transition-metal-free bromoetherification via aerobic oxidation of bromide has not been developed. The asymmetric reduction using a transition-metal catalyst may lead to isomerization, producing various internal alkene products as byproducts.[7] Therefore, it is also important to control the chemoselectivity of terminal alkenes in the enantioselective reduction using a transition-metal catalyst.[8,9] We report herein the asymmetric synthesis of chiral substituted tetrahydrofurans involving a transition-metal-catalyzed enantioselective reduction and an intramolecular bromoetherification via the aerobic



Scheme 1. Strategy for synthesis of chiral 2,5-disubstituted tetrahydrofuran derivatives.

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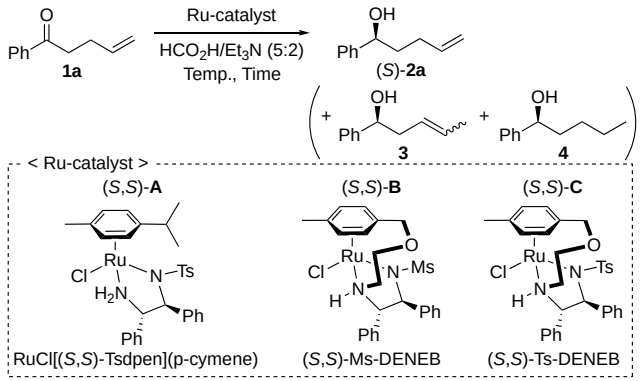
oxidation of bromide.

First, we focused on the chiral-ruthenium-catalyzed enantioselective transfer hydrogenation[9] for the enantioselective reduction of butenyl ketones and performed a screening for ruthenium catalyst in the reaction of 3-butenyl-phenyl-ketone (**1a**) (Table 1). Treatment of **1a** using RuCl[(*S*,*S*)-Tsdpen](*p*-cymene) ((*S*,*S*)-**A**) as the chiral catalyst in HCO_2H/Et_3N at room temperature gave the desired alcohol ((*S*)-**2a**)[10] in 56% yield with 94% ee together with 37% of recovered **1a** (entry 1). Use of tethered ruthenium catalysts ((*S*,*S*)-**B** and (*S*,*S*)-**C**) at room temperature improved the yield and enantioselectivity of (*S*)-**2a** without the formation of any byproduct (entries 3 and 6). However, the use of (*S*,*S*)-**A**–**C** at 60 ºC resulted in the formation of byproducts **3** and **4** resulting from reactions at the terminal olefin moiety, even though the reactivity of the reduction was increased (entries 2, 4, and 6). An enantioselective transfer hydrogenation of **1a** on a 1 mmol scale also gave (*S*)-**2a** in 94% yield with 97% ee (entry 7).

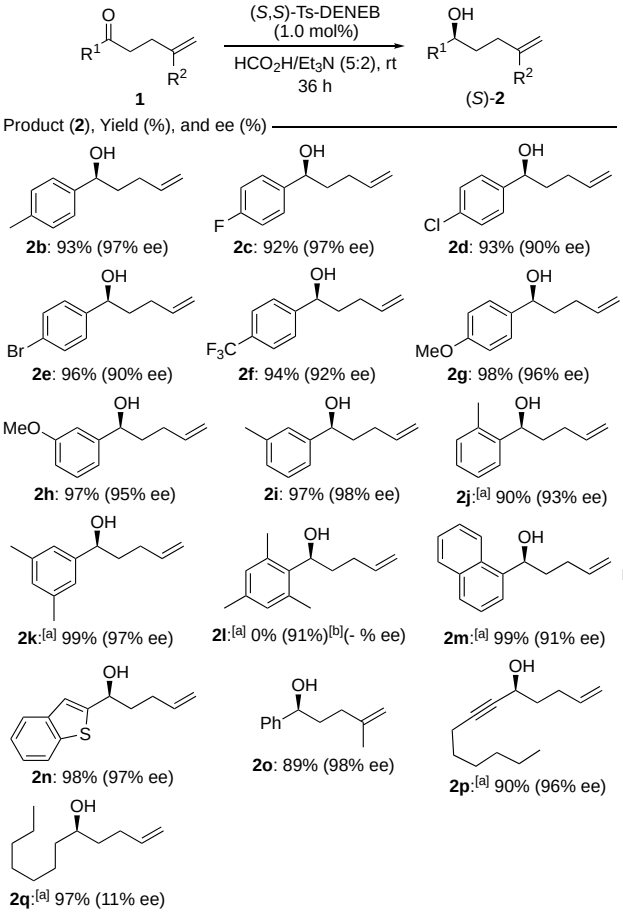
Table 1. Screening for chiral Ru catalyst in enantioselective transfer hydrogenation.



Entry	Cat.	Temp. [ºC]	Time [h]	Yield (**2a**/**3**/**4**) [%]	Ee of **2a** [%ee]
1	A	rt	24	56/0/0 [37][a]	94
2	A	60	24	68/7/5 [8][a]	90
3	B	rt	24	97/0/0	95
4	B	60	6	83/12/1	93
5	C	rt	24	99/0/0	96
6	C	60	6	78/16/4	95
7[b]	C	rt	36	94/0/0	97

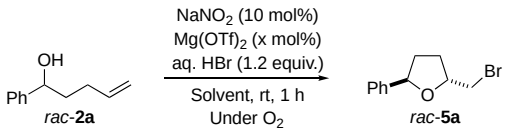
[a] Recovery of **1a**. [b] Reaction on 1 mmol scale.

To explore the substrate scope for the enantioselective transfer hydrogenation, butenyl ketones (**1**) were examined under the optimum conditions (Table 1, entry 7) (Scheme 2). Treatment of monosubstituted phenyl butenyl ketones bearing electron-donating groups and electron-withdrawing groups (**1b**–**1j**), as well as disubstituted phenyl butenyl ketone (**1k**) furnished corresponding alcohols (**2b**–**2k**) in excellent yields with 90–98% ee. Unfortunately, trisubstituted phenyl substrate (**2l**) was almost unreactive. Substrates with 1-naphthyl (**1m**), benzothiophene (**1n**), disubstituted alkene (**1o**), and



Scheme 2. Enantioselective transfer hydrogenation of **1** [a] (*S*,*S*)-Ts-DENEB (5.0 mol%) was used. [b] Recovery of **1l**.

Table 2. Screening for additive and solvent in bromoetherification of *rac*-**2a** via aerobic oxidation of bromide.



Entry	x	Solvent	Yield [%]	Dr of **5a** [*trans*:*cis*]
1	0	MeCN	80[19][a]	71:29
2	0	AcOEt	19[20][a][58][b]	68:32
3	0	DMF	33[12][a][50][b]	73:27
4	0	CH_2Cl_2	46[1][a][47][b]	65:35
5	0	THF	0[95][b]	-
6	0	MeCN:CH_2Cl_2 (1:1)	84[12][a]	71:29
7	0	MeCN:CH_2Cl_2 (1:2)	71[4][a][18][b]	68:32
8	10	MeCN:CH_2Cl_2 (1:1)	85[9][a]	69:31
9	20	MeCN:CH_2Cl_2 (1:1)	91[8][a]	69:31
10	20	MeCN:CH_2Cl_2 (1:1)	56[8][a][28][b]	70:30

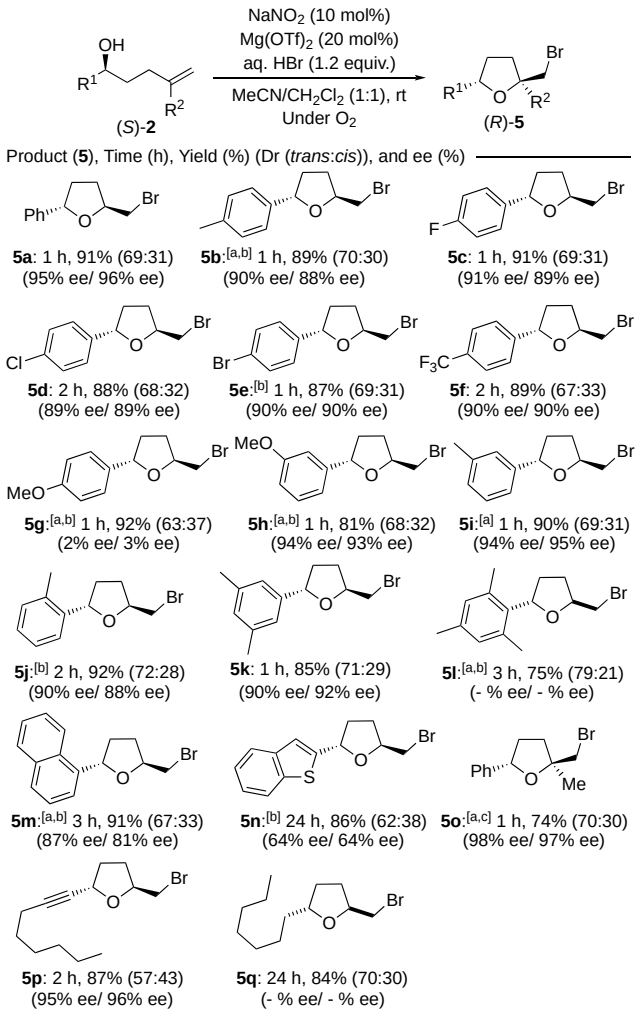
[a]Yield of α-(3,4-dibromobutyl)-benzenemethanol. [b]Recovery of **2a**. [c] Under air.

alkynyl (**1p**) groups also provided chiral alcohols (**2m**–**2p**) in excellent yields with high enantiomeric excess. The reaction of aliphatic ketone (**1q**) generated product (**2q**) in excellent yield but with unsatisfactory enantiomeric excess.

Next, we screened for the additive and the solvent in the bromoetherification of *rac*-**2a** to unfurl the asymmetric synthesis of 2,5-substituted tetrahydrofurans (Table 2).

Bromoetherification of *rac*-**2a** in MeCN provided *rac*-**5a** in 80% yield (entry 1). The use of CH_2Cl_2 as solvent gave *rac*-**5a** in 46 % yield together with a small amount of byproduct, indicating the high chemoselectivity of the reaction (entry 4). Other solvents did not improve the yield of *rac*-**5a** (entries 2, 3, and 5). Further screening for the reaction conditions (entries 6–10) revealed that the optimum conditions would be attained in the presence of 20 mol% $Mg(OTf)_2$ as the additive in the solvent mixture of MeCN and CH_2Cl_2 (1:1) under O_2, which gave *rac*-**5a** in 91% yield (entry 9).

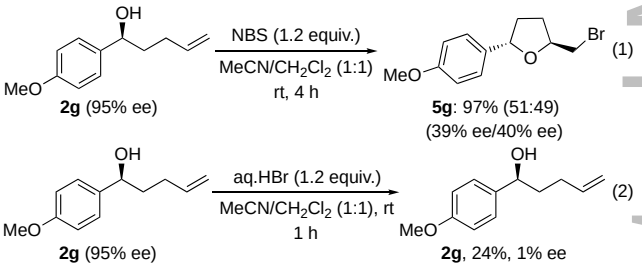
We further examined the substrate scope in the asymmetric bromoetherification of chiral substituted pentenyl alcohols ((*S*)-**2**) via the aerobic oxidation of bromide (Scheme 3).



Scheme 3. Asymmetric bromoetherification of (*S*)-**2** via aerobic oxidation of bromide. [a] MeCN/CH_2Cl_2 (1:1, 0.25 M). [b] $NaNO_2$ (20 mol%). [c] $NaNO_2$ (50 mol%).

When non-substituted alcohol (**2a**), *p*-substituted alcohols bearing Cl (**2d**), Br (**2e**), and CF_3 (**2f**) groups, *m*-substituted alcohols (**2h** and **2i**), and *o*-substituted alcohol (**2j**) were used in the bromoetherification, chiral bromomethyl tetrahydrofurans (**5a**, **5d**, **5e**, **5f**, and **5h**–**j**) were obtained in high yields (81–92%) with *trans*-selectivity (dr = 67:33–72:28) without loss of optical purity. Treatment of alcohols bearing *p*-Me (**2b**), *p*-F (**2c**), *m*-diMe (**2k**), and 1-naphthyl (**2m**) phenyl groups with $NaNO_2$/$Mg(OTf)_2$/aq. HBr under O_2 gave corresponding products (**5b**, **5c**, **5k**, and **5m**) with 81–92% ee, indicating slight racemization. In particular, the reaction of substrates with electron-rich aryl groups, such as *p*-MeO phenyl (**2g**) and benzothiophene (**2n**), was found to cause significant racemization of products **5g** and **5n** (2–64% ee). Alkynyl alcohol with 96% ee (**2p**) also underwent the bromoetherification to give corresponding product (**5p**) in 87% yield with the desired enantiomeric excess. The bromoetherification of racemic tri-substituted phenyl alcohol (**2l**) and aliphatic alcohol (**2q**) occurred to give desired products (**5l** and **5q**) in high yields (75% and 84%, respectively) with *trans*-selectivity (dr = 79:21 and 70:30, respectively).

To elucidate the racemization mechanism in the bromoetherification, we carried out supporting experiments of the reaction (Scheme 4). Bromoetherification of **2g** with NBS provided desired product (**5g**) in 97% yield but with low optical purity (39% ee/40% ee) (eq. 1). Treatment of **2g** with aq. HBr led to the low recovery of **2g** (24%) with 1% ee and the generation of many byproducts (eq. 2).[11]



Scheme 4. Mechanistic studies of the racemization in the bromoetherification.

Based on the results in Scheme 4, we suggest that the racemization of substrates in this reaction is caused by the bromo radical or proton under the acidic conditions.

We propose a reaction mechanism for the bromoetherification of chiral alkenyl alcohols (**2**) via the aerobic oxidation of bromide, including the racemization of alcohols, on the basis of mechanistic studies (Scheme 5). The aerobic oxidation of bromide with $NaNO_2$ and O_2 occurs to generate Br_2, which functions as a bromo cation or a bromo radical in situ.[2d,6] In addition, $Mg(OTf)_2$ as a Lewis acid catalyst assists in the formation of the bromo cation species by trapping the counteranion to control chemoselectivity of the aerobic bromoetherification. The bromo cation species reacts with the π-electron

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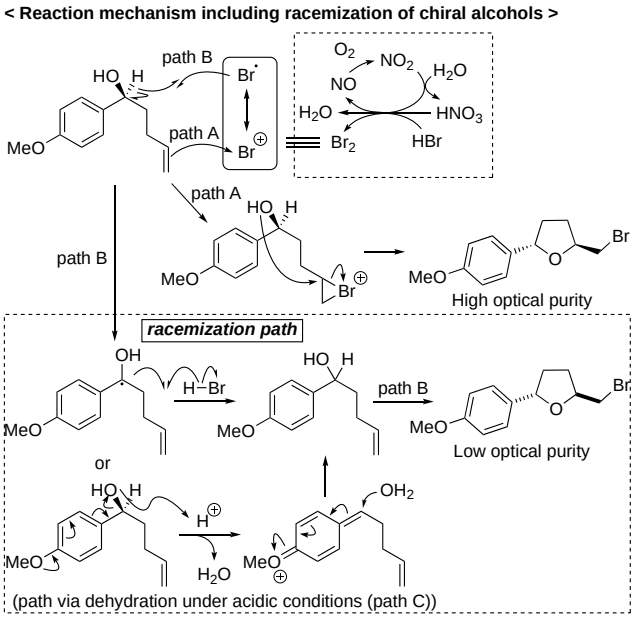
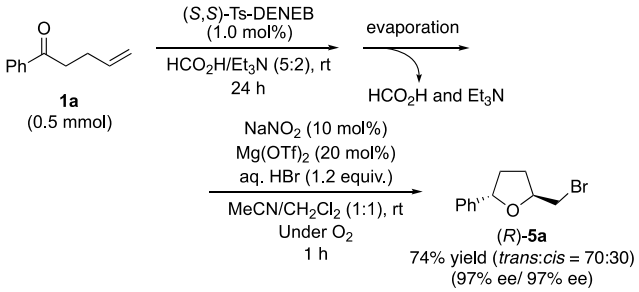


Scheme 5. Plausible reaction mechanism in the bromoetherification via aerobic oxidation.

on alkene to promote intramolecular cyclization. This electrophilic addition reaction of alkene is favored and the cyclization products have high optical purity (path A). On the other hand, the bromo radical abstracts a hydrogen atom from the substrate benzyl position to generate a benzyl radical intermediate that immediately promotes the racemization of substrate (path B). The concerted abstraction of benzylic hydrogen atom on substrate bearing a *p*-methoxy phenyl group (**2g**) with a strong resonance effect is more favored than the bromocyclization to obtain the low optical purity product. In addition, it is also possible that the racemization of these substrates occurs via formation of benzyl cation intermediate by dehydration under the acidic conditions (path C).

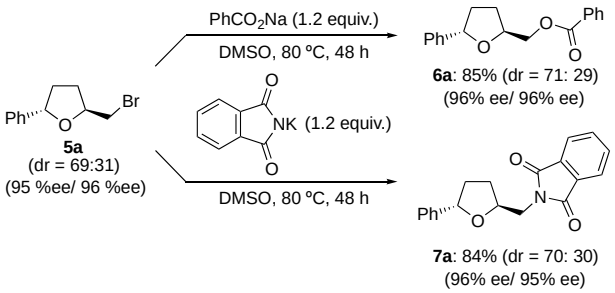
Finally, one-pot synthesis of chiral 2-bromomethyl-5-phenyl tetrahydrofuran (**5a**) was investigated from 3-butenyl-phenyl-ketone (**1a**) via the enantioselective transfer hydrogenation and the bromoetherification (Scheme 6). After the enantioselective transfer hydrogenation of **1a** with (*S*,*S*)-Ts-DENEB catalyst, the bromoetherification via aerobic oxidation of bromide proceed under the present conditions by evaporation of the crude product, which removes



Scheme 6. One-pot synthesis of chiral 2-substituted-5-bromomethyl tetrahydrofuran (**5a**).

HCO_2H and Et_3N, to give the desired product (**5a**) in 74% yield with high enantioselectivity (97% ee/97% ee).

To demonstrate the synthetic utility of the chiral bromoetherification product, we investigated the derivatization of 2-bromomethyl-5-phenyltetrahydrofuran (**5a**) via simple C–heteroatom bond formation to obtain heteroatom combined products (Scheme 7). Treatment of **5a** with sodium benzoate as the oxygen nucleophile and potassium phthalimide as the nitrogen nucleophile in DMSO at 80 ºC provided corresponding products (**6a** and **7a**) in high yields in unchanged diastereomeric and enantiomeric ratios.



Scheme 7. Derivatization of substituted bromomethyl tetrahydrofuran (**5a**).

In conclusion, we have developed an asymmetric synthesis of 2-substituted-5-bromomethyl tetrahydrofurans via the chiral-ruthenium-catalysed transfer hydrogenation of alkenyl 3-butenyl ketones. followed by the bromoetherification by the aerobic oxidation of bromide. This method controls the chemoselectivity of the substrates to give desired products with high stereoselectivity. The development of an asymmetric synthesis of chiral organic molecules by the aerobic oxidation of halogens and the application of chiral 2-substituted-5-bromomethyl tetrahydrofurans as chiral building blocks are underway in our laboratory.

Experimental Section

General Procedure for Ruthenium-catalyzed Enantioselective Transfer Hydrogenation of Alkenyl Ketones (1) (Table 1; entry 7 and Scheme 2).

A solution of 3-butenyl phenyl ketone (**1a**) (160.2 mg, 1.0 mmol) and (*S*,*S*)-Ts-DENEB (6.5 mg, 0.01 mmol) in a solution mixture of HCO_2H and Et_3N (5:2, 500 μL) was sttierd at room temperature for 36 h under argon atomosphere. To the reaction mixture was added water (10 mL), and the product was extracted with AcOEt (20 mL×3). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: hexane/AcOEt = 8/1) to give desired product **2a** (152.6 mg, 94% yield, 97% ee).

General Procedure for Bromo-etherification of Chiral Alkenyl Alcohols (2) by Aerobic Oxidation of Bromide (Table 2; entry 9 and Scheme 3).

To a solution of 1-phenyl-4-penten-1-ol (**2a**) (40.6 mg, 0.25 mmol), $NaNO_2$ (1.7 mg, 0.025 mmol), and $Mg(OTf)_2$ (16.1 mg, 0.050 mmol) in a solution mixture of MeCN and CH_2Cl_2 (1:1, 2.0 mL) was added 47% HBr aq. (34.7 μL, 0.30 mmol) under oxygen atmosphere. After the reaction mixture was stirred at room temperature for 1 h under oxygen atmosphere, saturated Na_2SO_3 aqueous solution (10 mL) was added and the product was extracted with AcOEt (20 mL×3). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: hexane/ether = 15/1) to give desired product **5a** (54.9 mg, 91% yield, *trans*:*cis* = 69:31, 95% ee/96% ee).

Acknowledgements

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[11] (*E*)-1-methoxy-4-(penta-1,4-diene-1-yl)benzene was obtained in 28% yield as byproduct in the reaction of **2g** with aq. HBr.

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UPDATE

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