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Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents and their application to sequential radical cyclization/cross-coupling reactions

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Abstract—Reactions of alkyl halides with arylmagnesium bromides in the presence of cobalt(II)(diphosphine) complexes are discussed. Treatment of 1-bromooctane with phenylmagnesium bromide with the aid of a catalytic amount of $CoCl_2$(dppp) [DPPP = 1,3-bis(diphenylphosphino)propane] yielded octylbenzene in good yield. The reaction mechanism would include single electron transfer from an electron-rich cobalt complex to alkyl halide to generate the corresponding alkyl radical. The mechanism was justified by $CoCl_2$(dppe)-catalyzed [DPPE = 1,2-bis(diphenylphosphino)ethane] sequential radical cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives that yielded benzyl-substituted cyclopentane skeletons.

1. Introduction

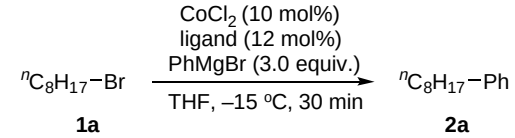
Transition metal-catalyzed cross-coupling reactions provide powerful tools for carbon–carbon bond formation. The cross-coupling reactions of β-hydrogen-containing unactivated alkyl halides with organometallic reagents had been difficult because of slow oxidative addition of alkyl halides to low valent transition metal and β-hydride elimination from alkyl-transition metal intermediates. For the past decade, considerable efforts have been made to overcome the difficulty in the use of alkyl halides in the cross-coupling reactions.[1,2] We have been interested in the potential of cobalt catalysts in the cross-coupling reaction.[3,4] Here we report the full details of the cobalt-catalyzed reaction of alkyl halides with arylmagnesium bromides.[5]

2. Results and discussions

2.1. Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents

The coupling reaction of 1-bromooctane (**1a**) with phenyl Grignard reagent was first investigated (Table 1). A number of ligands were screened, and 1,3-bis(diphenylphosphino)propane (DPPP) proved to be outstandingly effective for the phenylation reaction at −15 °C. Other ligands such as DPPE and DPPF were much less effective. The choice of the solvent was essential to obtain **2a** in satisfactory yield. A similar reaction in ether resulted in very low yield of **2a**. The excess, 3 equiv in this case, of the Grignard reagent is essential to attain satisfactory yield. The reaction with a stoichiometric amount of PhMgBr was sluggish.

Table 1. Cobalt-catalyzed phenylation reaction of 1-bromooctane (**1a**)



1a **2a**

Entry	Ligand	Yield (%)
1	DPPM	3
2	DPPE	15
3	DPPP	65
4	DPPH	1
5	DPPF	1
6	PPh_3 (24 mol%)	3
7	TMEDA	5

Ligands DPPM–DPPH represent $Ph_2P(CH_2)_nPPh_2$, $n=1$: DPPM; $n=2$: DPPE; $n=3$: DPPP; $n=6$: DPPH. DPPF and TMEDA denote 1,1′-bis(diphenylphosphino)ferrocene and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, respectively.

Keywords: Cross-coupling reaction; Cobalt; Aryl Grignard reagent; Radical reaction.
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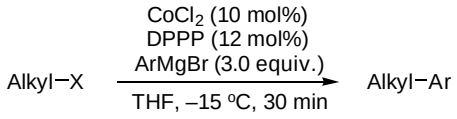
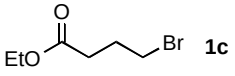
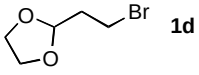
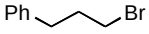
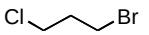
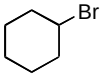
Various combinations of organic halides and aryl Grignard reagents were examined (Table 2). Not only phenyl Grignard reagent but also 4-methoxyphenyl and 2-thienyl Grignard reagents participated in the cross-coupling reaction. Unfortunately, the reaction with 2-methylphenyl Grignard reagent resulted in failure, yielding octane and 1-octene with half of **1a** untouched. Alkyl iodide **1b** was inferior to the corresponding bromide as the coupling partner. Ester and chloro moieties survived under the reaction conditions. Bromocyclohexane was subjected to the cobalt-catalyzed phenylation at 0 °C to yield cyclohexylbenzene in only 24% yield.

Table 2. Cobalt-catalyzed cross-coupling reactions of alkyl halides with aryl Grignard reagents



Entry	1	ArMgBr	2	Yield (%)
1	$^{n}C_8H_{17}$–Br **1a**	4-CH_3O–C_6H_4MgBr	**2b**	67
2	$^{n}C_8H_{17}$–Br **1a**	(2-Thienyl)MgBr	**2c**	54
3	$^{n}C_8H_{17}$–Br **1a**	2-CH_3–C_6H_4MgBr	**2d**	<1
4	$^{n}C_8H_{17}$–I **1b**	PhMgBr	**2a**	33
5	 **1c**	PhMgBr	**2e**	49
6	 **1d**	PhMgBr	**2f**	60
7	 **1e**	PhMgBr	**2g**	63
8	 **1f**	PhMgBr	**2h**	47
9	 **1g**	PhMgBr	**2i**	24

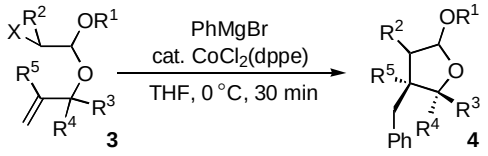
2.2. Cobalt-catalyzed sequential radical cyclization/cross-coupling reaction

We are tempted to assume that the oxidative addition process in this coupling reaction would proceed via a single electron transfer from an electron-rich cobalt complex to alkyl halide. Although oxidative addition of alkyl halides is much slower than that of aryl and vinyl halides via a three-centered addition mechanism, single electron transfer to alkyl halides allows facile activation of alkyl halides.

The single electron transfer that would operate in the present system was verified by the reactions of Ueno–Stork halo acetals **3**, which serves as a radical probe.[6] Treatment of bromo acetal **3a** with phenylmagnesium bromide in THF at 0 °C in the presence of $CoCl_2$(dppe) for 30 min afforded phenylated cyclic acetal **4a** in 80% yield (Table 3, entry 1). Several ligands such as TMEDA, DPPM, DPPE, DPPP, DPPB, PPh_3, and $P(OPh)_3$ were screened. Among them, DPPE proved to be extremely efficient. The use of other ligands resulted in lower yields of the phenylated product **4a** and formation of a non-phenylated byproduct (30–50%). $CoCl_2$ by itself and $CoCl(PPh_3)_3$ did not give satisfactory results. Use of a cobaloxime, $Co(dmgH)_2PyCl$,[7] resulted in recovery of **3a**.

A variety of halo acetals were examined, and the results are illustrated in Table 3, Scheme 1, and Scheme 2. Halo acetals bearing a terminal alkene moiety underwent phenylative cyclization to furnish the corresponding benzyl-substituted tetrahydrofuran derivatives in good to excellent yields (Table 3). It is noteworthy that the stereochemistry of the products was quite similar to that in the previous reports of radical reductive cyclization reactions.[8] This observation is highly suggestive of the same transition state of the cyclization step in the present reaction as in the free radical reaction. The allylic alcohols that constitute the substrates **3** were not detected in the reaction mixture. This means that β-alkoxy elimination, which could be facilitated by halogen–metal exchange did

Table 3. Cobalt-catalyzed phenylative cyclization[a]



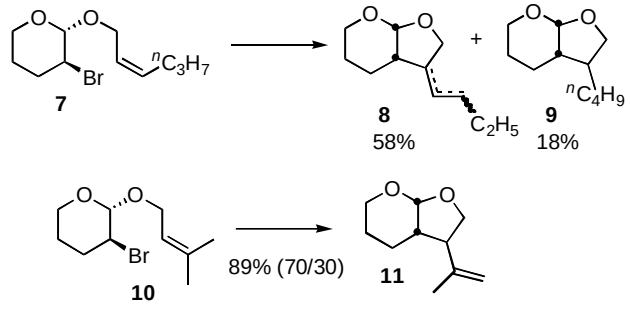
Entry	3	X	R^1	R^2	R^3	R^4	R^5	4	Yield (%)[b]
1	**3a**	Br	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	80 (55:45)
2	**3b**	I	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	78 (55:45)
3	**3c**	Cl	$^{n}C_4H_9$	H	H	$^{n}C_5H_{11}$	H	**4a**	No reaction
4	**3d**	Br	$(CH_2)_3$	—	H	$^{n}C_5H_{11}$	H	**4b**	71 (51:49)
5	**3e**	Br	$(CH_2)_3$	—	CH_3	CH_3	H	**4c**	84 (62:38)
6	**3f**	I	$(CH_2)_3$	—	CH_3	CH_3	H	**4c**	84 (60:40)
7	**3g**	Br	$(CH_2)_3$	—	H	H	CH_3	**4d**	51 (>99:1)
8	**3h**	I	$(CH_2)_3$	—	H	H	H	**4e**	21 (91:9)

[a] Substrate **3** (0.50 mmol), $CoCl_2$(dppe) (0.05 mmol), PhMgBr (1.1 mmol in 1 mL of THF), and THF (1 mL) were employed.

[b] Diastereomeric ratios are in parentheses. For **4a**, the $^{n}C_5H_{11}$ and benzyl groups are always on the opposite positions and the diastereoisomerism originates from the position of the R^1O group relative to the $^{n}C_5H_{11}$/benzyl groups. For **4b**, the $^{n}C_5H_{11}$ and benzyl groups are again trans and the positions of the R^1O and R^2 groups are always cis. Thus, the diastereoisomerism of **4b** emerges from the relative stereochemistry of the fused position and the $^{n}C_5H_{11}$/benzyl groups. For **4c**–**4e**, the relationship between the fused position and the benzyl group is responsible for the diastereoisomerism.

5a: R = H, X = I, Y = 4-CH_3–$C_6H_4SO_2N$ **6a**: 81% (Ar = Ph)
5b: R = $^nC_5H_{11}$, X = Br, Y = O **6b**: 59% (Ar = Ph)
5c: R = H, X = I, Y = CH_2 **6c**: 59% (Ar = 4-CH_3O–C_6H_4)

Scheme 1.



Scheme 2.

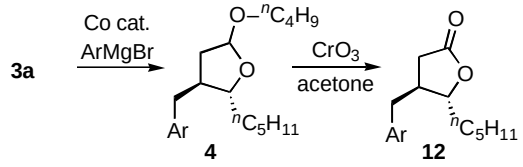
not take place. The β,β-di(alkoxy)alkylcobalt, if formed, probably undergoes fast β-alkoxy elimination. Hence, a mechanism involving halogen–cobalt exchange followed by intramolecular carbocobaltation might be improbable. Radical reaction is a preferable methodology to construct a quaternary carbon. This is indeed the case of **3g**, and bicyclic acetal **4d** was obtained as a single isomer. However, the reaction of **3h**, which has no substituents on the allyloxy group was sluggish. The expected product **4e** was obtained in only 21% yield in addition to allylbenzene. Chloro acetal **3c** resisted the reaction.

Nitrogen-containing substrate **5a** was also subjected to the cyclization reaction in the presence of the cobalt catalyst to yield 3-benzylpyrrolidine derivative **6a** (Scheme 1). Synthesis of carbocycle **6c** was also successful. Cyclic product **6c**, in addition to a small amount of biphenyl, was the only product in the ^1H NMR spectrum of the crude reaction mixture. Volatile methylcyclopentane and 1,5-hexadiene were the major byproducts (detectable by GC).

Cyclization onto an internal alkene moiety did not allow incorporation of a phenyl group (Scheme 2). Treatment of **7** with PhMgBr in the presence of $CoCl_2$(dppe) furnished a mixture of regio- and stereoisomers in regard to the double bond formed, accompanied with the non-phenylated cyclic acetal **9**. When **10** was employed, **11** was obtained exclusively via regioselective β-hydride elimination.

Not only PhMgBr but also a wide range of aryl Grignard reagents, including a 2-thienylmagnesium reagent, were available for use (Table 4). Jones oxidation of the products yielded β-arylmethyl-γ-lactones, which can be useful building blocks of some ligands.[9] Unfortunately, introduction of 2-substituted aryl groups was problematic. Steric effect of the substituents on a metal center is likely to interfere with the catalytic cycle.

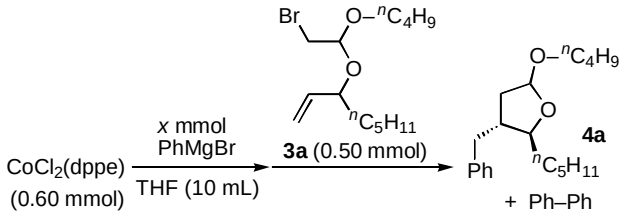
Table 4. Radical cyclization with various arylmagnesium bromides



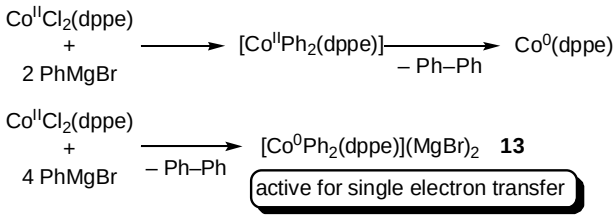
Entry	Ar	Yield of **4** (%)	Yield of **12** (%)
1	C_6H_5	**4a**, 80	**12a**, 97
2	3-CF_3–C_6H_4	**4f**, 65	**12b**, 83
3	4-CH_3O–C_6H_4	**4g**, 81	**12c**, 95
4	2-CH_3O–C_6H_4	**4h**, <5	—
5	2-CH_3–C_6H_4	**4i**, <15	—
6	2-Thienyl	**4j**, 63	**12d**, 75

2.3. Mechanism of cobalt-catalyzed phenylation reaction

To gain information about the reaction mechanism, the reaction of **3a** with a stoichiometric cobalt complex was examined with varying amounts of PhMgBr (Scheme 3). Treatment of **3a** (0.50 mmol) with a cobalt complex, prepared from 0.60 mmol of $CoCl_2$(dppe) and 1.2 mmol of PhMgBr, provided a trace of **4a**. Most of **3a** was recovered and 0.6 mmol of biphenyl was obtained. Accordingly, Co(II)Ph_2(dppe) was unstable under the



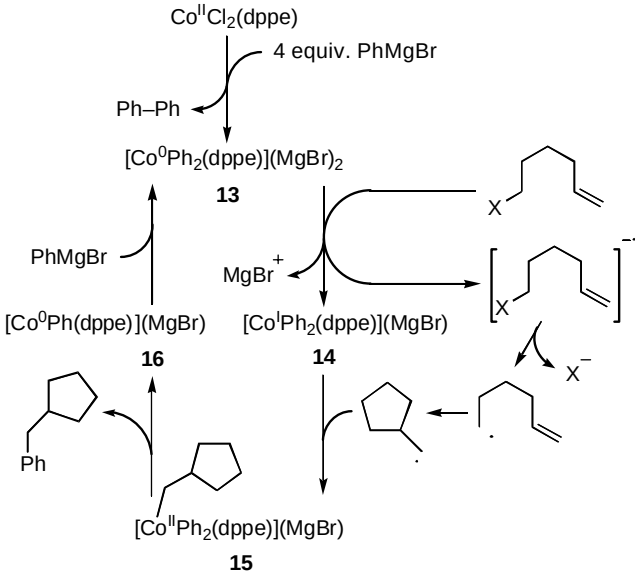
x	**3a**	**4a**	Ph–Ph
1.2	> 90%	Trace	0.6 mmol
1.8	> 80%	ca. 10%	0.6 mmol
2.4	< 5%	31%	0.8 mmol
3.0	< 1%	38%	0.7 mmol



Scheme 3.

reaction conditions and underwent reductive elimination. In fact, in the absence of **3a**, treatment of $CoCl_2$(dppe) with 2 equiv of PhMgBr in THF at 0 °C for 1 min and for 5 min gave biphenyl in 57 and 99% yields, respectively. A cobalt reagent, prepared from 0.60 mmol of $CoCl_2$(dppe) and 1.8 mmol of PhMgBr, also yield biphenyl (0.6 mmol), and most of **3a** remained unchanged. A complex generated by 0.60 mmol of $CoCl_2$(dppe) and 2.4 mmol of PhMgBr dramatically changed the outcome. The phenylated product **4a** was obtained in reasonable yield (31%), along with biphenyl (0.8 mmol) and other byproducts. Five equivalents of PhMgBr (3.0 mmol) exhibited outcome similar to 4 equiv of PhMgBr. Hence, the cobalt complex that is active for this reaction can be a 17-electron ate complex $[Co^0Ph_2(dppe)](MgBr)_2$ (**13**).

According to these results, we are tempted to propose a draft mechanism for the catalytic reaction as shown in Scheme 4. The reaction of $CoCl_2$(dppe) with 4 equiv of PhMgBr gives $[Co^0Ph_2(dppe)](MgBr)_2$ (**13**) with concomitant production of 1 equiv of biphenyl. The low valent ate complex effects a single electron transfer to a substrate to yield the anion radical of the substrate and cobalt(I) complex **14**. The immediate loss of bromide from the anion radical affords 5-hexenyl radical intermediate, which is transformed into a cyclopentylmethyl radical. The cobalt species **14** would then recombine with the carbon-centered radical to form divalent cobalt species **15**. Following reductive elimination provides the product and the cobalt(0) complex **16**, which is reconverted into **13** by the action of the remaining PhMgBr.



Scheme 4. A possible mechanism.

3. Conclusion

$CoCl_2$(dppp) effected cross-coupling reactions of primary alkyl halides and aryl Grignard reagents efficiently. The reaction can contribute to the establishment of universal cross-coupling reaction that allows arbitrary carbon–carbon bond formation. $CoCl_2$(dppe) catalyzed the sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives and aryl Grignard reagents to afford benzylcyclopentane skeletons. The sequential reaction not only provides a new method for multibond formation in a single operation but also justifies the existence of alkyl radical intermediates in the cross-coupling reaction.

4. Experimental

4.1. General

^{1}H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as a solvent, and chemical shifts were given in δ value with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. The elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Phosphine ligands were purchased from Tokyo Kasei Kogyo. Anhydrous $CoCl_2$ was purchased from Wako Pure Chemicals. The reaction was quite sensitive to water. Commercially available anhydrous $CoCl_2$ may contain some water. Completely anhydrous salt is clear blue, whereas purchased $CoCl_2$ is somewhat reddish-blue. Handling $CoCl_2$ under air as usual also caused low yield. Therefore, in each experiment, $CoCl_2$ was dried in a reaction flask carefully under reduced pressure (0.5 Torr) by heating with a hair dryer for 30 min immediately before use. Reaction flasks and syringes used were oven-dried and were cooled over silica gel in a desiccator. The preparation of halo acetals was carried out according to a literature method[8c] with corresponding vinyl ethers, allylic alcohols, and *N*-halosuccinimide.

4.2. General procedure for the cross-coupling reactions of alkyl halides with aryl Grignard reagents

The reaction of **1a** with phenyl Grignard reagent is representative. Anhydrous cobalt(II) chloride (13 mg, 0.10 mmol) was placed in a 30 mL reaction flask and heated in vacuo with a hair dryer. DPPP (50 mg, 0.12 mmol) and anhydrous THF (3.0 mL) were then added under argon. After the mixture was stirred at 25 °C for 5 min, 1-bromooctane (**1a**, 193 mg, 1.0 mmol) and phenylmagnesium bromide (1.0 M THF solution, 3.0 mL, 3.0 mmol) were sequentially added dropwise at −15 °C. While the Grignard reagent was being added, the mixture turned brown. After being stirred at −15 °C for 30 min, the reaction mixture was quenched with saturated ammonium chloride. The products were extracted with ethyl acetate (20 mL×3) and the combined organic layer was dried over sodium sulfate and concentrated. Silica gel column purification of the crude product with hexane as an eluent provided octylbenzene (**2a**, 123 mg, 0.65 mmol) in 65% yield.

4.3. A typical procedure for sequential radical cyclization/cross-coupling reaction

Anhydrous cobalt(II) chloride (6.5 mg, 0.05 mmol) was placed in a 25 mL flask and was heated with a hair dryer in vacuo for 30 min. After the color of cobalt salt became blue, anhydrous THF (1 mL) was added under argon. The mixture was stirred for about 15 min until it became homogeneous. A solution of 1,2-bis(diphenylphosphino)ethane in THF (0.33 M, 0.15 mL, 0.05 mmol) was then added to provide a green solution. Substrate **3a** (0.15 g, 0.50 mmol) and phenylmagnesium bromide (1.0 M THF solution, 1.1 mL, 1.1 mmol) were successively added dropwise to the reaction mixture at 0 °C. While the Grignard reagent was being added, the mixture turned black. After being stirred for 30 min at 0 °C, the reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with ethyl acetate (20 mL×3). The combined organic layer was dried over Na_2SO_4 and was concentrated. Silica gel column purification (hexane/ethyl acetate =20:1) of the crude product provided **4a** (0.12 g, 0.40 mmol) in 80% yield.

To obtain the corresponding lactone, **4a** was subjected to Jones oxidation. The crude oil can be directly oxidized in a similar manner. The oil was dissolved in acetone (5 mL), and Jones oxidant was added until the color of the mixture remained greenish-orange. Usual workup followed by silica gel column purification afforded **12a** in 97% yield.

4.4. Stereochemical assignment of the products

The trans stereochemistry of **12** was determined by comparison with known compounds that have an analogous structure. The chemical shifts of the γ-proton seem diagnostic of the stereochemistry. In the literature of Reissig,[10] the γ-protons of *trans*-β,γ-dialkyl-γ-lactones appeared at δ 4.01–4.45, whereas those of the cis isomers appeared at δ 4.43–4.71. In the present case, γ-proton of β-(arylmethyl)-γ-nonanolactone appeared at δ 4.2, which is strongly suggestive of trans relative configuration, given that the aryl group would have little influence on the chemical shift. NOE experiments, which showed small yet clear NOE, also revealed the selective formation of trans lactone (Fig. 1).

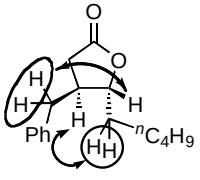
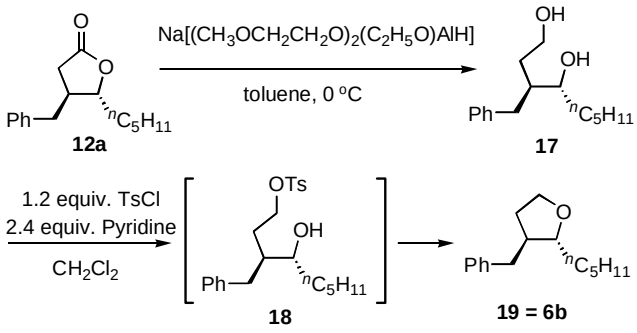


Figure 1. NOE correlation in lactone **12a**.

The relative configurations of bicyclic acetals **4** were not determined. The diastereomeric ratios in these phenylative cyclizations are similar to those in the previous free radical reductive cyclizations. It is worth noting that free radical cyclization of 4-substituted-5-hexenyl radical always afforded *trans*-1,2-substituted cyclopentane.[11]

The configuration of **6b** was determined as follows (Scheme 5). Reduction of trans lactone **12a** with 3 equimolar amount of $Na[(CH_3OCH_2CH_2O)_2(C_2H_5O)AlH]$ in toluene yielded diol **17** quantitatively.[12] Tosylation of secondary alcohol is much slower than that of primary one. Accordingly, crude diol **17** was subjected to monotosylation conditions (1.2 equiv TsCl/2.4 equiv pyridine/CH_2Cl_2, 0−25 °C). Expected mono-tosylated **18** underwent cyclization in the same pot to form tetrahydrofuran derivative **19** directly. The ^1H NMR spectrum of **19** was identical with **6b**, which clearly suggests **6b** was a trans isomer.



Scheme 5.

4.5. Characterization data

Spectral data for (**2b**,[13] **2c**,[14] **2d**,[15] **2e**,[16] **2f**,[17] **3**,[8c–f] **7–9**,[8d,f] **11**[8d]) were found in the literature. Spectral data of **4a**, **4f**, **4g**, and **4j** are not described here. The corresponding lactones were analyzed.

4.5.1. 7-Benzyl-8-pentyl-2,9-dioxabicyclo[4.3.0]nonane (4b). IR (neat) 2920, 2856, 1605, 1496, 1454, 1148, 1098, 966, 899, 748, 699 cm^{-1}; ^1H NMR ($CDCl_3$) For major isomer: δ 0.84 (t, *J*=6.9 Hz, 3H), 1.15–1.74 (m, 12H), 1.85–1.93 (m, 1H), 2.15–2.26 (m, 1H), 2.65 (dd, *J*=7.2, 13.8 Hz, 1H), 2.77 (dd, *J*=6.3, 13.8 Hz, 1H), 3.36 (dt, *J*=2.1, 11.1 Hz, 1H), 3.76 (dt, *J*=3.0, 8.7 Hz, 1H), 3.82–3.90 (m, 1H), 4.92 (d, *J*=3.9 Hz, 1H), 7.14–7.31 (m, 5H), for minor isomer: δ 0.87 (t, *J*=6.9 Hz, 3H), 1.17–1.83 (m, 12H), 1.85–1.96 (m, 1H), 2.20–2.31 (m, 1H), 2.66 (d, *J*=7.8 Hz, 2H), 3.60–3.64 (m, 1H), 3.76–3.84 (m, 1H), 3.90–3.96 (m, 1H), 5.26 (d, *J*=3.6 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 13.88, 20.65, 22.39 (2C), 26.08, 31.56, 36.65, 38.26, 44.60 (2C), 64.37, 85.94, 101.53, 126.29, 128.46 (2C), 129.01 (2C), 139.88, for minor isomer: δ 13.87, 20.19, 22.44, 23.18, 25.73, 31.82, 33.06, 35.23, 37.14, 47.89, 60.94, 80.87, 100.68, 126.17, 128.53 (2C), 128.56 (2C), 140.44. Found: C, 78.90; H, 9.96%. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78%.

4.5.2. 7-Benzyl-8,8-dimethyl-2,9-dioxabicyclo[4.3.0]-nonane (4c). IR (neat) 2946, 2880, 1738, 1496, 1454, 1384, 1242, 1144, 985, 906, 868, 747, 731, 698 cm^{-1}; ^1H NMR ($CDCl_3$) For major isomer: δ 1.15 (s, 3H), 1.18 (s, 3H), 1.50–1.83 (m, 4H), 1.96–2.06 (m, 1H), 2.50–2.75 (m, 3H), 3.36 (dt, *J*=2.4, 11.4 Hz, 1H), 3.82–3.90 (m, 1H), 4.88 (d, *J*=3.6 Hz, 1H), 7.19–7.33 (m, 5H), for minor isomer: δ 1.25 (s, 3H), 1.36 (s, 3H), 1.42–1.74 (m, 4H), 1.83–1.95

(m, 1H), 2.46 (dt, J=10.2, 6.0 Hz, 1H), 2.65 (dd, J=14.1, 6.0 Hz, 1H), 2.72 (dd, J=10.2, 14.1 Hz, 1H), 3.64 (dt, J=10.2, 2.7 Hz, 1H), 3.83 (dt, J=2.7, 11.1 Hz, 1H), 5.22 (d, J=3.6 Hz, 1H), 7.18–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 20.22, 21.89, 24.33, 20.35, 35.00, 44.10, 46.35, 64.34, 84.84, 100.55, 126.12, 128.38 (2C), 128.79 (2C), 140.38, for minor isomer: δ 20.24, 23.38, 25.57, 30.94, 31.62, 38.04, 51.03, 60.67, 79.35, 98.66, 126.13, 128.50 (2C), 128.56 (2C), 140.61. Found: C, 77.91; H, 9.24%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

4.5.3. 7-Benzyl-7-methyl-2,9-dioxabicyclo[4.3.0]nonane (4d). IR (neat) 2920, 2862, 1604, 1496, 1453, 1411, 1381, 1278, 1245, 1137, 1084, 1049, 1022, 964, 942, 895, 754, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.52–1.79 (m, 4H), 1.90–2.00 (m, 1H), 2.62 (d, J=13.5 Hz, 1H), 2.85 (d, J=13.5 Hz, 1H), 3.40 (d, J=8.1 Hz, 1H), 3.60–3.82 (m, 2H), 4.13 (d, J=8.1 Hz, 1H), 5.45 (d, J=3.9 Hz, 1H), 7.11–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.26, 23.03, 23.84, 40.16, 44.18, 44.55, 61.15, 76.13, 101.76, 126.24, 128.21 (2C), 129.92 (2C), 138.58. Found: C, 77.36; H, 8.80%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.58%.

4.5.4. 7-Benzyl-2,9-dioxabicyclo[4.3.0]nonane (4e). IR (neat) 2916, 1604, 1492, 1453, 1404, 1251, 1136, 1021, 947, 903, 750, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$) For major isomer: δ 1.50–1.67 (m, 3H), 1.72–1.81 (m, 1H), 1.92–2.01 (m, 1H), 2.58–2.78 (m, 3H), 3.61–3.68 (m, 1H), 3.77 (t, J=9.0 Hz, 2H), 3.88 (t, J=7.5 Hz, 1H), 5.28 (d, J=3.9 Hz, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) For major isomer: δ 19.42, 23.02, 33.26, 36.46, 42.41, 60.91, 69.82, 101.97, 126.23, 128.41 (2C), 128.58 (2C), 140.20. Found: C, 76.75; H, 8.31%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.51%.

4.5.5. *N*-(2-Iodoethyl)-*N*-[(4-methylphenyl)sulfonyl]-2-propenamine (5a). IR (Nujol) 2856, 1688, 1597, 1454, 1377, 1356, 1335, 1277, 1157, 1109, 1036, 997, 926, 901, 808, 775, 702, 663, 604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.21–3.26 (m, 2H), 3.40–3.45 (m, 2H), 3.80 (d, J=6.6 Hz, 2H), 5.16–5.23 (m, 2H), 5.62–5.75 (m, 1H), 7.33 (d, J=7.8 Hz, 2H), 7.70 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 1.84, 21.40, 50.05, 51.60, 119.69, 127.16 (2C), 129.91 (2C), 132.94, 136.35, 143.76. Found: C, 39.49; H, 4.34; N, 3.70%. Calcd for $C_{12}H_{16}O_2NSI$: C, 39.46; H, 4.42; N, 3.84%.

4.5.6. 3-(2-Bromoethoxy)-1-octene (5b). IR (neat) 2952, 2926, 2856, 1460, 1422, 1321, 1275, 1112, 1083, 994, 927, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=6.6 Hz, 3H), 1.22–1.68 (m, 8H), 3.45 (t, J=6.6 Hz, 2H), 3.60 (ddd, J=5.7, 6.9, 10.8 Hz, 1H), 3.64–3.71 (m, 1H), 3.81 (dt, J=10.8, 6.3 Hz, 1H), 5.16–5.23 (m, 2H), 5.62–5.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.92, 22.48, 24.89, 30.68, 31.63, 35.27, 68.31, 82.01, 117.06, 139.00. Found: C, 50.81; H, 7.96%. Calcd for $C_{10}H_{19}OBr$: C, 51.08; H, 8.14%.

4.5.7. 1-[4-(Methylphenyl)sulfonyl]-3-benzylpyrrolidine (6a). IR (neat) 3022, 2920, 2856, 1599, 1495, 1455, 1345, 1162, 1094, 1032, 816, 743, 701, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42–1.54 (m, 1H), 1.81–1.91 (m, 1H), 2.26–2.36 (m, 1H), 2.43 (s, 3H), 2.33 (d, J=7.5 Hz, 2H), 2.91 (dd, J=7.5, 9.9 Hz, 1H), 3.18 (dt, J=9.9, 7.5 Hz, 1H), 3.31–3.42 (d, J=8.1 Hz, 2H), 7.05 (d, J=8.1 Hz, 2H), 7.16–7.33 (m, 5H), 7.69 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.32, 30.89, 38.87, 40.22, 47.25, 52.66, 126.28, 127.49 (2C), 128.47 (2C), 128.58 (2C), 129.64 (2C), 133.89, 139.74, 143.37. Found: C, 68.28; H, 6.69; N, 4.36%. Calcd for $C_{18}H_{21}O_2NS$: C, 68.54; H, 6.71; N, 4.44%.

4.5.8. *trans*-3-Benzyl-1-oxa-2-pentylcyclopentane (6b). IR (neat) 3022, 2922, 2854, 1604, 1496, 1455, 1380, 1110, 1078, 1032, 1007, 905, 743, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=6.75 Hz, 3H), 1.19–1.48 (m, 8H), 1.57–1.68 (m, 1H), 1.89–2.11 (m, 2H), 2.54 (dd, J=9.3, 13.5 Hz, 1H), 2.78 (dd, J=5.7, 13.5 Hz, 1H), 3.49–3.55 (m, 1H), 3.80 (dd, J=6.2, 7.4 Hz, 2H), 7.15–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.90, 22.47, 25.93, 31.81, 32.41, 34.62, 39.25, 46.10, 66.62, 84.15, 126.07, 128.42 (2C), 128.85 (2C), 140.80. Found: C, 82.72; H, 10.61%. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41%.

4.5.9. 1-Cyclopentylmethyl-4-methoxybenzene (6c). IR (neat) 2946, 2862, 1613, 1584, 1513, 1464, 1299, 1246, 1177, 1039, 829, 806, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12–1.24 (m, 2H), 1.42–1.75 (m, 6H), 1.99–2.09 (m, 1H), 2.54 (d, J=7.5 Hz, 2H), 3.78 (s, 3H), 6.82 (d, J=8.7 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.83 (2C), 32.30 (2C), 41.07, 42.10, 55.15, 113.57 (2C), 129.70 (2C), 134.61, 157.71. Found: C, 82.12; H, 9.72%. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53%.

4.5.10. *trans*-3-Bromo-2-(3-methyl-2-butenoxy)-1-oxacyclohexane (10). IR (neat) 2924, 2872, 2852, 1776, 1676, 1442, 1377, 1204, 1130, 1086, 1072, 1021, 946, 869, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47–1.59 (m, 1H), 1.69 (s, 3H), 1.76 (s, 3H), 1.86–2.00 (m, 2H), 2.34–2.45 (m, 1H), 3.58 (ddd, J=8.4, 6.3, 5.1 Hz, 1H), 3.88–4.02 (m, 2H), 4.08 (dd, J=11.7, 6.9 Hz, 1H), 4.22 (dd, J=11.7, 6.6 Hz, 1H), 4.63 (d, J=5.1 Hz, 1H), 5.36 (dd, J=6.9, 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.83, 23.16, 25.67, 29.99, 49.48, 62.36, 64.26, 99.94, 120.11, 138.09. Found: C, 48.28; H, 6.62%. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88%.

4.5.11. *trans*-β-Benzyl-γ-nonanolactone (12a). IR (neat) 2928, 2856, 1768, 1604, 1455, 1205, 1173, 999, 944, 751, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=3.9 Hz, 3H), 1.16–1.58 (m, 8H), 2.29 (dd, J=7.5, 16.8 Hz, 1H), 2.39–2.51 (m, 1H), 2.59 (dd, J=8.1, 16.8 Hz, 1H), 2.68 (dd, J=8.1, 14.1 Hz, 1H), 2.83 (dd, J=6.6, 13.5 Hz, 1H), 4.20 (q, J=6.0 Hz, 1H), 7.13–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.30, 25.05, 31.30, 34.35, 34.73, 39.06, 42.33, 85.29, 126.86, 128.81 (2C), 128.84 (2C), 138.43, 176.46. Found: C, 77.91; H, 9.19%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

4.5.12. *trans*-β-[(3-Trifluoromethylphenyl)methyl]-γ-nonanolactone (12b). IR (neat) 2930, 2858, 1779, 1452, 1330, 1160, 1118, 1074, 1062, 947, 800, 704, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J=6.8 Hz, 3H), 1.19–1.60 (m, 8H), 2.29 (dd, J=7.5, 16.8 Hz, 1H), 2.42–2.54 (m, 1H), 2.61 (dd, J=8.3, 16.8 Hz, 1H), 2.76 (dd, J=8.4, 13.8 Hz, 1H), 2.91 (dd, J=6.6, 13.8 Hz, 1H), 4.20 (q, J=6.0 Hz, 1H), 7.35–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.72, 22.25, 25.01, 31.23, 34.32, 34.56, 38.77, 42.09, 85.02, 123.77 (q, J=3.7 Hz), 124.01 (q, J=271.3 Hz), 125.37 (q, J=3.7 Hz),

129.33, 131.22 (q, J=31.9 Hz), 132.21, 139.46, 175.90. Found: C, 64.95; H, 6.77%. Calcd for $C_{17}H_{21}O_2F_3$: C, 64.96; H, 6.73%.

4.5.13. *trans*-β-[(4-Methoxyphenyl)methyl]-γ-nonanolactone (12c). IR (neat) 2924, 2856, 1771, 1613, 1513, 1466, 1249, 1179, 1035, 945, 818, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J=6.75 Hz, 3H), 1.20–1.59 (m, 8H), 2.28 (dd, J=7.5, 16.8 Hz, 1H), 2.35–2.47 (m, 1H), 2.59 (dd, J=8.1, 16.8 Hz, 1H), 2.63 (dd, J=8.1, 13.8 Hz, 1H), 2.77 (dd, J=6.6, 13.8 Hz, 1H), 3.80 (s, 3H), 4.19 (q, J=6.0 Hz, 1H), 6.85 (d, J=8.7 Hz, 2H), 7.06 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.31, 25.05, 31.29, 34.36, 34.65, 38.14, 42.46, 55.20, 85.23, 114.16 (2C), 129.77 (2C), 130.40, 158.53, 176.50. Found: C, 73.66; H, 8.87%. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

4.5.14. *trans*-β-(2-Thienylmethyl)-γ-nonanolactone (12d). IR (neat) 2928, 2856, 1771, 1467, 1439, 1421, 1260, 1204, 1182, 1000, 945, 850, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.00–1.63 (m, 8H), 2.34 (dd, J=7.5, 17.1 Hz, 1H), 2.42–2.53 (m, 1H), 2.70 (dd, J=8.4, 20.1 Hz, 1H), 2.92 (dd, J=7.8, 14.7 Hz, 1H), 3.04 (dd, J=6.6, 14.7 Hz, 1H), 4.23 (q, J=6.3 Hz, 1H), 6.82 (d, J=3.3 Hz, 1H), 6.95 (dd, J=3.3, 5.1 Hz, 1H), 7.19 (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.81, 22.30, 25.02, 31.28, 33.10, 34.49, 34.58, 42.48, 84.98, 124.33, 125.82, 127.14, 140.62, 176.18. Found: C, 66.64; H, 8.17%. Calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99%.

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References and notes

1. For reviews: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (b) Terao, J.; Kambe, N. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 1192–1204. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (d) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624–629.
2. Examples published in 2005: (a) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794–1798. (b) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511. (c) Fisher, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. (d) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483. (e) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Hird, M. *Chem. Commun.* **2005**, 4161–4163. (f) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3807.
3. (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137–4139. (b) Mizutani, K.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 832–833. (c) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240–1241. (d) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640–5648. (e) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3488–3490.
4. Recent reports on cobalt-catalyzed coupling reactions, see: (a) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159–6162. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163–6166. (c) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67–69. (d) Korn, T. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 2947–2951. (e) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607–3610.
5. A part of this work was communicated: Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374–5375.
6. (a) Salom-Roig, X. J.; Dénès, F.; Renaud, P. *Synthesis* **2004**, 1903–1928. (b) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564–5566. (c) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742.
7. (a) Pattenden, G. *Chem. Soc. Rev.* **1988**, *17*, 361–382. (b) Ali, A.; Harrowven, D. C.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 2851–2854. (c) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875–5877. (d) Okabe, M.; Tada, M. *J. Org. Chem.* **1982**, *47*, 5382–5384.
8. (a) Knochel, P. *Synlett* **1995**, 393–403. (b) Stadtmüller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. Eur. J.* **1996**, *2*, 1204–1220. (c) Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039–2049. (d) Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651–653. (e) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225–235. (f) Fujita, K.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1727–1736.
9. (a) Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654–6655. (b) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183–205.
10. Reissig, H.-U.; Angert, H.; Kunz, T.; Janowitz, A.; Handke, G.; Bruce-Adjei, E. *J. Org. Chem.* **1993**, *58*, 6280–6285.
11. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
12. According to the literature, we tended to obtain the corresponding lactol, which was to be silylated and then subjected to reduction with triethylsilane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate. However, the experiment resulted in the formation of the diol. Málek, J. *Org. React.* **1998**, *36*, 324.
13. Soulié, C. *Tetrahedron* **2001**, *57*, 1035–1040.
14. Sotoyama, T.; Hara, S.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1865–1866.
15. Abrams, S. R.; Shaw, A. C. *J. Org. Chem.* **1987**, *52*, 1835–1839.
16. Kurono, N.; Sugita, K.; Takasugi, S.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6097–6108.
17. Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617.