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Dynamic Covalent Chemistry of the Nicholas Ether-Exchange Reaction

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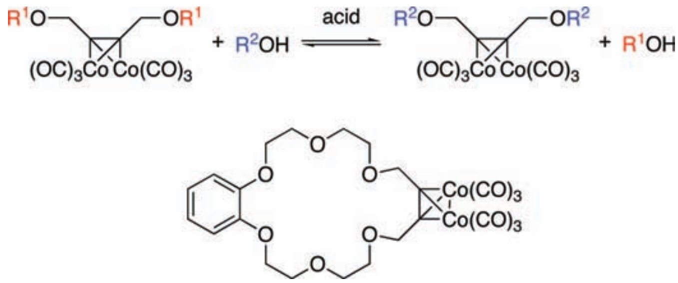
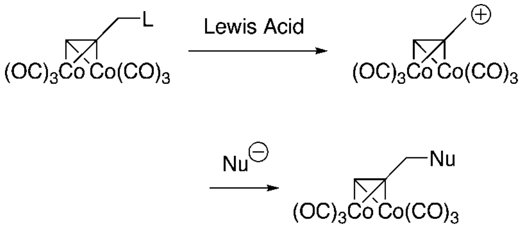
ABSTRACT



The Nicholas ether-exchange reaction was found to be reversible and can be used to synthesize complex molecules in dynamic covalent chemistry (DCC). The Nicholas ether-exchange reaction is used to prepare 20-Crown-6 ether in the presence of potassium salt at low temperature.

Dynamic covalent chemistry (DCC) is a method used to obtain a thermodynamically stable product by a reversible chemical reaction under equilibrium conditions.[1] It is a powerful method to construct macrocycles and self-assemblies because any errors that occur while constructing covalent bonds in complex molecules can be revised during equilibrium. Reactions used for DCC are currently limited—only the ester-exchange, olefin metathesis, disulfide-exchange, and imine-exchange reactions are well studied. Therefore, new DCC reactions are strongly desired.

Scheme 1. Nicholas Reaction



Our investigation focused on the Nicholas reaction: S_N1-type reaction at the propargyl position of the alkyne−cobalt carbonyl complex (Scheme 1).[2] Since the cobalt carbonyl moiety strongly stabilizes the α cation, the ether group at the α to the alkyne−cobalt carbonyl complex can be a leaving group in the presence of strong acid. Therefore, we expected that etherification under the Nicholas reaction condition is reversible, and the ether-exchange reaction occurs as the equilibrium. Although etherification using the Nicholas reaction has been reported,[3] the reversibility of the reaction has not been studied extensively. To the best of our knowledge, there were some examples of the isomerization of the cobalt−propargyl ether complex,[3b,4] although there

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(1) (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (b) Lehn, J.-M. *Prog. Polym. Sci.* **2005**, *30*, 814–831. (c) Takata, T. *Polym. J.* **2006**, *1*, 1–20. (d) Meyer, C. D.; Joiner, C. S.; Stoddart, J. F. *Chem. Soc. Rev.* **2007**, *36*, 1705–1723.

(2) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214. (b) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133–4170.

(3) (a) Quintal, M. M.; Closser, K. D.; Shea, K. M. *Org. Lett.* **2004**, *6*, 4949–4952. (b) Ortega, N.; Martı´n, T.; Martín, V. S. *Org. Lett.* **2006**, *8*, 871–873. (c) Hope-Weeks, L. J.; Mays, M. J.; Solan, G. A. *Eur. J. Inorg. Chem.* **2007**, *310*, 1–3114.

(4) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749–5759.

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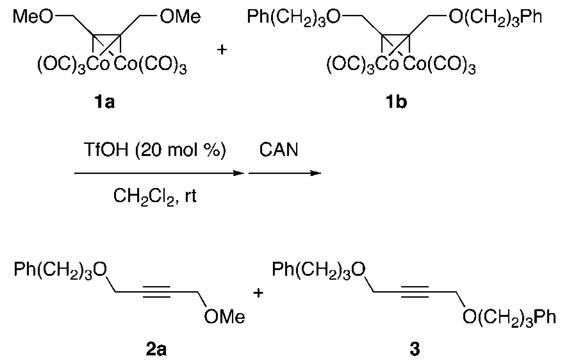
was no example of intermolecular ether exchange by the Nicholas reaction. In this paper, we report the DCC of the Nicholas ether-exchange reaction and the synthesis of crown ether as an application of this reaction.[5]

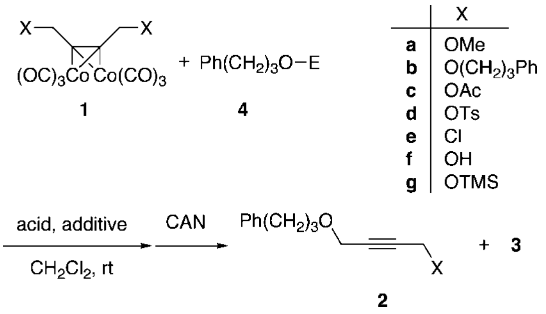
To study the equilibrium nature of the Nicholas ether-exchange reaction, a mixture of two alkyne complexes (**1a** and **1b**) was treated with trifluoromethanesulfonic acid (TfOH) (Scheme 2). After the oxidative treatment of the mixture with cerium(IV) diammonium nitrate (CAN) to remove the cobalt carbonyl moiety,[6] the products were isolated. Along with **3** that was formed from **1b**, the ether-exchange product **2a** was obtained. Therefore, the ether-exchange reaction between reactants **1a** and **1b** occurred under the Nicholas reaction condition. When the reaction was carried out for 24 h, the asymmetrical ether (**2a**) was isolated with 42% yield. Since the theoretical yield of **2a** at equilibrium is 50%, this indicates that the Nicholas ether-exchange reaction is reversible and can be used for DCC.

Scheme 2. Nicholas Ether-Exchange Reaction



Given that the Nicholas ether-exchange reaction is reversible, quantitative etherification is possible when the byproduct of the ether-exchange reaction is removed from the reaction system. Thus, the reaction of **1** with 2 equiv of alcohol **4** was carried out in CH_2Cl_2 at room temperature for 24 h to investigate the effect of the leaving groups (X and E) in the ether-exchange reaction (Table 1). The monosubstituted product **2** and the bis-substituted product **3** were isolated after CAN treatment. When the reaction was carried out with reactant **1a** in the presence of molecular sieves as the methanol absorbent, the yield of ether slightly improved (runs 1−3). This result prompted examination of various acid catalysts for etherification (runs 4−10). Although TMSOTf and BF_3OEt_2 were as effective as TfOH, a better acid catalyst than TfOH was not found. Therefore, the effect of the leaving group in **1** (X) was examined (runs 11−14). When **1d** (X = OTs) and **1e** (X = Cl) were used, **2** was not observed, although the yield of desired ether **3** was low. When **1f** (X = OH) was used, the yield of **3** drastically increased, and only a trace of **2f** was observed. Since the deactivation of TfOH by the produced water was of concern, the addition of dehydrating material was examined (runs 15−18). While molecular sieves only slightly increased the yield of **3**, $MgSO_4$ or $CaCl_2$ prevented the etherification reaction. When TMS ether was used instead of alcohol in the presence of TMSOTf, **3** was obtained in good yield (run 19).[7] The best result was obtained when the reaction was carried out with **1g** (X = OTMS) at a high concentration condition (run 23). The TBDMS ether was not effective (runs 24 and 25). Thus, etherification was effectively carried out when siloxane was the counterpart of the ether.

Table 1. Etherification by the Nicholas Ether-Exchange Reaction



run	1	E	acid[a]	concn/M	additive[b]	yield/%	
						2	3
1	**a**	H	TfOH	0.01	none	34	21
2	**a**	H	TfOH	0.01	MS4A	47	21
3	**a**	H	TfOH	0.01	MS5A	40	19
4	**a**	H	TFA	0.01	MS5A	0	0
5	**a**	H	MsOH	0.01	MS4A	trace	trace
6	**a**	H	TMSOTf	0.01	MS4A	0	0
7	**a**	H	Et_2AlCl	0.01	MS4A	0	0
8	**a**	H	$ZnCl_2$	0.01	MS4A	0	0
9	**a**	H	AgOTf	0.01	MS4A	0	0
10	**a**	H	BF_3OEt_2	0.01	MS4A	37	15
11	**c**	H	TfOH	0.01	none	34	1
12	**d**[c]	H	TfOH	0.01	none	0	10
13	**e**[c]	H	TfOH	0.01	none	0	33
14	**f**	H	TfOH	0.01	none	trace	52
15	**f**	H	TfOH	0.01	MS3A	8	62
16	**f**	H	TfOH	0.01	MS4A	trace	62
17	**f**	H	TfOH	0.01	$MgSO_4$	37	16
18	**f**	H	TfOH	0.01	$CaCl_2$	4	7
19	**f**	TMS	TMSOTf	0.01	none	trace	74
20	**c**	TMS	TMSOTf	0.01	none	41	31
21	**g**	TMS	TMSOTf	0.01	none	0	69
22	**c**	TMS	TMSOTf	1	none	33	30
23	**g**	TMS	TMSOTf	1	none	0	83
24	**f**	TBDMS	TMSOTf	0.01	none	ND	49
25	**g**	TBDMS	TMSOTf	0.01	none	ND	17

[a] 20 mol % for **1**. [b] 500 mg for 0.25 mmol of **1**. [c] Cobalt complex was prepared in situ and used without purification.

Since DCC is particularly effective for the construction of macrocycles, the synthesis of crown ether **6** was inves-

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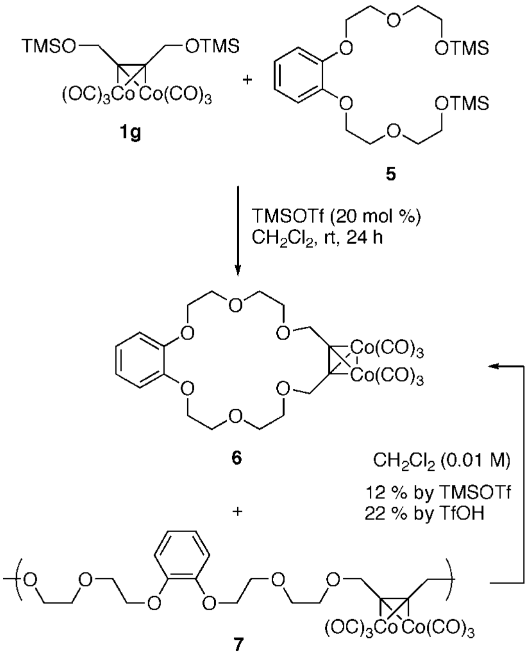
(5) Trityl ether has also been used for DCC: (a) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1972**, 231–232. (b) Furusho, Y.; Oku, T.; Rajkumar, G. A.; Takata, T. *Chem. Lett.* **2004**, *33*, 52–53.

(6) Seyferth, D.; Wehman, A. *J. Am. Chem. Soc.* **1970**, *92*, 5520.

(7) Yokozawa, T.; Nishimori, M.; Endo, T. *Macromol. Chem. Phys.* **1996**, *197*, 1361–1371.

tigated using reactant **1g** and disilyl ether **5** as shown in Scheme 3. When macrocyclization was carried out under the best conditions mentioned above, [1 + 1] macrocyclic crown ether **6** was obtained, although the main product was polymer **7**. When the concentration was reduced to 0.01 M, the yield of **6** increased because macrocyclization is thermodynamically favored under the lower concentration. Although the reaction was carried out for 24 h, the system reached equilibrium within 3 h. It should be noted that a Friedel−Crafts type alkylation of the electron-rich aromatic ring was not observed, indicating the stability of the α cation of the cobalt carbonyl complex and the high chemoselectivity of the Nicholas ether-exchange reaction.

Scheme 3. Macrocyclization



concn/M	yield/%	
	6	**7**
1	13	62
0.01	50	3

Since the Nicholas ether-exchange reaction is DCC, a remacrocyclization of polymer **7** to form **6** was expected. When the polymer was treated with TMSOTf, **6** was obtained in 12% yield. TfOH was the better acid catalyst for remacrocyclization of **7** than TMSOTf, and **6** was obtained in 22% yield. The yield of **6** was lower than that of direct macrocyclization because the terminal silyl groups of **7** were mostly hydrolyzed during the workup.

To increase the yield of crown ether, the use of the template effect was investigated (Table 2). When KOTf was used as the template, the yield of **6** improved under the high concentration conditions, although no change was observed under the low concentration conditions (runs 1−4). Although macrocyclization is not thermodynamically favored under the concentrated conditions, the template effect altered the effect of concentration since the complexation of **6** with potassium ion lowered the potential of **6**, and complexation is more favored as the concentration increases. Therefore, the reaction was carried out at a low temperature to improve complexation. The yield substantially increased at −40 °C, although the reaction proceeded slowly (runs 5 and 6). Since no yield improvement of **6** was observed in the absence of KOTf (run 7), it became obvious that the temperature effect originated from the stronger complexation at a lower temperature. The template effect acts more effectively under the condition in which the complexation is favored: lower temperature and high concentration condition. To facilitate the equilibrium process, the reaction was first carried out at ambient temperature, and the system was then cooled to shift the equilibrium. Since the Nicholas ether-exchange reaction is DCC, a high yield of **6** was achieved in a

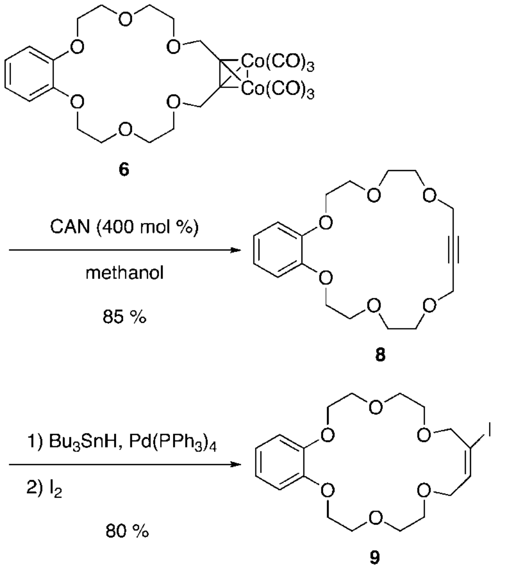
Table 2. Template Effect in the Preparation of Crown Ether

$$\mathbf{1g} + \mathbf{5} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{TMSOTf, MOTf}} \mathbf{6}$$

run	template[a]	concn/M	temp	time/h	yield/%
1	none	0.01	rt	24	50
2	KOTf	0.01	rt	24	49
3	none	1	rt	24	13
4	KOTf	1	rt	24	25
5	KOTf	1	−40 °C	24	39
6	KOTf	1	−40 °C	48	65
7	none	1	−40 °C	24	14
8	KOTf	1	rt to −40 °C	3−24	66
9	NaOTf	1	rt to −40 °C	3−24	35
10	RbOTf	1	rt to −40 °C	3−24	36
11	CsOTf	1	rt to −40 °C	3−24	30

[a] 100 mol % for **5**.

Scheme 4. Modification of the Cobalt Moiety in the Crown Ether



short reaction period (run 8). Further, other alkali metal salts used as the template were examined, although a smaller template effect was observed (runs 9−11).

To demonstrate product **6** as the functional crown ether, the deprotection of the cobalt carbonyl moiety was investigated. When **6** was treated with 400 mol % of CAN, crown ether bearing triple bond **8** was obtained in high yield (Scheme 4). The use of excess CAN resulted in the oxidation of the aromatic ring. It is expected that crown ether **8** can be further functionalized by the reaction of the triple bond. As the application of **8**, crown ether **9** bearing a vinyl iodide moiety was easily prepared,[8] which is a versatile reactant for the transition metal complex-catalyzed coupling reaction.

In summary, it was demonstrated that the Nicholas ether-exchange reaction is reversible and can be used for DCC. Cross-etherification was successfully achieved when siloxane was the leaving molecule. As an application of the Nicholas ether-exchange reaction, the synthesis of crown ether was successfully carried out in the presence of potassium salt as the template. Investigations of further applications of the Nicholas ether-exchange reaction for constructing various supramolecules are currently in progress.

Supporting Information Available: Experimental procedures and characterization data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Paterson, I.; Fessner, K.; Finlay, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1996**, *37*, 8803–8806.