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Umpolung of 4,4-disubstituted 2-hydroxycyclohexa-2,5-dienones for the regiodivergent synthesis of disubstituted catechols

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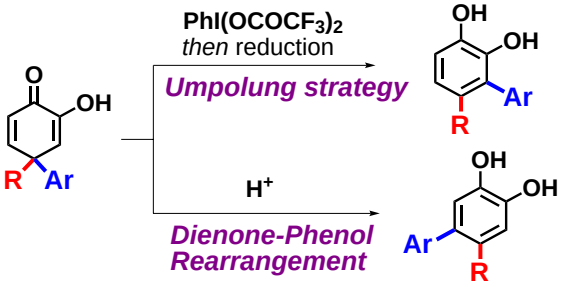
Abstract

The umpolung of 4,4-disubstituted 2-hydroxycyclohexa-2,5-dienones **1** with $PhI(OCOCF_3)_2$ achieved the migration into the more electron-rich C3 position, providing exclusively 3,4-disubstituted catechols **3**. Acid-induced rearrangement of **1** produced 4,5-disubstituted catechols **2**. These two reactions enabled the highly selective production of two regioisomers of disubstituted catechols, especially biaryls containing catechol moieties, from the common intermediates **1**.

Keywords: catechols, hypervalent iodine reagent, rearrangement.

Graphical Abstract



A novel regioselective rearrangement method using umpolung has been developed for the synthesis of two regioisomers of disubstituted catechols.

1. Introduction

Catechols are ubiquitous structures found in various functional molecules such as natural products, bioactive molecules, and pharmaceuticals. A comprehensive medicinal chemistry database identified 78 drugs containing one or more catechol moieties.[1] In addition, biaryl compounds are a promising class of compounds in drug discovery research mainly because of their unique 3D skeleton, which is different from typical pharmaceuticals containing central chirality.[2] For example, apomorphine hydrochloride serves as an antiparkinsonian

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medication.[3] 2-Aryldopamine analogs have some effects on D1 and D2 dopamine receptors,[4a] and 6-aryldopamine analogs were also synthesized.[4b] Alkylated 2,3-dihydroxybiphenyls were prepared to evaluate the substrate specificity of the extradiol dioxygenase BphC.[5] And, altenusin B and its derivatives confer neuroprotection against oxidative insults[6] (Fig. 1a). Analysis of known multisubstituted catechols based on the positions of carbon substituents on the catechol ring revealed that 3,4-disubstituted catechols and 4,5-disubstituted catechols are the major components. Therefore, it is important to develop a simple, reliable, and regioselective synthetic method(s) for these disubstituted catechols, particularly those containing biaryl framework.

Reported synthetic methods for disubstituted catechols can be classified into three main categories. The first class is oxidation reactions, that is, introduction of hydroxyl group(s) into substituted phenols and their derivatives,[5,7a-7f] substituted nitrobenzenes,[7g] and substituted cyclohexenones.[7h,7i] The second class includes the introduction of a substituent to dihydroxylbiaryl derivatives[4a,5] or introduction of an aryl moiety to catechols.[4b] And the third class includes the carbon skeleton transformation reactions, such as the Diels–Alder reaction of *ortho*-quinones[8a] and ring expansion reactions of substituted 2-alkoxycyclopentenones.[8b] However, there may be room for improvement regarding low regioselectivity when introducing hydroxy groups or substituents, low yields, and harsh reaction conditions that limit the coexistence of substituents or functional groups.

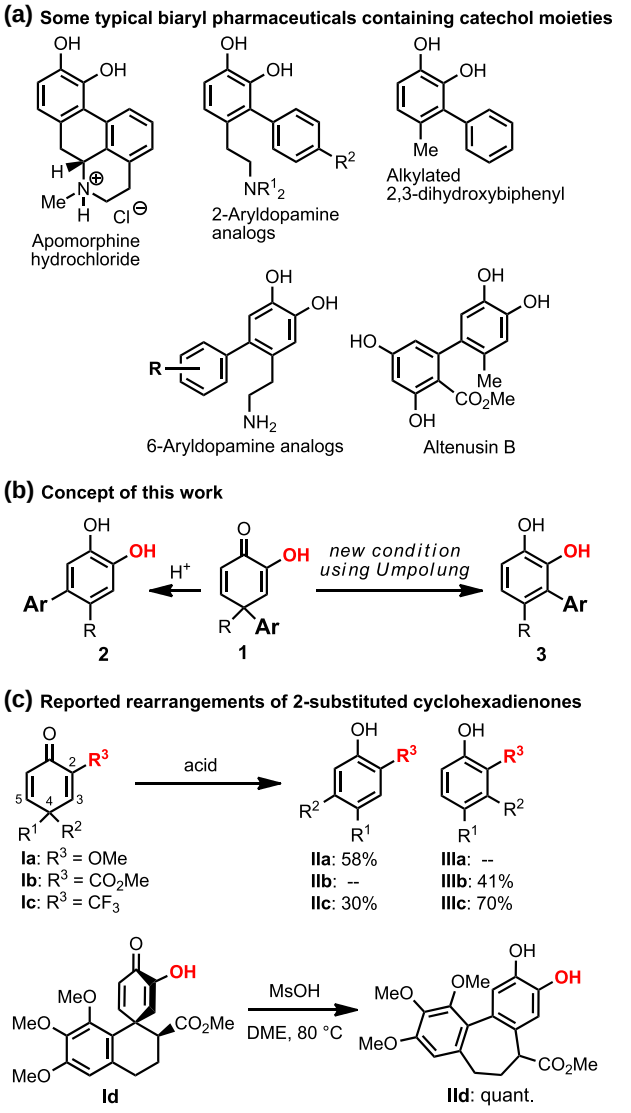

Fig. 1. Regiodivergent syntheses of disubstituted catechols by dienone–phenol rearrangements. a) Some typical biaryl pharmaceuticals containing a catechol moiety. b) Concept of this work. c) Reported rearrangements of 2-substituted cyclohexadienones **Ia** to **Id**.

Under such background, we focused on the dienone–phenol rearrangement to develop a method for the regioselective synthesis of 4,5-disubstituted catechols **2** and 3,4-disubstituted catechols **3** from 4,4-disubstituted 2-hydroxycyclohexa-2,5-dienones **1** as common starting materials (Fig. 1b). According to previous studies on the acid-mediated rearrangement reactions of 2,4,4-trisubstituted cyclohexa-2,5-dienones, the electronic nature of the C2 substituent significantly affects the migration direction of the C4 substituent. For example, **Ia** with an electron-donating methoxy group at the C2 position caused the migration of the C4 substituent into C5 to give **IIa**, and **Ib** with an electron-withdrawing methoxycarbonyl group at the C2 position caused the migration into C3 to give **IIIb**.[9] In addition, **Ic** with a trifluoromethyl group at the C2 position gave a mixture of two products, **IIc** and **IIIc** (Fig. 1c).[10] We have previously reported an acid-mediated rearrangement of spirocyclohexadienone **Id** with a hydroxy group at the C2 position that quantitatively produced catechol **IId**, in which the C4 aryl substituent migrated to C5 (Fig. 1c).[11] Based on these data, we expected that if a C4 aryl substituent in **1** could migrate to the C3 position, it would lead to a new type of reaction generating **3** (Fig. 1b), even though this reaction is contrary to the migration tendency described above. However, no such reports have been made so far.

We herein report successful examples of such unprecedented dienone–phenol rearrangement of **1** to give **3** by utilizing the umpolung concept. We have also confirmed that the acid-mediated rearrangement of **1** produces the migration of the C4 aryl group into C5 to form **2**. Thus, our protocol provides a method for the synthesis of both biaryl regioisomers **2** and **3** containing catechol moieties from common starting materials **1** with exclusive regioselectivity (Fig. 1b).

2. Results and discussion

The previously reported results (Fig. 1c) indicate that the C4 substituent migrates to the more electron-deficient position of the C3 or C5 position of cyclohexa-2,5-dienone. Indeed, in our study of the reaction of **1a** with TfOH at 0 °C in $CHCl_3$, the migration to the C5 position occurred to produce the 4,5-disubstituted catechol **2a** quantitatively. Subsequently, we expected that the installation of a strongly electron-withdrawing group to the C2 hydroxy group of **1a** would alter the migration direction to provide 3,4-disubstituted catechols **6** (Scheme 1). We tried a range of O-protective groups under the same reaction conditions and found that even C2-O-nonafluorobutanesulfonoyl (Nf) derivative **4a** preferentially afforded **5a** (83% yield) along with their regioisomer **6a** in only 17% yield (for the details, see section 2-2 in the online supplementary material).

The aforementioned results can be attributed to the enol structure in **1a** and **4a**, which increases the electron density at the C3 position. To achieve the highly regioselective rearrangement of the C4 substituent to the C3 position, we planned to induce an umpolung at the C3 using a hypervalent

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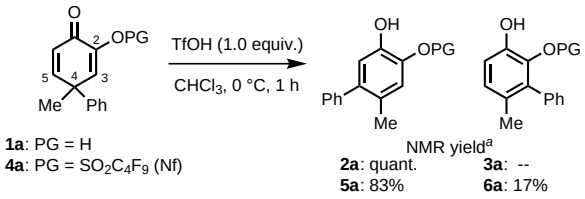
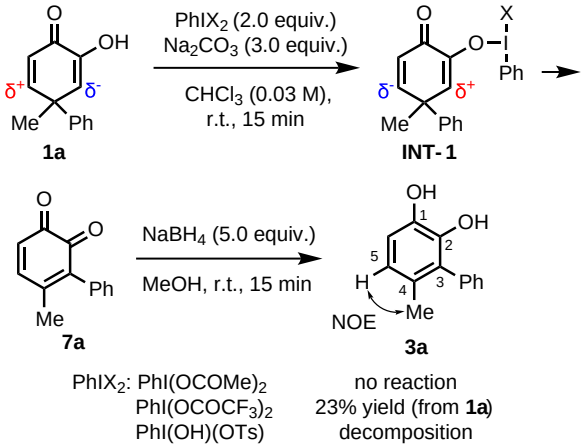
iodine reagent.[12] Thus, the reaction intermediate **INT-1**, generated by the reaction of the hydroxy group of **1a** and a hypervalent iodine reagent, is assumed to have a much lower electron density at the C3 position than at C5 due to the strong leaving ability of the PhI moiety, and therefore, the C4 substituent preferentially migrates to C3. Based on this hypothesis, **1a** was treated with three hypervalent iodine reagents (2 equiv.) and Na_2CO_3 (3 equiv.) in commercial $CHCl_3$ (containing EtOH as a stabilizer) for 15 min at room temperature. When $PhI(OCOCF_3)_2$ (PIFA) was used, the phenyl group at C4 in **1a** migrated to C3 forming *ortho*-quinone **7a** (for structure determination of **7a**, see section 2-3-1 in the online supplementary material). However, **7a** was unstable and gradually decomposed during isolation. Therefore, $NaBH_4$ and MeOH were directly added to the crude reaction mixture to reduce **7a** to give catechol **3a** (23% NMR yield from **1a**) (Scheme 2). Its regioisomer **2a** was not identified in the crude product, indicating that this rearrangement proceeded with complete regioselectivity. A similar reaction with $PhI(OCOMe)_2$ did not proceed at all, while that with PhI(OH)OTs produced decomposition products.

Next, the reaction conditions were modified to improve the yield of **7a**. Since it was difficult to directly quantify the yield of **7a**, it was evaluated by the NMR yield of **3a** obtained by the one-pot migration/reduction sequence instead (the $NaBH_4$ reduction of **7a** to give **3a** was confirmed to proceed quantitatively[13]).

First, the yield of **3a** was found to vary depending on the small amount of stabilizer contained in $CHCl_3$. Namely, the reaction of **1a** with PIFA (1.5 equiv.) in commercial $CHCl_3$ containing 0.3% to 1.0% EtOH was conducted at 0 °C for



Scheme 1. Acid-mediated rearrangement of **1a** and **4a**. [a]Determined by ^{1}H NMR analysis of a crude product with 1,1,2,2-tetrachloroethane as an internal standard.



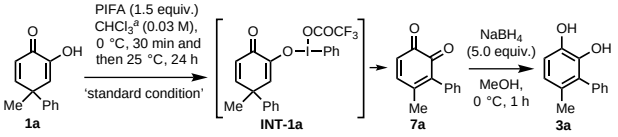
Scheme 2. Rearrangement of **1a** mediated by hypervalent iodine reagents.

30 min[14] and then at 25 °C for 24 h. $NaBH_4$ and MeOH were added to the reaction mixture in one pot to give **3a** in 32% NMR yield (Table 1, entry 2). However, the yield of **3a** increased to 42% when the reaction was carried out under the same condition in commercial $CHCl_3$ containing approximately 150 ppm amylene (entry 1). Next, when PIFA was reduced to 1.1 equiv. under the condition of entry 1, the yield of **3a** decreased (entry 3). The higher reaction concentrations caused concomitant decomposition of **7a**, reducing the yield of **3a** (entry 4). Since the yield of **3a** increased when the reaction with PIFA was carried out for 24 h at 15 °C instead of 25 °C (entry 5), it was found to be important to conduct the oxidation–rearrangement reaction at around 15 °C where the decomposition of **7a**, which proceeded in parallel during the reaction, was suppressed to some extent (see the time course experiments presented in the following paragraph).

In the initial studies, Na_2CO_3 was added to capture the byproduct trifluoroacetic acid as illustrated in Scheme 2; however, the yield of **3a** was slightly higher under the condition without Na_2CO_3 (entry 5) than under the condition with Na_2CO_3 (entry 6). These results suggested that trifluoroacetic acid promotes the rearrangement. However, the addition of various Lewis acids only gave complex mixtures (entry 7). Other factors, such as solvents, bases, PIFA equiv., concentrations, and temperatures, were further examined (for details, see section 2-3-2 in the online supplementary material), and the condition of entry 5 was determined to be the best.

To obtain information on the time required for the complete rearrangement, the time course study of the conversion of **1a** to **7a** was performed at various reaction times, and each crude product was subjected to $NaBH_4$ reduction in one pot to obtain the NMR yield of **3a**. The results are summarized in Fig. 2. We found that there is a time lag between the decrease of **1a** and the generation of **3a**, that is, **7a**. The yield of **3a** began to decrease at approximately 24 h. This may be due to the gradual decomposition of **7a** proceeding in parallel with its formation. From these results, it is estimated that the process that produces **7a** after generating **INT-1a**, that is, the

Table 1. Optimization of reaction conditions for PIFA-mediated rearrangement of **1a**.



Entry	Deviation from "standard condition"	Overall yield (%) of **3a** from **1a**[b]
1	None	42
2	$CHCl_3$ with EtOH as a stabilizer	32
3	1.1 equiv. of $PhI(OCOCF_3)_2$	34
4	In 0.1 M	6
5	0 °C, 30 min and then 15 °C, 24 h	50 (42[c])
6	0 °C, 30 min and then 15 °C, 24 h, with Na_2CO_3 (3.0 equiv.)	43
7	With Lewis acid[d]	Complex mixture

[a]Commercial $CHCl_3$ with amylene as a stabilizer was used.
[b]Determined by ^{1}H NMR analysis of a crude product with dimethylsulfone as an internal standard.
[c]Isolated yield.
[d]BF_3•Et_2O, $AlCl_3$, $FeCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, and $In(OTf)_3$ were examined.

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elimination of a trifluoroacetate ion and PhI, migration of the C4 phenyl group to the C3 position, and deprotonation/aromatization, takes time. Similar reactions of **1a** or **1b** with PIFA were performed using $CDCl_3$ as a solvent, and the time course of the reaction was monitored in detail by ^{1}H NMR and ^{19}F NMR analysis, but only **1a,b**, **7a,b**, PIFA, trifluoroacetic acid, and PhI were observed at any time point, with no characteristic signals supporting the formation of **INT-1** or any other intermediates.

The optimal reaction condition (Table 1, entry 5) for the conversion from **1a** to **7a** was used as condition A to examine adaptable substrate scope (Table 2). The reaction proceeded well with **1b** and **1c** with substituents on the benzene ring and **1d** with a heterocycle. A similar reaction proceeded for **1e** with an elongated alkyl chain. The compounds **1f** and **1g**, in which two aromatic groups were attached to the C4 position, were also good substrates for this rearrangement; however, **1g** produced a 1:1.5 mixture of two isomers, that is, the product with the 4-methoxyphenyl group migrated and that with the Ph group migrated, respectively (for the structure determination of the products, see page 19 in the online supplementary material). In every single case for all these entries, no regioisomer **2** was observed in each crude product.

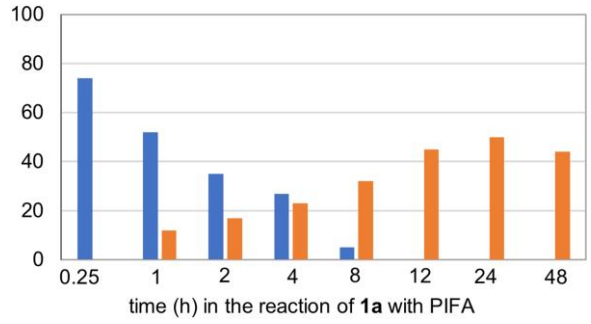


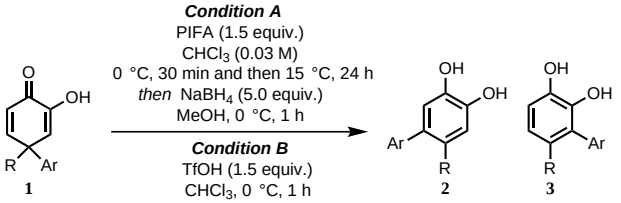
Fig. 2. Effects of reaction time in the reaction of **1a** and PIFA. The reaction was performed under the same condition as entry 5 in Table 1. Blue bar: recovery rate (%) of **1a**. Orange bar: yield (%) of **3a**.

Next, the rearrangement was performed on the same substrates **1a** to **1g** in the presence of TfOH (1.5 equiv.) at 0 °C for 1 h in $CHCl_3$ (condition B). Under this condition, the migration of the C4 aryl substituent to the C5 position was observed for all substrates, yielding **2**, and **3** was not formed at all (Table 2).

These two conditions A and B were applied to a spiro compound **1h** for synthesizing oligoarenes, core structures for the preparation of functional polycyclic (hetero)aromatic hydrocarbons, highly promising material with diverse applications in molecular electronic devices, organic spintronics, biomedical materials, and so on.[15a-15c] First, a symmetrical triphenylene **2h**,[16a-16c] containing a catechol moiety, was quantitatively obtained by the TfOH-mediated dienone–phenol rearrangement of **1h** under condition B. Oxidative rearrangement of **1h** under condition A gave its regioisomer, triphenylene-1,2-dione **7h**[17a,17b] in 75% yield (Scheme 3). In both reactions, the rearrangement product was obtained as a single isomer, indicating that the migration direction was completely controlled.

As shown in Table 2, the substrates with an alkyl group and an aryl group at the C4 position caused only aryl group migration. This behavior is the same as the migration tendency of the Wagner–Meerwein rearrangement, where substituents that stabilize the bridged carbocation intermediates preferentially undergo the migration. In the case of compound **1g** with two different aromatic groups at the C4 position, the more preferable migrating substituent is determined by a balance between the stabilizing effect for the bridged carbocation by the migrating group and the stabilization of the local C4 carbocation by the remaining substituent. And the

Table 2. Two-way rearrangement of **1** under two different reaction conditions.



Entry	1	R	Ar	Condition	Isolated yield (%) 2	3
1	**1a**	Me	Ph	A	**2a** –	**3a** 42
2	**1a**			B	**2a** quant.	**3a** –
3	**1b**	Me	C_6H_4-4-F	A	**2b** –	**3b** 51
4	**1b**			B	**2b** quant.	**3b** –
5	**1c**	Me	C_6H_2-3,4,5-$(OMe)_3$	A	**2c** –	**3c** 53
6	**1c**			B	**2c** quant.	**3c** –
7	**1d**	Me	2-thienyl	A	**2d** –	**3d** 34
8	**1d**			B	**2d** 72	**3d** –
9	**1e**	Et	Ph	A	**2e** –	**3e** 66
10	**1e**			B	**2e** quant.	**3e** –
11	**1f**	Ph	Ph	A	**2f** –	**3f** 62
12	**1f**			B	**2f** quant.	**3f** –
13	**1g**	Ph	C_6H_4-4-OMe	A	**2g** –	**3g** 44[a]
14	**1g**			B	**2g** quant.	**3g** –

[a]A 1:1.5 mixture of two regioisomers with Ph and C_6H_4-4-OMe groups swapped was obtained.

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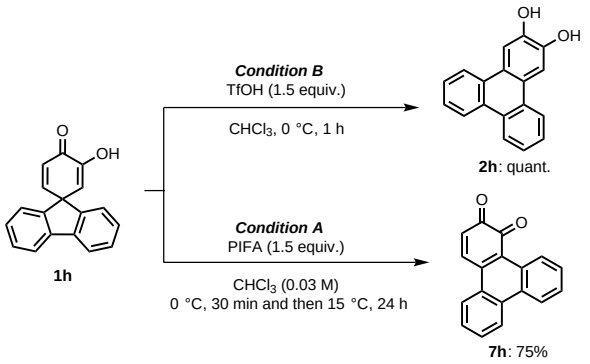

Scheme 3. Two-way rearrangement of **1h** under two different reaction conditions.

predominant migration of the Ph group in **1g** implies that the stabilization of the local C4 carbocation plays a stronger role in determining the migrating substituent.

3. Conclusion

We have synthesized 3,4-disubstituted catechols **3** by the hypervalent iodine reagent (PIFA)-mediated umpolung at the C3 position of 4,4-disubstituted 2-hydroxycyclohexa-2,5-dien-1-ones **1** to achieve unprecedented migration of the C4 aryl substituent to the C3 position. In addition, the acid-induced dienone–phenol rearrangement of **1** produced 4,5-disubstituted catechols **2**. By selecting these two rearrangement conditions, two regioisomers of biaryl compounds containing disubstituted catechol moieties have been synthesized with exclusive selectivity. Symmetrical or unsymmetrical tetracyclic compounds **2h** and **7h**, obtained in this study, will be applied to the synthesis of polycyclic (hetero) aromatic hydrocarbons.[15,18] Studies to improve the yield of the oxidation–rearrangement reaction and the application of the products are currently in progress in our laboratory.

Supplementary data

Supplementary material is available at *Bulletin of the Chemical Society of Japan* online.

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Conflict of interest statement. None declared.

Data availability

Experimental procedures and spectroscopic data are available in Supporting Information.

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