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Concerted [1,3]-Rearrangement in Cationic Cobalt-Catalyzed Reaction of *O*-(Alkoxycarbonyl)-*N*-arylhydroxylamines

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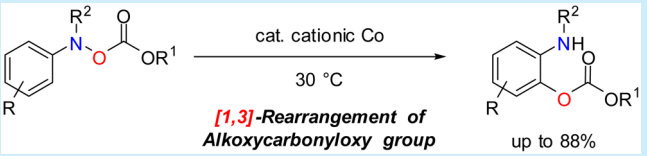
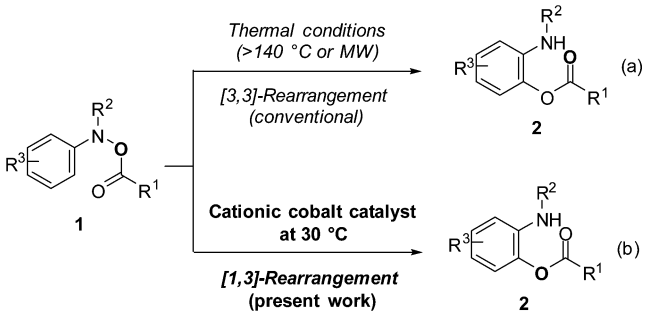
Supporting Information

ABSTRACT: *O*-(Alkoxycarbonyl)-*N*-arylhydroxylamines were efficiently converted to 2-aminophenol derivatives by cationic cobalt catalysts at 30 °C. The results of ^{18}O-labeling experiments suggested that rearrangement of the alkoxycarbonyl group from the aniline nitrogen to the *ortho* position proceeded in an unprecedented [1,3] manner.



Metal catalysts have enabled various kinds of organic transformations to proceed under much milder conditions with higher functional group compatibility. The effectiveness of metal-catalyzed transformation is often due to a change of the reaction pathway driven by suitable complexation of the metal catalyst with the substrate. Here, we show that such a change of the reaction mode by metal catalysts occurred in the classical rearrangement reaction of *O*-acyl-*N*-arylhydroxylamines **1** to *O*-acylated 2-aminophenol **2** (Scheme 1).[1,2] That

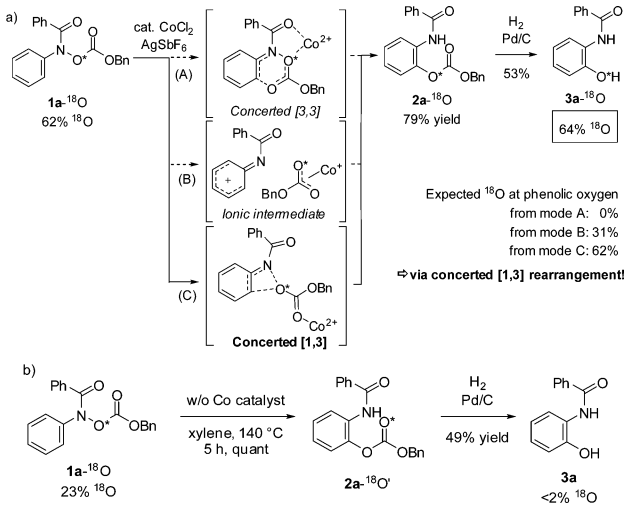
Scheme 1. Rearrangement of *O*-Acyl-*N*-arylhydroxylamines



is, the focused rearrangement reaction of **1** has been extensively investigated to proceed typically under elevated temperature (>140 °C) or microwave irradiation in a concerted [3,3] manner (Scheme 1a). In this paper, we report that the pathway of the well-known rearrangement reaction was dramatically switched to an unprecedented [1,3] manner by using cationic cobalt catalysts, which proceeded at 30 °C, efficiently affording a wide repertoire of the 2-aminophenol derivatives **2**, which have been frequently utilized in pharmaceutical chemistry (Scheme 1b).[3]

Initially, the screening of the metal catalysts for the reaction of **1** disclosed that the cationic metal species such as Co^{2+}, Cu^{2+}, and Zn^{2+} afforded the desired 2-aminophenol derivative **2** (see Supporting Information). In particular, the combination of $CoCl_2$ (10 mol %) and $AgSbF_6$ (20 mol %) exhibited an excellent catalytic activity for the reaction of **1a**, which has benzoyl and benzyloxycarbonyl (Cbz) groups on the nitrogen and oxygen atoms, respectively, in 1,2-dichloroethane (DCE) at 30 °C, affording **2a** in 82% yield (eq 1).[4] According to previous works,[1] in order to determine whether the migration of the CbzO group proceeded in a concerted [3,3] manner (Scheme 2a, mode A)[8] as in a thermally induced reaction,[1c,d] or via

Scheme 2. ^{18}O-Labeling Experiments



heterolytic cleavage of the N−O bond[1b] by the Lewis acid (mode B),[5] we conducted ^{18}O-labeling experiments using **1a**-^{18}O with an oxygen-18 content at the hydroxylamine moiety of 62%.[6,7] To our surprise, the cobalt-catalyzed reaction followed by hydrogenolysis of the migrated Cbz group afforded the aminophenol **3a**-^{18}O with ^{18}O content at the phenolic oxygen of 64%. The complete retention of the labeled ^{18}O

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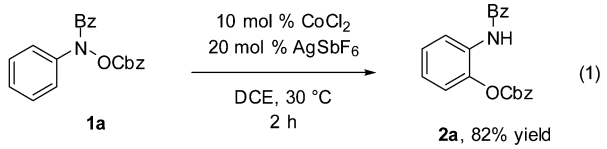
Org. Lett. XXXX, XXX, XXX−XXX

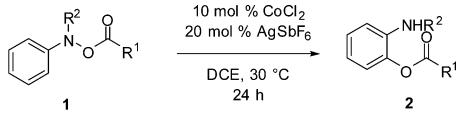
strongly indicated that the rearrangement of the benzyloxycarbonyloxy group did not proceed in a [3,3] manner or through ionic N−O bond cleavage but exclusively in an unprecedented [1,3] manner (Scheme 2a, mode C).[9,10] Indeed, the thermally induced reaction of **1a**-^{18}O (23% ^{18}O) in the absence of the cobalt catalyst in xylene at 140 °C[1g] followed by hydrogenative deprotection afforded **3a** with an ^{18}O content at the phenolic oxygen of less than 2%, indicating that the thermally induced reaction of **1a** proceeded in a concerted [3,3] manner (Scheme 2b).



1a **2a**, 82% yield (1)

Various alkoxycarbonyloxy groups, such as CbzO (**1a**), methoxycarbonyloxy (**1b**), and AllocO (**1c**) groups showed good migrating abilities (eq 1 and Table 1, entries 1 and 2),

Table 1. Substitution Effect at the Hydroxylamine Moiety[a]

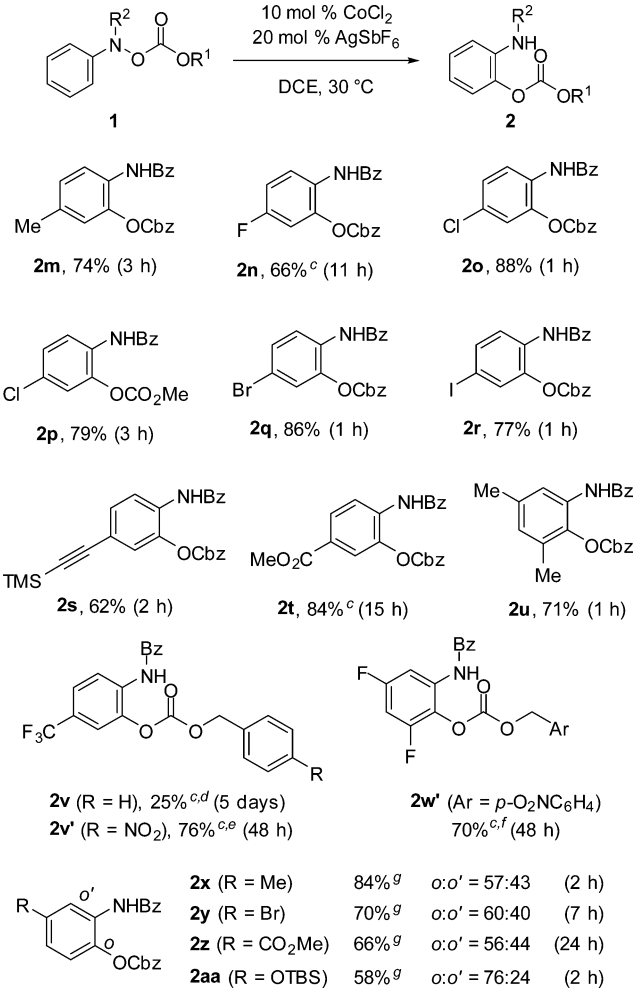


1 **2**

entry	1	R^1	R^2	time (h)	2	yield[b] (%)
1	**1b**	OMe	Bz	3	**2b**	75[c]
2	**1c**	*O*-allyl	Bz	2	**2c**	75
3	**1d**	Ph	Bz	120		<1
4	**1e**	Me	Bz	120		<1
5	**1f**	OMe	Boc	6	**2f**	64[c]
6	**1g**	OMe	Alloc	4	**2g**	45
7	**1h**	OMe	Cbz	5	**2h**	64
8	**1i**	OMe	CO_2Me	4	**2i**	72[c]
9	**1j**	OMe	*p*-$MeOC_6H_4C(O)$	2	**2j**	60[c]
10	**1k**	OMe	*p*-$F_3CC_6H_4C(O)$	24	**2k**	61
11	**1l**	OMe	Ac	120	**2l**	44

[a]The reactions of **1** (0.4 mmol) were conducted in the presence of 10 mol % $CoCl_2$ and 20 mol % of $AgSbF_6$ in DCE (1.6 mL) at 30 °C. [b]Isolated yield. [c]^{1}H NMR yield using dibromomethane as an internal standard.

Scheme 3. Substrate Scope[a,b]



[a]The reactions of **1** (0.4 mmol) were conducted in the presence of 10 mol % $CoCl_2$ and 20 mol % of $AgSbF_6$ in DCE (1.6 mL) at 30 °C. [b]Isolated yield. [c]^{1}H NMR yield using dibromomethane as an internal standard. See the SI for details. [d]Yield brsm (41% of **1v** was recovered). [e]Yield brsm (28% of **1v'** was recovered). [f]Yield brsm (34% of **1w'** was recovered). [g]Combined yield of the two regioisomers.

whereas, in sharp contrast, substrates **1d** and **1e**, which have an acyl group on the oxygen atom of the hydroxylamine moiety, did not undergo the rearrangement under the present reaction conditions and decomposed (entries 3 and 4). On the other hand, various acyl groups, such as acetyl and benzoyl, and alkoxycarbonyl groups, such as Boc, Alloc, and Cbz, were tolerated as the protecting group of the nitrogen atom under the optimized reaction conditions (entries 5−11), as summarized in Table 1. It is noteworthy that the reaction of **1j** having an electron-rich *p*-methoxybenzoyl group proceeded much faster than that of **1k** having an electron-deficient *p*-(trifluoromethyl)benzoyl group (entries 9 and 10). The reaction of substrates having a substituent at the ortho position, such as methyl group, did not give the desired product.

The reaction was applicable for synthesizing a wide repertory of multisubstituted aminophenol derivatives (**2m**−**aa**), as summarized in Scheme 3. In particular, highly reactive functional groups, such as bromo, iodo, and alkynyl groups, were compatible in the present rearrangement reaction to afford the desired products **2q**, **2r**, and **2s** in good yields. Moreover, products **2o**, **2p**, and **2t** having electron-withdrawing functional groups on the aromatic ring, which are generally less efficiently synthesized through electrophilic substitution reactions, were obtained in good yields. Notably, our catalytic conditions successfully promoted the rearrangement of **1v'** and **1w'**, having a 4-(trifluoromethyl)phenyl and 3,5-difluorophenyl group, respectively, by using a *p*-nitrobenzyloxycarbonyl group in place of Cbz.[11,12] Thus, the present method is potentially useful for the synthesis of 2-aminophenols having highly electron-withdrawing functional groups, which are inaccessible by thermal [3,3]-rearrangement reactions. The reaction of *meta*-substituted substrates **1x**−**aa** afforded c.a. 1:1 mixtures of the 5- and 3-substituted 2-aminophenols, regardless of the character of the substituent.

In order to gain further insight into the mechanism of the unprecedented [1,3]-rearrangement reaction, first crossover experiments using equally reactive substrates **1a** and **1p** were conducted. The reaction of the mixture under the standard reaction conditions gave only products **2a** and **2p** derived from the starting materials; no crossover products were observed by

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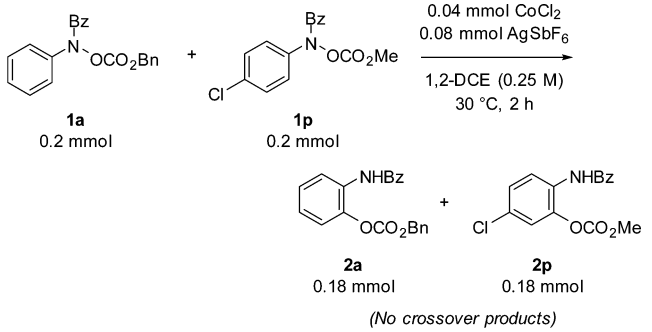
Org. Lett. XXXX, XXX, XXX−XXX

HRMS (Scheme 4). This result strongly indicates that migration of the alkoxycarbonyloxy group takes place intra-

Scheme 4. Crossover Experiment



molecularly. In addition, intra- and intermolecular isotope effects were not observed, suggesting that the C−H bond cleavage occurs after C−O bond formation at the *ortho* position (see the SI). At the present stage, we speculate that cationic cobalt catalyst functions as a Lewis acid not only to lower the LUMO of the migrating alkoxycarbonyloxy group[12] but also to change the geometry of the transition state from [3,3] to [1,3], allowing the rearrangement to proceed at 30 °C with high functional group compatibility.[13]

In conclusion, we have discovered the unprecedented [1,3]-rearrangement of *N*-(alkoxycarbonyl)-*N*-arylhydroxylamines by using cationic cobalt catalysts, synthesizing useful 2-aminophenol derivatives in an efficient manner under mild reaction conditions. Further mechanistic studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00700.

Experimental procedures as well as full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(4) For details of the optimization of reaction conditions, see the Supporting Information.

(5) For a review, see: Tabolin, A. A.; Ioffe, S. L. *Chem. Rev.* **2014**, *114*, 5426.

(6) **1a**-^{18}O was prepared from nitrobenzene-^{18}O. Rajendran, G.; Santini, R. E.; Van Etten, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 4357. Deprotection of the Cbz group of **1a**-^{18}O under basic conditions afforded the corresponding *N*-hydroxylamine with an oxygen-18 content of 65%, unambiguously indicating that the oxygen-18 in **1a**-^{18}O exists at the hydroxylamine moiety. See the Supporting Information.

(7) The percentage of oxygen-18 content was determined by the intensity of the mass spectrum.

(8) Metal-catalyzed [3,3] rearrangement involving N−O bond cleavage: Wu, Q.; Yan, D.; Chen, Y.; Wang, T.; Xiong, F.; Wei, W.; Lu, Y.; Sun, W.-Y.; Li, J. J.; Zhao, J. *Nature Commun.* **2017**, DOI: 10.1038/ncomms14227.

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(11) The thermal reaction of **1v** and **1v′** in xylene at reflux resulted in decomposition of the starting materials, while that of **1w′** gave **2w′** in 29% yield. The reaction of **1v′** at 60 °C gave **2v′** in low chemical yield (26%) due to competitive decomposition of the starting material **1v′**.

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(13) Our preliminary attempts to find transition state(s) for the cationic Co-catalyzed [1,3]-rearrangement were unsuccessful, obviously due to convergent failure of "naked cationic cobalt" species. Therefore, it is necessary to develop ligand-coordinated metal catalysts for the present reaction in order to carry out further computational studies to understand the details of the unprecedented [1,3]-rearrangement. Such studies are currently underway in our laboratory.

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