

Tetraalkylammonium-Templated Stereoselective Norrish–Yang Cyclization

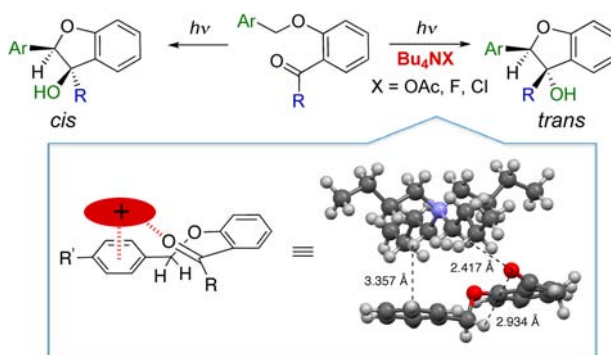
Shinji Yamada,^{*,†} Azusa Iwaoka,[†] Yuka Fujita,[†] and Seiji Tsuzuki[‡]

Department of Chemistry, Ochanomizu University, Bunkyo-ku, Tokyo 112-8610, Japan,
and National Institute of Advanced Industrial Science and Technology (AIST),
Tsukuba, Ibaraki 305-8568, Japan

yamada.shinji@ocha.ac.jp

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ABSTRACT



Tetrabutylammonium salts serve as templates for the Norrish–Yang cyclization of 2-benzyloxy-acylbenzenes to give *trans*-dihydrobenzofuranols in high stereoselectivities. The dual cation– π interactions between an ammonium with a benzene ring and a carbonyl group play a key role in changing the conformation of the substrate, which was supported by *ab initio* calculations.

Norrish–Yang cyclization is an attractive method for the activation of C–H bonds through intramolecular H-abstraction by an excited carbonyl group,¹ providing various products with a quaternary C-center, and has been applied to the synthesis of natural products.² However, methods for controlling the stereochemistry of the products remain unexplored due to the difficulty associated with the conformational control of the excited state as well as the reactive intermediate except for in solid-state reactions.^{1b}

Recently, template-mediated regio- and stereoselective photochemical reactions,³ such as [2 + 2],⁴ [2 + 4],⁵ and [4 + 4]⁶ cycloaddition reactions, and photoelectron transfer reactions⁷ have extensively been explored, where artificial templates form complexes with substrates through H-bonds. Continuing our research on the application of cation– π interactions⁸ in synthetic organic photochemistry,⁹ we focused on the use of ammonium ions as

[†] Department of Chemistry, Ochanomizu University.

[‡] National Institute of Advanced Industrial Science and Technology.

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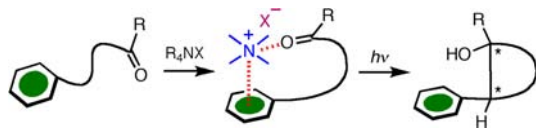
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Scheme 1. Schematic Representation of Norrish–Yang Cyclization through Dual Interactions between an Ammonium with a Benzene Ring and a Carbonyl Group



the cationic template in Norrish–Yang cyclization reactions, while interactions between an ammonium with a benzene ring⁸ and a carbonyl group^{10,11} have already been reported. The concept underlying our strategy is outlined in Scheme 1. The conformation of the substrate can be controlled by the formation of a complex with tetraalkylammonium. The Norrish–Yang cyclization of this dual interaction system would thus produce two stereogenic centers reflecting the conformation of the complex. Here, we report tetrabutylammonium halides and acetate can serve as templates for these reactions.

2-Benzyloxyacetophenones (**1a–1d**) and 2-benzyloxybenzophenones (**2a–2d**) were employed as substrates for the Norrish–Yang cyclization reactions. Irradiation of **1a**¹² in a CH₃CN solution (0.1 M) with a 450 W high-pressure mercury lamp gave *cis*-dihydrobenzofuranol (**4a**) as a major product with a *trans/cis* ratio of 17:83, as shown in Table 1 (entry 1), which is in line with that previously reported.¹² A variety of cationic organic compounds, such as pyridinium, imidazolium, and ammonium salts, were employed to survey their ability to act as a template for this reaction, as these cationic compounds have been known to interact with an aromatic ring.⁵ The stereochemistry of the products was determined through a comparison of the ¹H NMR spectral data with those previously reported.^{12b} Among these templates, Bu₄NF was the most effective to give *trans*-dihydrobenzofuranol as a major product (entries 2–11). It should be noted that the selectivity was significantly decreased in the presence of 10% water (entry 12). The highest selectivity was obtained when Bu₄NOAc was used as a template (entry 13). Interestingly, the conversions were significantly increased by the addition of Bu₄NX, suggesting that these templates enhance the reaction rate by changing the conformation of the substrate. In contrast, Bu₄NBF₄ and Bu₄NPF₆ had little influence on the selectivity (entries 14 and 15). The effect of the anions on the selectivity was in the order AcO[−] ≥ F[−] > Cl[−] > Br[−] ≫ PF₆[−], BF₄[−], which is almost in agreement with the order of the coordinating property, suggesting the importance of the H-bond with the reaction intermediate. In addition, CsF did not affect the selectivity (entry 16),

indicating the importance of an ammonium cation as a template. The use of CF₃Ph as a solvent gave **4a** exclusively (entry 17). On the other hand, the addition of Bu₄NCl, Bu₄NF, and Bu₄NOAc dramatically inverted the stereo-selectivity to give **3a** (entries 18–20).

Similar results were obtained in the case of **2a**. The Norrish–Yang cyclization of **2a** shows *cis*-selectivity (entry 21), whereas irradiation in the presence of Bu₄NXs predominantly afforded the *trans*-product **5a**, with Bu₄NF and Bu₄NOAc again being highly effective templates (entries 22–25). Decreasing the amount of Bu₄NF from 5.0 to 3.0 equiv did not affect the selectivity (entry 26). However, further decreasing the amount from 3.0 to 0.5 equiv resulted in a reduction in the selectivity (entries 27 and 29). An increase in the concentration from 0.1 to 0.3 M

Table 1. Norrish–Yang Cyclization of **1a** and **2a**^a

entry	compd	template	equiv	time (h)	conv (%) ^b	<i>trans</i> : <i>cis</i> ^b
1	1a	—	0	10	35	17:83
2	1a	C ₅ H ₅ NMeBr	2.5	10	9	44:56
3	1a	[emim][Cl] ^c	5	5	53	71:29
4	1a	[emim-OH][Cl] ^d	5	5	18	42:58
5	1a	[bmim][Cl] ^e	5	5	24	18:82
6	1a	Et ₄ NBr	5	5	41	62:38
7	1a	Pr ₄ NBr	5	5	10	65:35
8	1a	Bu ₄ NBr	5	5	39	68:32
9	1a	Oct ₄ NBr	5	5	21	66:34
10	1a	Bu ₄ NCl	5	10	100	74:26
11	1a	Bu ₄ NF ^f	5	10	96	84:16
12	1a	Bu ₄ NF ^f	5	10	86	48:52 ^{g,h}
13	1a	Bu ₄ NOAc	5	10	100	91:9
14	1a	Bu ₄ NBF ₄	5	10	87	27:73
15	1a	Bu ₄ NPF ₆	5	10	100	18:82
16	1a	CsF	5	10	72	21:79
17	1a	—	0	6	17	0:100 ⁱ
18	1a	Bu ₄ NCl	5	10	100	91:9 ^j
19	1a	Bu ₄ NF ^f	5	10	93	93:7 ⁱ
20	1a	Bu ₄ NOAc	5	10	100	88:12 ⁱ
21	2a	—	0	5	100	39:61
22	2a	Bu ₄ NBr	5	3	100	62:38
23	2a	Bu ₄ NCl	5	5	99	72:28
24	2a	Bu ₄ NF ^f	5	3	100	85:15
25	2a	Bu ₄ NOAc	5	3	79	85:15
26	2a	Bu ₄ NF ^f	3	3	100	85:15
27	2a	Bu ₄ NF ^f	1	3	100	78:22
28	2a	Bu ₄ NF ^f	1	3	80	84:16 ^j
29	2a	Bu ₄ NF ^f	0.5	3	100	63:37

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^a 0.1 M CH₃CN solution was used unless otherwise noted. ^b Determined by ¹H NMR spectra. ^c [emim][Cl]: 1-ethyl-3-methylimidazolium chloride. ^d [emim-OH][Cl]: 1-hydroxyethyl-3-methylimidazolium chloride. ^e [bmim][Cl]: 1-butyl-3-methylimidazolium chloride. ^f Trihydrate was used. ^g A 9:1 mixture of CH₃CN and H₂O was used as a solvent. ^h Dihydroisobenzofuranols were also obtained in a 31% yield as byproducts (see, ref 12b). ⁱ CF₃Ph was used as a solvent. ^j A 0.3 M solution was used.

increased the selectivity, despite the use of 1 equiv of TBAF (entry 28). These results show the importance of the association between the substrate and the template, confirming the role of the ammonium salt as a template.

In order to clarify the contribution of the cation– π interaction to these reactions, the effect of the substituent R^2 on the aromatic ring on stereoselectivity was examined (Table 2). Irradiation of **1b–1d** in CH_3CN gave *cis*-dihydrobenzofuranols **4b–4d** as major products, respectively (entries 1, 3, and 5). On the other hand, in the presence of Bu_4NF , photolysis of **1b** and **1c**,¹³ both having electron donating groups, produced *trans*-dihydrobenzofuranols **3b** and **3c**, respectively, in high selectivities (entries 2 and 4). Irradiation of **1d**, having a trifluoromethyl group, afforded **3d** in lower selectivity (entry 6). Similar results were also obtained for **2b–2d** (entries 7–12). These results confirmed that the substituent on the benzyl aromatic ring affects the stereoselectivity. The selectivities increased in the order $\text{OMe} > \text{CH}_3 > \text{H} > \text{CF}_3$,¹⁴ strongly suggesting the contribution of the cation– π interaction between the ammonium and the benzyl moieties.

Table 2. Norrish–Yang Cyclization of **1b–1d** and **2b–2d**

1: $R^1 = \text{Me}$ 2: $R^1 = \text{Ph}$
 b: $R^2 = \text{CH}_3$ c: $R^2 = \text{OMe}$ d: $R^2 = \text{CF}_3$

3: $R^1 = \text{Me}$ 4: $R^1 = \text{Me}$
 5: $R^1 = \text{Ph}$ 6: $R^1 = \text{Ph}$

entry	substrate	template	time (h)	conv (%)	3:4 or 5:6 ^a
1	1b	—	24	35	20:80
2	1b	Bu_4NF	24	84	93:7
3	1c	—	24	70	11:89
4	1c	Bu_4NF	24	99	94:6
5	1d	—	24	33	23:77
6	1d	Bu_4NF	24	6	59:41
7	2b	—	3	100	37:63
8	2b	Bu_4NF	3	99	88:12
9	2c	—	3	100	42:58
10	2c	Bu_4NF	3	57	88:12
11	2d	—	3	100	45:55
12	2d	Bu_4NF	3	92	72:28

^a Determined by ^1H NMR spectra.

Studies on the dependence of the ^1H and ^{13}C NMR chemical shifts on the concentration of Bu_4NF revealed the existence of an interaction between the ammonium and the carbonyl group. The $\Delta\delta$ values, which represent the differences between the chemical shifts in the presence and

absence of Bu_4NF , were obtained to clarify the existence of the interaction (see Supporting Information (SI)).

To elucidate the role of the ammonium ion in the control of stereoselectivity, the conformational changes produced by the addition of Bu_4N^+ were investigated by *ab initio* calculations using the Gaussian 09 program.¹⁵ Details of the computational methods are given in the SI. Six stable conformers of **1a** were obtained by geometry optimizations. Figure 1a shows a conformer capable of intramolecular H-abstraction due to having a much shorter $\text{O}\cdots\text{H}-\text{CHPh}$ distance (2.32 Å), although the energy is 2.03 kcal/mol higher than that of the lowest energy conformer at the MP2/6-311G** level. The geometry optimization for the complexes formed between **1a** and Bu_4N^+ gave seven stable geometries. Among the seven orientations, three have a structure in which two interactions exist between an ammonium with a benzene ring and a carbonyl group. These comprise 96% of the population in all of the orientations. Figure 1b shows the most stable orientation of the complex with a $\text{C}=\text{O}\cdots\text{H}-\text{CHPh}$ distance of 2.934 Å, which would permit H-abstraction by a carbonyl group. The H-atom of the α -methylene moiety is close to the centroid of the benzene ring (3.357 Å).

A comparison of the conformation of **1a** and the orientation of the complex shown in Figure 1 revealed significant differences in the geometries of **1a**. While the two benzene rings of the conformer in **1a** are in a *syn* orientation, those of the complex are in an *anti* orientation, showing the remarkable effect of the ammonium on conformational change. Although the distances between the N-atom of the ammonium and the aromatic ring and the carbonyl group are greater than those for the sum of van der Waals radii of the corresponding atoms,¹⁶ the cationic charge of the N-atom is distributed to the C-atoms next to the N-atom,^{8a} which is suggested by calculations¹⁷ and the X-ray structure of a complex of an ammonium with an enolate.¹⁸

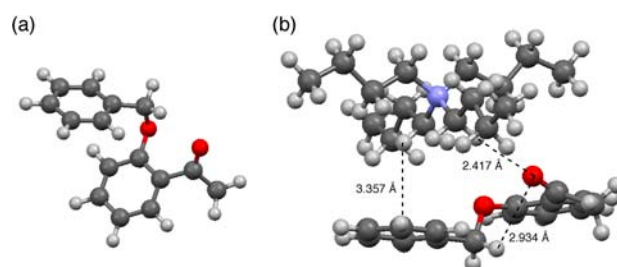


Figure 1. (a) A conformer of **1a** capable of H-abstraction and (b) the most stable orientation for a complex of **1a** with Bu_4N^+ .

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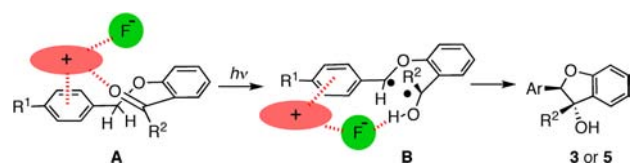
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Scheme 2. Postulated Reaction Mechanism for TBAX-Templated Norrish–Yang Cyclization



The stabilization energy of the complex shown in Figure 1b was calculated for that orientation to be -15.3 kcal/mol. The electrostatic (-10.6 kcal/mol) and induction (-4.3 kcal/mol) components are mainly responsible for the strong attraction. The significant contribution of the electrostatic and induction components toward the stabilization energy suggests that these interactions can be categorized as cation– π interactions.¹⁷

Taken together, the above results led us to conclude that the mechanism for the stereoselective Norrish–Yang cyclization of 2-benzoyloxyacetylbenzenes is as shown in Scheme 2. As predicted by the calculations, the substrate forms a complex **A** with Bu_4N^+ through dual interactions at the aromatic ring and the carbonyl group. The abstraction of the benzyl hydrogen by an excited carbonyl group produces a biradical and a hydroxy group as shown in **B**. Ring closure of the biradical would thus produce *trans*-dihydrobenzofuranol **3** or **5**. Although the role of the counteranions toward the stereoselectivity still remains unclear, the H-bond acceptor ability seems to be an important factor. The halide and acetate ions can form a H-bond with the hydroxy group of the intermediate **B**, which would contribute to the stabilization of the conformation of **B**. The order of the basicity of the anions are $\text{AcO}^- > \text{F}^- > \text{Cl}^- > \text{Br}^-$, which corresponds closely with the order of their stereoselectivities (Table 1, entries 7, 10, 11, and 13, and entries 22–25). On the other hand, the noncoordinating anions, PF_6^- and BF_4^- , are much less effective (Table 1, entries 14 and 15). The observation that a solvent containing 10% water significantly decreased the selectivity supports the contribution of the H-bond to the

selectivity (Table 1, entry 12). These results strongly suggest the importance of the H-bond in the intermediate **B**. It has been reported that the H-bonded conformation of a biradical is the key to stereoselectivity in the Norrish–Type II reaction of β -methoxy ketones.¹⁹ Moreover, as the combination of an ion pair and a H-bond has been postulated in the several catalytic reactions using ionic liquids²⁰ and in the ammonium betaine catalysis in Mannich reactions,²¹ the ion pair of the ammonium cation and the anion may contribute to the stabilization of the intermediate **B**.

Although there have been several examples of the use of organic cations as a template for organic synthesis, such as formation of hosts,²² catenane syntheses,²³ and macrocyclic RCM reactions,²⁴ to the best of our knowledge, there has been little work on their application to stereoselective reactions.

In summary, we have reported that TBAXs serve as templates for diastereoselective Norrish–Yang cyclizations. The dual interactions between an ammonium with a benzene ring and a carbonyl group significantly changed the conformation of the substrate. The counteranions also have a significant effect on the stereoselectivity. The weakly basic anions are speculated to stabilize the intermediary biradical by forming a H-bond with the hydroxy group of the intermediate, the cyclization of which leads to *trans*-dihydrobenzofuranols in high stereoselectivities. As TBAXs are common reagents, they would be useful for various template-controlled organic syntheses.

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Supporting Information Available. Experimental and computational details, characterization data, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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