Changing the *Ortho/Para* Ratio in Aromatic Acylation Reactions by Changing Reaction Conditions: A Mechanistic Explanation from Kinetic Measurements[1]

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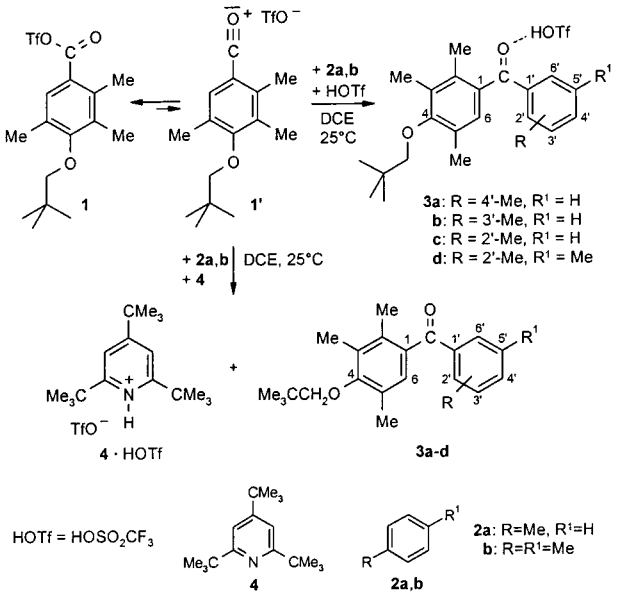
Abstract: Kinetic measurements of the acylation of toluene (**2a**) and *p*-xylene (**2b**), side-chain deuterated toluene (**2a**-d_3), as well as perdeuterated toluene (**2a**-d_8) and *p*-xylene (**2b**-d_{10}) with the aroyl triflate **1** in 1,2-dichloroethane reveal a strong dependence of the isotope effect on reaction conditions. In the presence of trifluoromethanesulfonic acid (HOTf), the second-order rate constants k_H/k_D observed are in the order of 1.75−1.94, whereas in the presence of 2,4,6-tri-*tert*-butylpyridine (**4**) rate constants k_H/k_D of 1.14−1.25 are found. The primary kinetic isotope effects observed correlate with the *ortho*/*para* ratio of the acylation of toluene. In the presence of **4** a relatively high percentage (∼30%) of *ortho* product is obtained, whereas under acidic conditions the ratio is only 10%. The correlation between isotope effects and isomer distributions is obviously due to the rate of deprotonation of the corresponding σ-complex intermediates. Assuming a bent structure for σ-complexes, the conformation giving deprotonation is preferred in the *para* σ-complex in comparison with *ortho* complex.

Introduction

In their first fundamental mechanistic investigations of Friedel−Crafts acylations Olah et al. already supposed that the *ortho/para* isomer ratios might depend on the rate of deprotonation of the Wheland intermediate.[3] Primary kinetic isotope effects k_H/k_D in the order of 1.5 to 3.25[3,4a] indicate that the σ-complex intermediates are relatively stable, and thus their follow-up reactions can be influenced specifically. These mechanistic studies were performed in organic solvents with acylium salts as acylating agents.[3] Since acylations of aromatics normally are carried out either with an excess of Friedel−Crafts catalyst or in superacidic systems, the deprotonation of the intermediate σ-complex has not yet been studied kinetically. Investigations of the deprotonation step to change the *ortho/para* ratio specifically by changing reaction conditions have also not yet been carried out.

In a previous publication[1] we have reported on the mechanism of the acylation of aromatics with carboxylic trifluoromethanesulfonic anhydrides (acyltriflates). The extraordinary reactivity of acyltriflates, also in the absence of Friedel−Crafts catalysts or strong Brønsted acids, makes it possible to perform acylations of aromatics even in the presence of a base. Both steps of aromatic acylations with acyltriflates, the formation of σ-complexes as well as their deprotonation, can therefore be studied. Scheme 1 represents the model reaction we have investigated

Scheme 1



kinetically.[1] The acylation of aromatics with acyltriflates was followed kinetically both in the presence of 2,4,6-tri-*tert*-butylpyridine (**4**) as well as with an excess of trifluoromethanesulfonic acid (HOTf).[1] Due to steric reasons, the pyridine derivative **4** does not react with aroylium ions formed by dissociation of aroyltriflates.[1] The rate constants of aroylations determined in the presence of **4** as well as in the presence of HOTf refer directly to the corresponding concentrations of acylium ion **1′**.[1]

Acylations under basic conditions proceeded 5 to 10 times faster than the comparable reactions in the presence of 150 mol % HOTf (Scheme 1). This result indicates that the deprotonation

(1) Electrophilic Aromatic Substitution. Part 41: for part 40 see: Effenberger, F.; Eberhard, J. K.; Maier, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 12572−12579.

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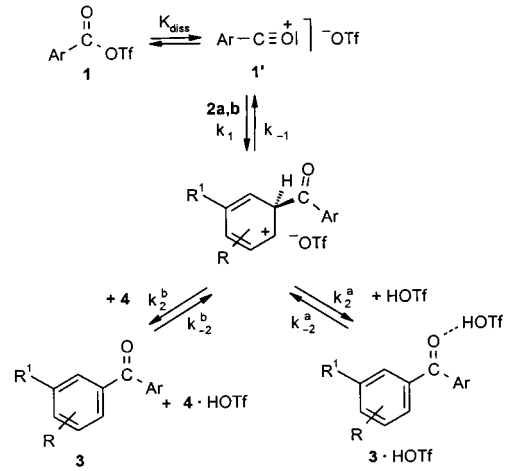
Scheme 2



step contributes to the rate of the overall reaction, and thus confirms earlier findings[3,4] of a primary kinetic isotope effect in aromatic acylations.

Since variation of reaction conditions, i.e., working in acidic or basic media, causes also a change of the *ortho/para* isomer ratios,[1] we have now investigated the rate of the deprotonation step of the intermediate σ-complexes by kinetic measurements.

Results and Discussion

For a kinetic treatment, the model reaction shown in Scheme 1 is summarized schematically in Scheme 2. The dissociation step (**1** ⇄ **1′**) is to be considered not rate-determining.[1] For $k_1 \ll k_{-1}$, k_2, and $k_{-2} = 0$, which is realistic for electrophilic aromatic acylations, the general rate law given in eq 1 can be deduced.[5]

$$v = k_1[\mathrm{ArH}][\mathbf{1'}]\frac{k_2}{k_{-1} + k_2} \qquad (1)$$

with $k_2 = k_2^b[\mathbf{4}]$ or $k_2 = k_2^a$. From this it follows that if $k_{-1} \approx k_2$ or $k_{-1} \gg k_2$ (Scheme 2), the overall reaction rate is influenced by the deprotonation step. In case of $k_{-1} \gg k_2$ there will be a linear dependence on the deprotonation rate, otherwise the deprotonation rate affects partially the overall reaction rate. The magnitude of a primary kinetic isotope effect, as experimental proof for the influence of the deprotonation step, depends on the rate of the back reaction (k_{-1}) and the deprotonation (k_2) of the σ-complex.[5] With exception of the azo coupling which is performed in aqueous medium,[6] the validity of eq 1 has not been proved so far.[7]

Isotope Effects in the Acylation of Toluene and *p*-Xylene in the Presence of HOTf and of Base, Respectively. In general, primary kinetic isotope effects are obtained by determining the rate constants of reactions of the deuterated and the corresponding not deuterated compounds.[8] This is possible in the presence of HOTf, where the concentration of acylium ion **1′** corresponds to the concentration of **1** (Scheme 1). In these cases we were able to calculate k_{obs}^a via the integrated second-order rate law[9] based on gas chromatographically determined concentration time data as shown in Figure 1b,a. To check for side reactions we plotted the concentration of educts ([**1** + **1′**]) together with the concentration of educts calculated from determined product concentration ([**1** + **1′**] = [**1** + **1′**]^0 − [**3**]). In the reaction with deuterated aromatics in the presence of base, the concentration of acylium ion **1′** cannot be followed easily. IR spectroscopy failed in the presence of deuterated aromatics due to overlapping of the acylium ion band at 2188 cm^{-1} with

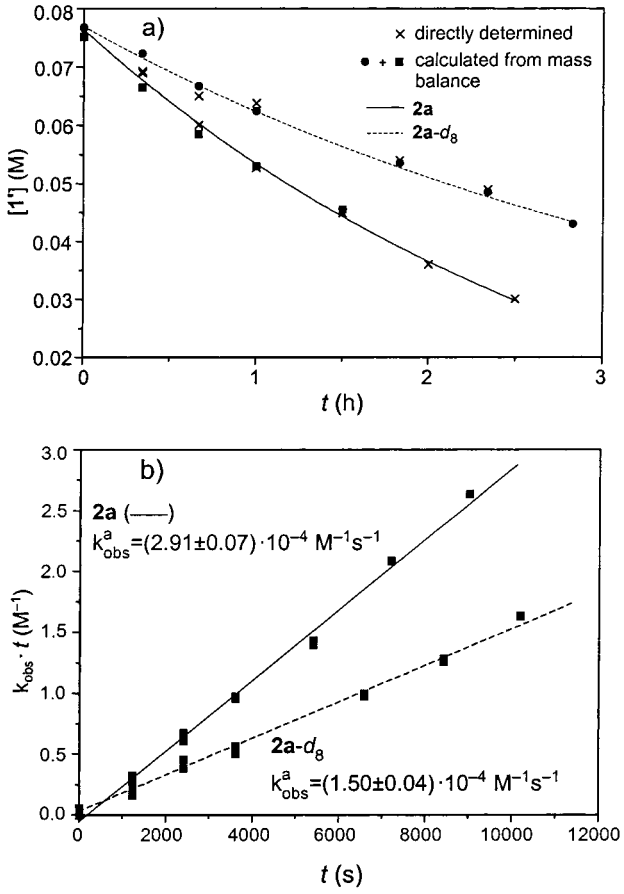


Figure 1. Reaction profile (a) and determination of rate constants (b) of the reaction of toluene (**2a**) and deuterated toluene (**2a**-d_8) with acylium ion **1′** in DCE at 25 °C in the presence of HOTf.

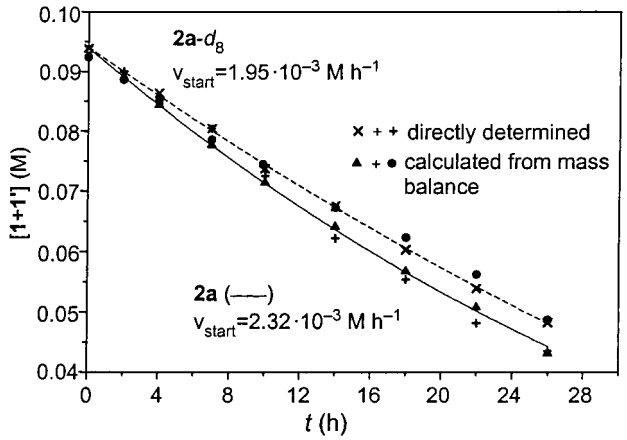


Figure 2. Reaction profile and derived initial velocities (v_{start}) of the reaction of acylium ion **1′** with toluene (**2a**) and deuterated toluene (**2a**-d_8) in DCE at 25 °C in the presence of base **4**.

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Table 1. Isotope Effects k_H/k_D on the Second-Order Rate Constant k_{obs} in the Acylation of **2a**,**b** with Acylium Ion **1′** in the Presence of HOTf and **4**, Respectively, at 25 ± 0.2 °C in 1,2-Dichloroethane

							k_H/k_D obs	
aromatics **2**	(M)	[**1**] (M)	[HOTf] (M)	[**4**] (M)	k^a_{obs}(**2**,**2**-*d*) (10^{-4} M^{-1} s^{-1})	v_{start}(**2**,**2**-*d*) (10^{-3} M h^{-1})	from comparative reactions	from competitive reactions
2a, **2a**-d_8	0.374	0.076	0.141		2.91 ± 0.07, 1.50 ± 0.04		1.94 ± 0.10	1.85 ± 0.20
2b, **2b**-d_{10}	0.325	0.062	0.105		4.66 ± 0.5, 2.63 ± 0.5		1.77 ± 0.05	1.75 ± 0.17
2a, **2a**-d_3	0.374	0.086	0.129		3.36 ± 0.06, 3.06 ± 0.09		1.10 ± 0.05	
2a, **2a**-d_8	0.374	0.093		0.150		2.32, 1.95	1.19 ± 0.07	1.19 ± 0.05
2b, **2b**-d_{10}	0.340	0.124		0.200		8.22, 6.64	1.25 ± 0.08	1.14 ± 0.06

Table 2. Distribution of Isomeric Ketones **3a**−**c** in the Acylation of Toluene (**2a**) with Anhydride **1** in the Presence of HOTf and **4**, Respectively, at 25 ± 0.2 °C in 1,2-Dichloroethane

[**1**] (10^3 M)	[HOTf] (10^3 M)	[**4**] (10^3 M)	isomer ratios (%)		
			ortho (**3a**)	*meta* (**3b**)	*para* (**3c**)
138.6		247.5	29.3 ± 0.2	0.5 ± 0.1	70.1 ± 0.2
93.2		149.9	28.6 ± 0.2	0.5 ± 0.1	70.9 ± 0.2
74.0	141.0		8.7 ± 0.3	0.6 ± 0.1	90.5 ± 0.4
68.0	136.8		9.6 ± 0.2	0.6 ± 0.1	89.8 ± 0.2
85.2	128.8		10.3 ± 0.2	0.7 ± 0.1	88.9 ± 0.1

the C−D vibration bands. Since the rate constant K_{diss} (Scheme 2) depends on the conversion in the presence of base,[1] the calculation of the concentration of **1′** is not possible. Therefore we determined the isotope effect k_H/k_D using the initial velocity v_{start}, where k_H/k_D equals v_H/v_D.

Besides these comparative measurements, isotope effects can also be determined by competitive reactions. We have therefore investigated the isotope effect of toluene (**2a**) using mass spectrometry,[8] whereas for xylene (**2b**) the product ratios were determined by ^{1}H NMR spectroscopy because in mass spectrometry different fragmentations of deuterated and not deuterated **3d** occur.

Figures 1 and 2 show the results of the kinetic measurements of acylations of toluene (**2a**) and perdeuterated toluene-d_8 (**2a**-d_8) with **1′** in the presence of both HOTf (Figure 1) and the pyridine **4** (Figure 2). The experimental data show good agreement of isotope effects obtained by comparative and competitive determination, respectively. The results are summarized in Table 1.

As can be seen from Table 1, there is a significant primary kinetic isotope effect in the presence of HOTf, whereas in the presence of base the rates determined are only in the range of the secondary isotope effect found for toluene-d_3 (**2a**-d_3). Kinetic isotope effects of 1.75−1.95 obtained in the acylation of **2a**, **2a**-d_8 and **2b**, **2b**-d_{10} in the presence of HOTf are comparable with published data[4] for similar reactions.

With these investigations we are also able to confirm experimentally the supposed relationship[3] between primary kinetic isotope effects and the *ortho/para* distribution in aromatic acylations. In Table 2 the isomer ratios of the acylation of toluene (**2a**) with triflate **1** depending on the reaction conditions are listed. As expected, the amount of *meta*-product **3b** is small and nearly constant independent of reaction conditions. Approximately 10% *ortho* substitution product **3a** was obtained in the presence of HOTf, whereas in the presence of base a significant increase of *ortho* product to nearly 30% results.

The deprotonation rate of the σ-complex intermediates obviously influences the product formation in aromatic acylations. From our experimental results we can exclude the markedly lower ratio of *ortho* product **3a** in the presence of acid as a result of reversibility of the acylation for two reasons. The *ortho/para* ratio **3a**/**3c** remains constant during the whole reaction. Under the applied reaction conditions a transformation of the *ortho* into the *para* product could not be detected.

Interpretation of the Experimental Results. From eq 1, written in the form of eq 2, the following deductions for the *ortho*/*para* ratio in the presence of base and acid, respectively, can be drawn.

$$v = k_{obs}[ArH][\mathbf{1'}] \qquad \text{with } k_{obs} = k_1 \frac{1}{1 + k_{-1}/k_2} \qquad (2)$$

In the presence of base k_{-1}/k_2 is assumed to be nearly zero, i.e., only k_1 determines the product formation. The *ortho*/*para* ratio is influenced neither by deprotonation (k_2) nor by the back reaction (k_{-1}). The overall rate therefore depends only on the reaction of the electrophile **1′** with the aromatic compound, and according to eq 1 nearly the maximal rate is observed. Thus, as expected, only a small primary kinetic isotope effect results.

In the presence of HOTf, however, the deprotonation rate of the σ-complex decreases ($k^a_2 \approx k_{-1}$), resulting in a primary kinetic isotope effect and a decrease of the overall reaction rate. That means, a faster back reaction (k_{-1}) and/or a slower deprotonation (k_2) of the *ortho* σ-complex in the presence of HOTf favors the *para* product.

The different course of aromatic acylation reactions with aroyltriflates in the presence of HOTf and base, respectively, can be described qualitatively by energy profiles (Figure 3).

The results of our investigations presented in this publication allow a general interpretation of the *ortho*/*para* isomeric ratio of electrophilic aromatic acylation reactions depending on reaction conditions.

The normal Friedel−Crafts acylation, which requires more than equimolar amounts of the $AlCl_3$ catalyst, gives besides ⩾90% of *para* product only small amounts of *ortho* product (1−9%).[10] In addition to the factors already discussed in the literature[11] for positional selectivity in aromatic acylations, the reaction behavior of the intermediate σ-complex has to be considered according to the equation given in Figure 3b.

In previous investigations[12] it was demonstrated that rearomatization of Wheland intermediates occurs from a bent conformation with the leaving group in a quasiaxial position (Scheme 3). The rate of deprotonation (k_2), as well as the rate of back reaction (k_{-1}) of the σ-complexes, therefore depends markedly on the preference of conformations α or β.

Due to the bulkyness of the onium complex of the acyl group with $AlCl_3$, the bent *ortho* σ-complex prefers the α-conformation

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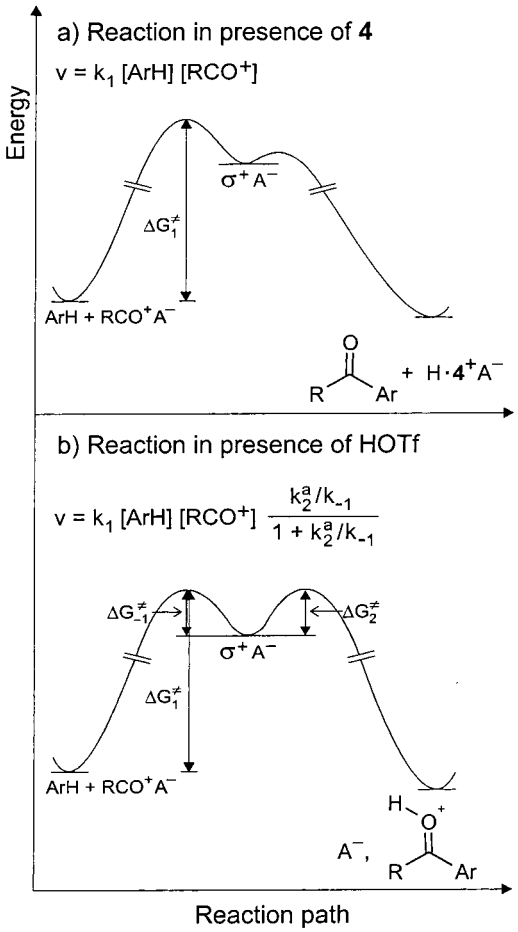
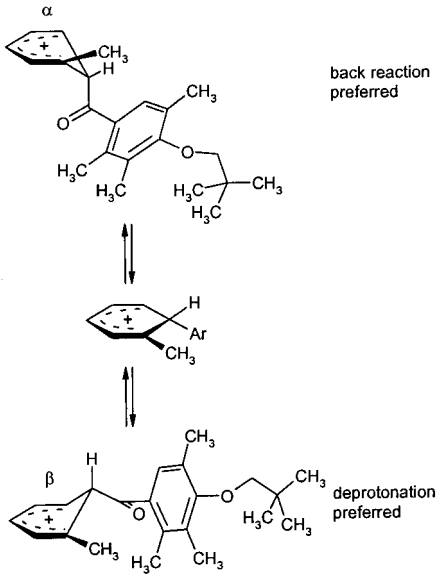


Figure 3. Energy profile of the reaction of acylium ion **1′** with aromatics in the presence of base **4** and HOTf, respectively.

Scheme 3



(Scheme 3), resulting in a decreasing deprotonation rate k_2, whereas the back reaction becomes more probable.[12] In the *para* σ-complex, for steric reasons the β-conformation should be preferential and thus deprotonation (k_2) under rearomatization will be favored against the back reaction (k_{-1}). In terms of the equation given in Figure 3b this results in $(k_2/k_{-1})_{para} > (k_2/k_{-1})_{ortho}$. Therefore the *para* isomer is formed in a higher ratio as expected considering only the values of k_1.

It is now also possible to interpret unusual *ortho*/*para* ratios we have observed and published earlier. The benzoylation of toluene with benzoyl triflate affords a markedly enhanced percentage of *ortho* product (up to 30%) as could be demonstrated by both the benzoylation with benzoyl triflate in the presence of a base (27% *ortho* product)[13] and the conversion of toluene with benzoyl chloride and catalytic amounts (5 mol %) of trifluoromethanesulfonic acid.[14]

Experimental Section

General. ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) in $CDCl_3$ as solvent and TMS as internal standard. Mass spectrometry was performed on a Varian MAT 711. Gas chromatography was performed with a Carlo Erba Fractovap 4160 with FID and on column injector, 0.45 bar hydrogen, 20 m column, phases PS086 or SDPE08, temperature program 40 °C isotherm per 1 min, heating rate 10 °C/min, and 300 °C end temperature. 1,2-Dichloroethane (DCE) was purified as described in the literature[15] but freshly distilled under Ar from CaH_2. Toluene (**2a**) and *p*-xylene (**2b**) were distilled over a Spaltrohr column, dried (CaH_2), and freshly distilled. Trifluoromethanesulfonic acid (3 M) was twice fractionally distilled. Tri-*tert*-butylpyridine (**4**) was prepared according to ref 16. Deuterated toluene (**2a**-d_3) was purchased from Cambridge Isotope Laboratories, toluene **2a**-d_8 from Merck, and *p*-xylene **2b**-d_{10} from Aldrich, and all compounds **2**-*d* were used without further purification.

Preparation of a Solution of Triflate 1. A solution of 4-(2,2-dimethylpropoxy)-2,3,5-trimethylbenzoic acid chloride[1] in dichloroethane (DCE) (10 mL) was added to a stirred suspension of AgOTf (1.1 equiv) in DCE (10 mL). After 30 min, precipitated AgCl was filtered off and washed with 2 mL of DCE. The combined filtrates were transferred to a 25 mL graduated flask under Ar atmosphere which was filled up with DCE. The concentration was then determined by GC from at least two samples.

Determination of Isotope Effects. (a) For comparative reactions, two aliquots (10 mL) of the same solution of **1** in DCE containing HOTf (concentrations in Table 1) were each taken and transferred to a 25 mL graduated flask which was filled up with DCE to 23 mL. After standing at 25 °C for 1 h, to one aliquot was added the deuterated and to one the not deuterated aromatic compound **2**. The flasks were filled up with DCE to 25 mL, and the reaction was started by shaking. Samples were taken at different time intervals, worked up as described under (b) and analyzed by GC according to ref 1. (b) For competitive reactions, a solution of **1** in DCE, containing HOTf and **4**, respectively, was transferred to a 25 mL graduated flask which was filled up with DCE to 22 mL (for concentrations see Table 1). After the mixture was left to stand at 25 °C for 1 h, both the respective deuterated and not deuterated aromatic compound **2** were added (1 mL each, Table 1). The flask was filled up with DCE to 25 mL, and the reaction was started by shaking. To the samples taken after different time intervals was added aqueous Na_2CO_3 solution (5%), and the reaction mixture was stirred for 1 h. After being extracted with DCE, the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. In the case of toluene, the reaction was evaluated by mass spectrometry (EI, 70 eV) by using the ratio M_H^+/M_D^+ ($M_H^+ = 324$; $M_D^+ = 331$) as a measure for the isotope effect. In the case of xylene, the product ratio was determined by NMR spectroscopy.

Isolation of Deuterated Anhydrides 3-*d* from Comparative Reactions. To the remaining reaction mixture was added aqueous Na_2CO_3 solution (5%). After being stirred for 2 h, the reaction mixture was extracted with diethyl ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. The crude products were chromatographed on silica gel with petroleum ether/dichloromethane (1:1) and recrystallized from MeOH/H_2O.

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Data for 3a-d_3: Colorless crystals, mp 95−96 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H, $C(CH_3)_3$), 2.13 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 6.95 (s, 1H, Ar−H6), 7.24 (AA′, J = 8.0 Hz, 2H, Ar−H2′,6′), 7.70 (BB′, J = 8.0 Hz, 2H, Ar−H3′,5′). MS (EI, 70 eV) *m*/*z* (%) 327 (27) [M^+], 312 (3) [$M^+ - CH_3$], 309 (20) [$M^+ - CD_3$].

Data for 3a-d_7: Colorless crystals, mp 95.5−96.5 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H, $C(CH_3)_3$), 2.13 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 6.95 (s, 1H, Ar−H6). Anal. Calcd for $C_{22}H_{21}D_7O_2$ (331.4): C, 79.93; H, 6.38; D, 4.22. Found: C, 79.89; H, 6.48; D, 4.32. MS (EI, 70 eV) *m*/*z* (%) 331 (26) [M^+], 316 (10) [$M^+ - CH_3$], 313 (19) [$M^+ - CD_3$].

Data for 3d-d_9: Colorless crystals, mp 78−79 °C (MeOH/H_2O); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H, $C(CH_3)_3$), 2.20 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.39 (s, 2H, CH_2), 6.94 (s, 1H, Ar−H6). Anal. Calcd for $C_{23}H_{21}D_9O_2$ (347.4): C, 79.52; H, 6.09; D, 5.18. Found: C, 79.39; H, 5.96; D, 5.10. MS (EI, 70 eV) *m*/*z* (%) 347 (26) [M^+], 332 (5) [$M^+ - CH_3$], 329 (24) [$M^+ - CD_3$].

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