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Base- and Catalyst-Induced Orthogonal Site Selectivities in Acylation of Amphiphilic Diols

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00830 Read Online

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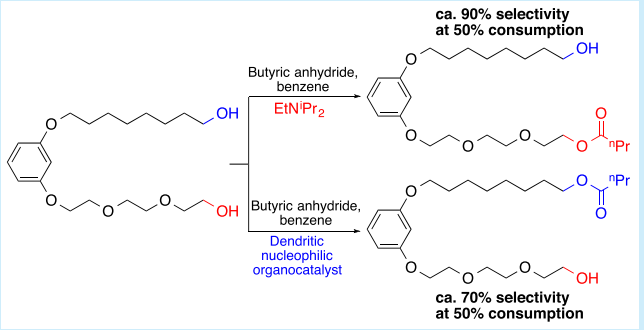
ABSTRACT: Seeking to selectively functionalize natural and synthetic amphiphiles, we explored acylation of model amphiphilic diols. The use of a nucleophilic catalyst enabled a remarkable shift of the site selectivity from the polar site, preferred in background noncatalyzed or base-promoted reactions, to the apolar site. This tendency was significantly enhanced for organocatalysts comprising an imidazole active site surrounded by long/branched tails. An explanation of these orthogonal modes of selectivity is supported by competitive experiments with monoalcohol substrates.



Site-selective organic transformations, one of the emerging synthetic methodology advances,[1] enable selective modifications of natural products, which otherwise necessitate more tedious methods, e.g., total synthesis with a heavy use of protective groups.[2] Furthermore, such methodology enables last-step diversification of synthetic products. Focusing their study of site-selective methods on functionalities abundantly present in natural products, a number of research groups have demonstrated nonenzymatic site-selective modifications of alcohols in natural product substrates as well as in entirely synthetic molecules.[3−5] Mostly, the selectivity in these cases originated from highly specific intermolecular substrate−catalyst interactions.[6] Occasionally, it originated from subtle differences in the reactivities of the reagents or their match with the respective alcohol functionalities, catalysts, or auxiliary bases.[4b,7]

In the past years we became interested in selective functionalization of natural and synthetic amphiphilic molecules, particularly site-selective acylation of amphiphilic diols—a method that can be highly useful in facilitating the construction of various building blocks for supramolecular assemblies, e.g., amphiphilic dendrons and Janus dendrimers.[8] Furthermore, a great number of natural products are amphiphilic, and in many of them hydroxyl groups are situated in both polar and apolar regions of the molecule.[9] While site-selective acylation of various di- and polyols, particularly glycoside derivatives, has been described,[3a−d,4,6c] those studies did not include such amphiphilic substrates.[10] Herein we report our approach to site-selective acylation of alike amphiphiles.

N-Alkylimidazoles are known, readily modifiable acylation catalysts.[11] Recently we demonstrated that using dendron-like catalysts with an active imidazole unit near a focal point and long peripheral hydrocarbon or oligoether tails enabled a substantial improvement of the chemoselectivity in certain Morita−Baylis−Hillman reactions.[12] Since site selectivity is sometimes considered as an extension of chemoselectivity,[13] we decided to capitalize on our previous findings and apply a similar design to acylation catalysts designated to site-selectively promote butyrylation of model amphiphiles. The proposed catalysts were based on the layout depicted in Figure 1a, while *N*-benzylimidazole (**BnIm**) was chosen as our reference catalyst.

Among the synthesized benzylimidazole-cored catalysts (Figure 1b and Scheme S1), the catalyst **G1(C12)** incorporates three long linear hydrocarbon tails around the catalytic core. In the second-generation catalyst **G2(C12)**, five long linear lipophilic tails and two aromatic branching units surround the imidazole-bearing core.[14] Finally, in the second-generation dendritic catalyst **G2(C5)**, branching points are incorporated into the three aliphatic peripheral groups, providing tighter lipophilic shielding of the catalytically active unit.

In order to study selective functionalization of diol amphiphiles, the model substrate **1** comprising two primary-alcohol-terminated arms (one hydrocarbon, another oligoether) and an aromatic resorcinol-derived core was prepared by stepwise alkylation (Scheme S2). The two monobutyrate

Received: March 4, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00830
Org. Lett. XXXX, XXX, XXX−XXX

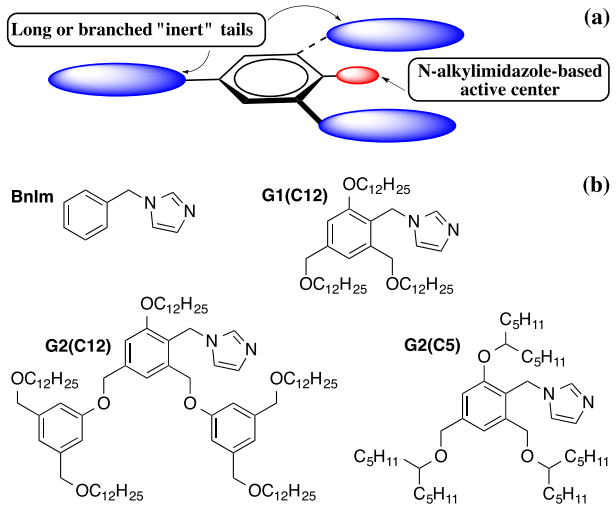
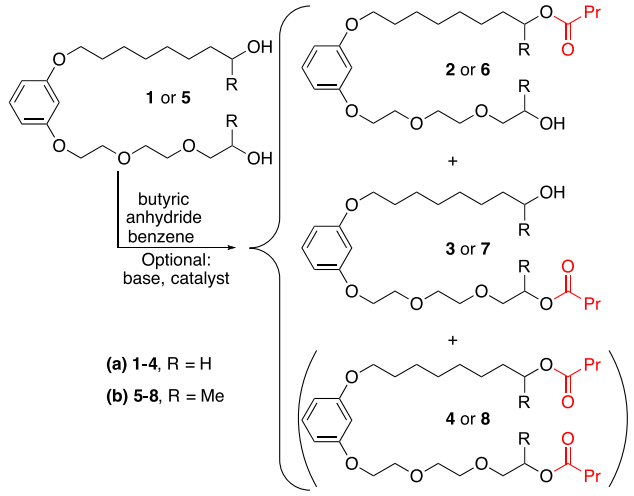


Figure 1. (a) Catalyst design and (b) the actual structures.

esters **2** and **3** and the dibutyrate **4** derived from **1** were isolated in the subsequently described experiments (Scheme 1a) and fully characterized. HPLC characterization of **1** and its butyrate derivatives enabled easy monitoring of all acylation experiments.

Scheme 1. Acylation of the (a) Primary and (b) Secondary Diol Model Substrates



The new catalysts were examined in the model reaction (Scheme 1a), with a particular emphasis on determining the ratio between the two monoester products at 50% consumption of the starting diol **1**. This consumption ensured that the amount of the diacylated product did not exceed 10%. These experiments (Table 1) revealed that the reaction promoted by **BnIm** is almost nonselective (the ratio between the products of the monoacylation at the apolar arm (**2**) and the polar arm (**3**) is 1.05:1), while all of the catalysts that we prepared demonstrate a higher preference for the acylation at the apolar arm.[15] However, the highest **2**:**3** ratio was only 1.5:1 (catalyst **G2(C5)**).

While attempting to achieve better selectivity, we examined the noncatalyzed reaction more thoroughly (Table 2, entries 1 and 2). We found that the background reaction of **1** with butyric anhydride in benzene at room temperature is very slow

Table 1. Acylation of the Model Primary Diol with a Catalyst and a Base[a]

entry	catalyst	reaction time (min)	**2**:**3** ratio
1	**BnIm**	80	1.05:1
2	**G1(C12)**	40	1.48:1
3	**G2(C12)**	60	1.24:1
4	**G2(C5)**	50	1.50:1

[a]Reaction conditions: 0.1 mmol of **1**, 0.4 mmol of butyric anhydride, 0.3 mmol of DIPEA, and 0.005 mmol of a catalyst in 1 mL of benzene at room temperature. The reactions were followed by HPLC, and the time and **2**:**3** ratio were interpolated for 50% consumption.

Table 2. Acylation of the Model Diols without a Catalyst and/or a Base[a]

entry	substrate	catalyst	reaction time (h)	**2**:**3** or **6**:**7** ratio
1	**1**	–	12	1:2.17
2[b]	**1**	–	2	1:11.1
3	**1**	**BnIm**	2	1.49:1
4	**1**	**G1(C12)**	1.33	1.86:1
5	**1**	**G2(C12)**	3	1.84:1
6	**1**	**G2(C5)**	1.5	2.30:1
7	**5**	–	23	1:2.00
8[b]	**5**	–	14.3	1:16.7
9	**5**	**BnIm**	11.5	1.90:1
10	**5**	**G1(C12)**	8	1.94:1
11	**5**	**G2(C5)**	15	2.21:1

[a]Reaction conditions: 0.1 mmol of substrate, 0.4 mmol of butyric anhydride, and 0.005 mmol of a catalyst in 1 mL of benzene at room temperature. The reactions were followed by HPLC, and the time and the **2**:**3** or **6**:**7** ratio were interpolated for 50% consumption. [b]In the presence of 0.3 mmol of DIPEA.

in the absence of a catalyst and a base and that the acylation on the polar arm of the substrate is preferred under these conditions, with an approximate ratio of 1:2.2 between the formed monoesters (**2**:**3** ratio). Furthermore, when the reaction is performed in the presence of DIPEA as the base (3 equiv) but without the catalyst, the rate is comparable to that of the catalyzed reactions, but the **2**:**3** ratio is lowered to 1:11, thus bringing the amount of **3** in the mixture of the monoacylated products to 92%.

This dramatic influence of the base enabled highly selective acylation of the alcohol on the oligoether arm. At the same time, it hinted that the limited selectivity for **2** in the catalyzed experiments may originate from the opposing preferences for the acylation site imparted by the base and the catalyst. Accordingly, we repeated the catalytic experiments without the stoichiometric base in the reactions (Table 2, entries 3–6). Remarkably, the reaction rates were only slightly reduced compared with the parallel base-including experiments, while the **2**:**3** ratio was now influenced much more by the catalyst design, spanning between 1.5:1 and 2.3:1 (**BnIm** and **G2(C5)**, respectively). Though the highest **2**-favoring selectivity leads at the moment only to 70% of this product in the mixture of the two monoacylated products at 50% consumption, the latter set of experiments clearly demonstrates that the catalyst modifications strongly affect the site selectivity and could be further explored for enlarging the percentage of the product of the monoesterification on the apolar arm in the reaction mixture. Furthermore, while under optimal conditions favoring one of the monoesters, a 30 or 43% absolute yield of the preferred monoacylated product (**2** or **3**, respectively) is

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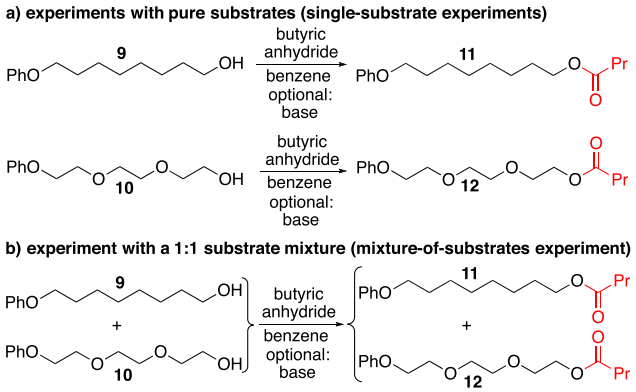
produced at 50% consumption (chosen for examination in order to minimize the influence of diacylation), prolonging the reaction time could substantially improve these yields, to 39% (at 80% consumption) or 69% (at 90% consumption) respectively.[16,17]

An additional model substrate **5** with the same resorcinol-derived core but harboring secondary alcohol sites on the hydrocarbon and oligoether arms was prepared via a convergent synthesis (Scheme S3). When this substrate was examined under various conditions described above, the reactivity and selectivity patterns of the acylation (Scheme 1b and Table 2, entries 7−11) followed the same trend as with the primary diol model substrate. Thus, the reaction with DIPEA only and without a catalyst led to a **6**:**7** ratio of ca. 1:17 (94% of **7** in the mixture of the monoacylated products). On the other hand, in the reaction catalyzed by **G2(C5)** in the absence of base, a **6**:**7** ratio of 2.2:1 was achieved, producing 69% of the product **6** in the mixture of the monoacylated products at 50% consumption.

In an attempt to understand the origins of the results described above, we conducted a series of experiments with truncated substrates **9** and **10** incorporating only one alcohol-decorated site of diol **1**, a hydrocarbon arm or an oligoether arm, respectively (Scheme 2 and Figure 2).[18] When a mixture

Scheme 2. Acylation with the Truncated Model Substrates



of these two substrates was subjected to the acylation under base- and catalyst-free conditions (Scheme 2b and Figure 2a, triangle-marked lines), the rate of the transformation of **9** was only slightly decreased while the rate of the transformation of **10** was substantially increased compared with the equivalent experiments with pure substrates **9** and **10** (Scheme 2a and Figure 2a, square-marked lines). It seems that the acylation of the alcohol on the oligoether chain (**10**) is assisted by the apolar alcohol **9**, but not vice versa. The reason for this may be the hydrogen-bond activation of the electrophile (anhydride) exerted by the apolar alcohol, while such activation by the alcohol of the oligoether substrate is negligible because of the internal hydrogen bond of the latter. In the case of the diol substrate **1**, the activation of the electrophile by the hydrocarbon arm of the diol will enable an intramolecular mode of reaction (along with the intermolecular pathways) that will place the alcohol of the other arm in a suitable position to attack the activated electrophile (Figure 3a), thus amplifying the effect observed with the mixture of the single-site substrates and providing the aforementioned **2**:**3** ratio of 1:2.2. Intermolecular hydrogen bonding of sterically unhindered primary alcohols to the acylating agents, directing

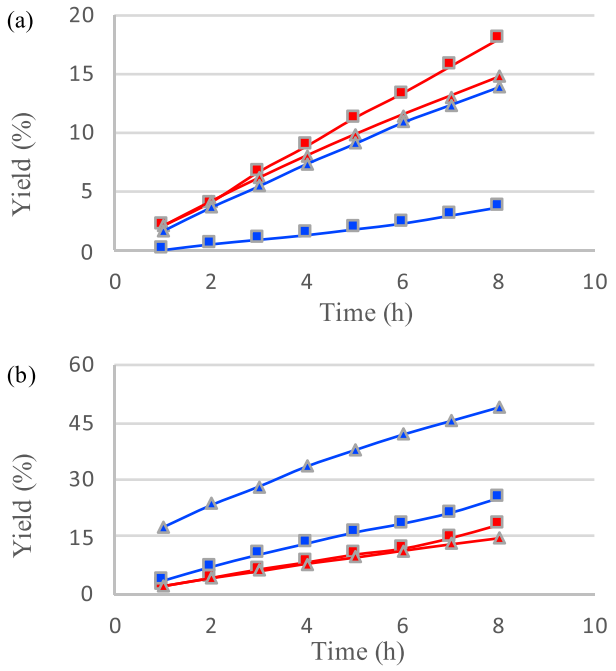


Figure 2. (a) Base- and catalyst-free or (b) base-induced acylation of truncated substrates (**9** and **10**). Red lines/markers show the formation of **11**, and blue lines/markers show the formation of **12**; square markers (■) are for single-substrate experiments, and triangle markers (▲) are for mixture-of-substrates experiments. For reaction conditions, see the Supporting Information.

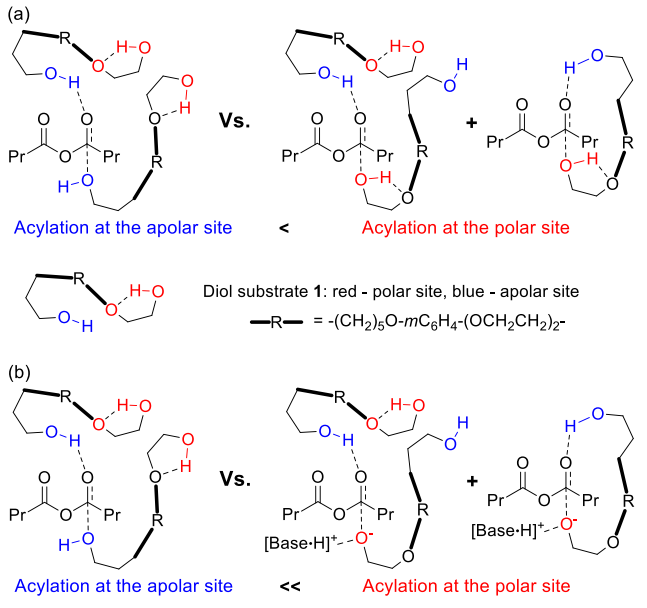


Figure 3. Rationalization of the (a) substrate-controlled and (b) base-controlled selectivities.

the reaction to occur at another alcohol site of the substrate, was implicated as the rationale behind the site selectivity in acylations of diols and carbohydrates.[6c,19] Moreover, stabilization of transition states and intermediates by hydrogen bonding was proposed in a number of computational studies that analyzed acylations by carboxylic anhydrides.[20]

The addition of DIPEA as the base (but not any imidazole-based catalyst) had a profound accelerating effect on the acylation of **10** when it was tested as the only substrate (blue

https://dx.doi.org/10.1021/acs.orglett.0c00830
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square-marked lines, Figure 2b vs Figure 2a), and even more so when it was used in a mixture with **9** (blue triangle-marked lines, Figure 2b vs Figure 2a). At the same time, the base did not have any substantial effect on the acylation of **9** when it was tested separately or in a mixture with **10** (compare red lines, Figure 2b vs Figure 2a). The most likely explanation for these observations is the difference in the acidities of the two alcohols. Although we lack pK_a data in benzene or similar apolar solvents,[21] in water β-alkoxy substituents usually lower the acidity constants of alcohols by approximately an order of magnitude.[22] It is conceivable that the base strength of DIPEA is sufficient to promote acylation of **10** through specific- or general-base catalysis but too low to affect the acylation of **9**.[23] In the acylation of diol **1**, such base catalysis reinforces the pre-existing preference for the acylation at the polar site, thus bringing the site selectivity to the remarkable 11:1 value (Figure 3b).

In the case of imidazole-based catalysts applied in the acylation experiments with substrates **9** and **10** in the absence of DIPEA, the transformation of **9** was always faster than that of **10**, both in the experiments with a single substrate and in the experiments with the mixture of substrates. This finding correlates with the preference for the acylation on the apolar arm in the corresponding experiments with diol **1**. Moreover, these experiments with the catalysts and without the stoichiometric base demonstrated that the *N*-alkylimidazole moiety is only weakly basic in benzene. The rates of these acylations are only slightly lower than those of acylations carried out with the same catalysts in the presence of base, i.e., protonation of the catalyst by the stoichiometric amount of butyric acid generated during the reaction is negligible. Hence, the *N*-alkylimidazole group in the catalysts is not basic enough to fully or partially deprotonate even the oligoether-arm alcohol (as DIPEA does), while it is nucleophilic enough to promote the alternative catalytic pathway proceeding through the acylimidazolium intermediate.[24] The latter, being an activated electrophile, can react with both alcohol functionalities even in the absence of the hydrogen-bond activation and prefers to react with the apolar alcohol, presumably since the product and thus the transition state for such acylation are lower in energy (Figure 4a).[25]

The combination of the various acylation mechanisms that are active in a given experiment according to its conditions defines the overall selectivity and the rate of the reaction. In the experiments with the imidazole-based catalysts, we attribute the enhanced preference of the new catalysts to acylate the site at the apolar arm (compared to **BnIm**) to the combination of their increased nucleophilicity,[11a] which channels more of the reaction via the pathway with the cationic intermediate (Figure 4b), and the more lipophilic environment around the catalytic center, which encourages the access of the amphiphilic substrates to the catalytic center in an "apolar arm first" mode (Figure 4c).

In conclusion, we identified two sets of conditions that encourage site-selective acylation of the model amphiphilic substrates with a carboxylic anhydride in benzene (Scheme 3). While one set directed the acylation to the alcohol site situated at the polar oligoether part of the molecule, the other set, involving a specially designed catalyst, boosted the acylation at the alcohol site of the apolar hydrocarbon-based part.

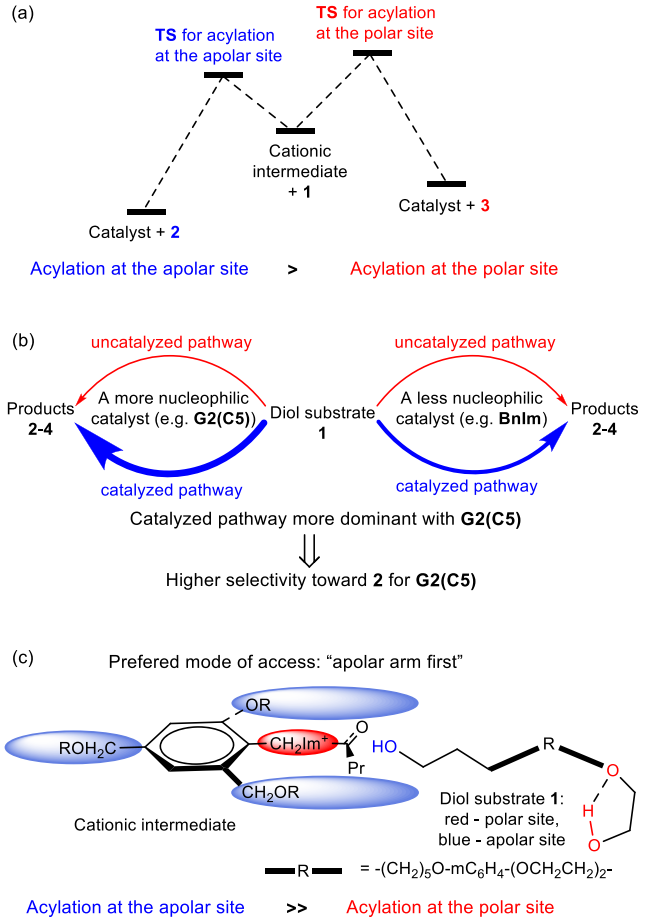
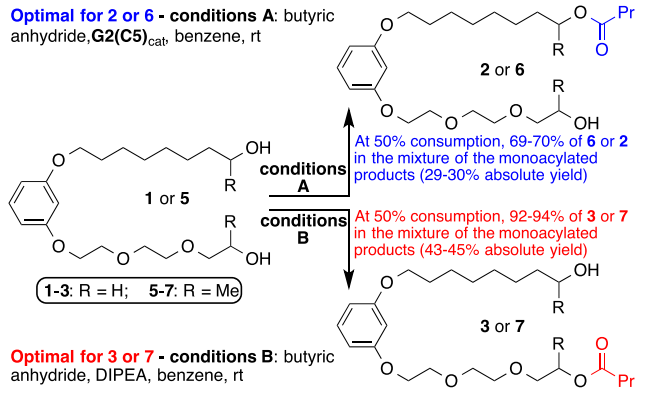


Figure 4. Rationalization of the catalyst-controlled selectivity.

Scheme 3. Orthogonal Selectivities in the Acylation of Diol Model Substrates



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00830.

Synthetic schemes, experimental procedures, characterization data, results of additional catalytic experiments, preliminary DFT calculation data, NMR spectra, and HPLC monitoring of the catalytic experiments (PDF)

https://dx.doi.org/10.1021/acs.orglett.0c00830
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Israel Science Foundation (Grant 955/10) and the United States−Israel Binational Science Foundation (BSF) (Grant 2012193). We thank Dr. Maria Kramer (Tel Aviv University) for assistance in the characterization of one of the intermediates.

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(14) A closely related second-generation catalyst **G2(C6)** with shorter *n*-hexyl terminal appendages replacing the *n*-dodecyl tails, which was prepared in an analogous way, exhibited performance similar to that of **G2(C12)** and thus was excluded from this communication.

(15) While for a number of reasons butyric anhydride and benzene were chosen as the acylating agent and the solvent, respectively, for the model reaction, experiments with acetic anhydride as the acylating agent or THF as the solvent under conditions otherwise equivalent to those in Table 1 demonstrated similar selectivity trends (Table S1).

(16) The yields were determined by HPLC monitoring.

(17) Preliminary experiments with acetic anhydride or benzoic anhydride as the acylating agent under conditions otherwise equivalent to those in entries 2 and 6 of Table 2 demonstrated similar selectivity trends, although with narrower spans of the analogue of **2** to analogue of **3** ratio (Table S2).

(18) The full extent of these studies will be published elsewhere; herein we describe only findings most relevant to the experiments with diol substrates **1** and **5**.

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(21) Preliminary DFT calculations at the BP86(D3)/def2-SVP level of theory demonstrated that in the gas phase the acidity constant of the alcohol of the apolar arm is ca. 24-fold larger than that of the alcohol of the polar arm (see the Supporting Information).

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(23) The base catalysis may occur in concert with the hydrogen-bond activation of the electrophile or in parallel to the above-described hydrogen-bond-induced base-free acylation.

(24) For this frequently invoked pathway, see: Connors, K. A.; Pandit, N. K. *Anal. Chem.* **1978**, *50*, 1542−1545. (b) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643. (c) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212−12213.

(25) The preferred product possesses intramolecular hydrogen bond at the polar alcohol site and a more stable ester at the apolar site (due to the lack of the electron-withdrawing inductive effect of the β-oxygen). Preliminary DFT calculations at the BP86(D3)/def2-SVP level of theory show that the difference in the free energy of the esters alone is ca. 0.5 kcal/mol (see the Supporting Information).

https://dx.doi.org/10.1021/acs.orglett.0c00830
Org. Lett. XXXX, XXX, XXX−XXX