Mild Organic Base-Catalyzed Primary Alcohol-Selective Aroylation Reaction Using N-Aroylcarbazoles for Underexplored Prodrugs

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ABSTRACT: We report a highly primary alcohol-selective aroylation reaction using *N*-aroylcarbazoles (NAroCs). The aroylation proceeded smoothly in the presence of DBU, which most likely works as a general base catalyst in the reaction system. The synthetic utility was displayed in the primary alcohol-selective aroylation of complex drug molecules and natural products to their prodrugs. Stoichiometrically generated carbazole, the starting material of NAroCs could be easily recovered. We also established safer multigram and multidecagram scale preparation methods of NAroCs, which are easy-to-handle bench-stable reagents.

Derivatization of biologically active natural products or drug molecules into their prodrugs has been one of the most reliable strategies in medicinal chemistry for drug discovery[1,2]. Prodrugs often find some improved drug performance or property, such as bioavailability, cell-permeability, target selectivity, lower side effects, chemical stability, and/or in vivo half-life. Due to the benefits, a vast number of prodrugs have been developed for clinical applications. Their occupation of all approved drugs over the past decade reaches approximately 10% today[2]. Even the advanced drug treatments inevitably encounter systematic side effects of steroids[3] and cancer chemotherapy[4]. Synthetic chemists could tackle this long-standing challenge by supplying some underexplored prodrugs, which might have lower side effects [5].

Alcohols are among the most common functionalities in pharmaceuticals, and typically converted into carboxylic esters for prodrug development. A large number of alcohol-derived carboxylic esters have been applied to clinical practice as prodrugs. Their vast majority consist of aliphatic or α,β-unsaturated carboxylic acids, as exemplified by the esters of chloramphenicol and hydrocortisone (Figure 1A).[6] Aromatic carboxylic esters, *i.e.* aroylates possess the potential to be promising alternatives to existing ester-type prodrugs. Their benzene rings would stabilize the neighboring ester carbonyl groups by resonance[7] and offer opportunity for structural modification on the rings, suggesting the possibility that aroylate-type prodrugs could have greater chemical stability[8] and appropriate steric/electronic property[9], which may lead to lower side effects. Despite these attractive aspects, they still remain extremely rare even in investigation stage[10].

We reason that this is attributed to the lack of practical selective *O*-aroylation reactions applicable to highly functionalized molecules. For example, primary alcohol selective aroylation reactions using enzymes[11-14] often proceed with extremely high selectivity and functional group tolerance, while they mostly require some expensive enzyme and also the process to identify the optimal enzyme for each substrate. To avoid such substrate specificity issue, complementary non-enzymatic approaches indicating primary alcohol-selectivity have been developed (Figure 1B). The high selectivities were enabled by bulky nucleophilic catalysts[15-16], very low temperature[17-20], tin acetal[21-22], weak Lewis acids[23-25], a weak inorganic base[26], or
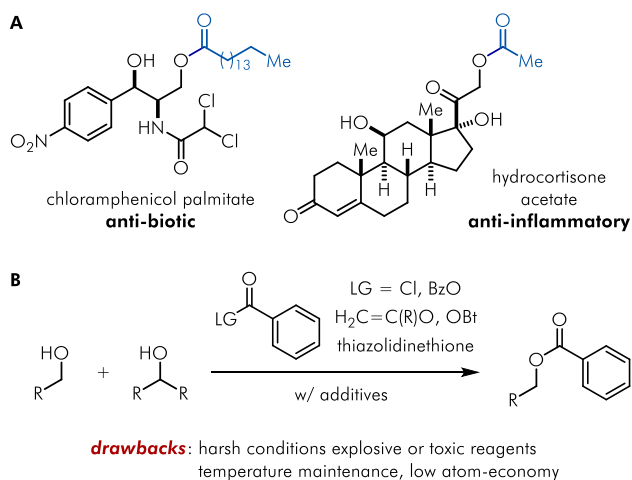

Figure 1. (A) Selected examples of carboxylic ester-type prodrugs. (B) Existing non-enzymatic primary alcohol-selective benzoylation reactions.

taylor-made reagents[27-29]. However, these methods require (i) microwave irradiation and/or reflux condition[15,26], (ii) a base-free condition which generates hydrogen chloride in-situ[25], (iii) sodium hydride which generates alkoxide species and a stoichiometric amount of hydrogen gas[27], (iv) a potentially-explosive HOBt ester[28], (v) toxic metals[15,21-24], (vi) low temperature[17-20] which causes difficulty when scaling up or (vii) one or more equivalent of a condensation reagent or benzoic anhydride which forms benzoic acid as the stoichiometric waste[16,27,29]. The industrial application of these benzoylation reactions would be limited by such drawbacks on functional group tolerance, atom economy, safety and scalability.

We envisioned that a primary alcohol-selective aroylation free from these disadvantages could be achieved by applying *N*-aroylcarbazole (NAroC) as the aroylating reagent. It was previously speculated that *N*-benzoylcarbazle (NBzC) is twisted in solution so that the carbazole ring lies in a plane perpendicular at of the benzoyl group based on its NMR data (Figure 2A)[30]. It is suggested that the both reaction faces of NAroC would be equally shielded by the carbazole C_1 and C_8 protons to suppress reactions of bulkier nucleophiles (Figure 2B). We previously
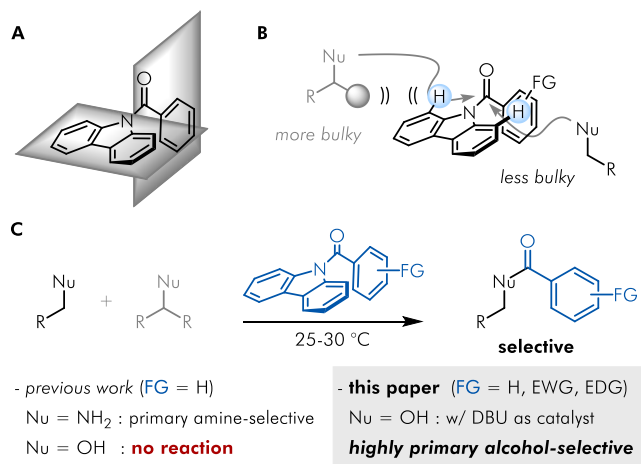
Figure 2. (A) Twisted structure of NBzC in solution. (B) Our reaction design. (C) Highly primary nucleophile-selective benzoylation and aroylations.

demonstrated that NBzC enables such selective reaction in an *N*-benzoylation system where other coexisting nucleophiles including alcohols remained intact (Figure 2C left bottom)[31].

Overcoming this low reactivity of alcohols would result in the aimed reaction. In this paper, we describe a reagent controlled highly primary alcohol-selective aroylation reaction using NAroC under a mild base-catalyzed condition. (Figure 2C right bottom). This protocol enables to supply underexplored prodrugs bearing a wide range of functionality and aroyl groups. Stoichiometrically forming carbazole could be easily recovered, and a safer multidegagram preparation of NAroCs was also established. A general base catalyzed mechanism was proposed based on the experimental observations.

We initiated this study by identifying the suitable additive for the planned benzoylation using 1-octanol **1a** and NBzC **2a** (Table 1, entries 1–15). First, we examined a stoichiometric amount of Brønsted acids with various pKa values and Lewis acids, which are known as excellent additives in existing acylation systems (entries 1–6).[7b] Although only highly acidic sulfonic acids and FeCl$_3$ could furnish octyl benzoate **3aa**, the yields were unsatisfactory due to the low conversion of the starting materials (17–40% yields, entries 3–5). Next we screened basic additives with a variety of basicities and/or nucleophilicities (entries 7–14). Among them only DBU with stronger basicity efficiently accelerated the aimed reaction to give **3aa** quantitaly (entry 14). When the amount of DBU was reduced to 0.30 equivalent, the yield of **3aa** remained quantitative with the reaction time extended to 24 h (entry 15). With this promising additive in hand, we confirmed the reactivity of bulkier secondary and tertiary alcohols (2-octanol **1b** and *t*-BuOH **1c**) with DBU. As we envisioned, none or just subtle amounts of their benzoates (**3ba** and **3ca**) were detected in their ^{1}H NMR spectra (entries 16–17).

Having identified DBU as an appropriate alcohol activator, we examined the substrate scope of primary alcohols with or without other functionalities including secondary and/or tertiary hydroxy groups (Scheme 1). First, a variety of mono alcohols (**1d**–**1h**) were evaluated, and they gave the corresponding benzoates (**3da**–**3ea**) in high yields (80–100%). Next we surveyed the primary alcohol-selective reactions of complex drug molecules having secondary hydroxy groups. When using

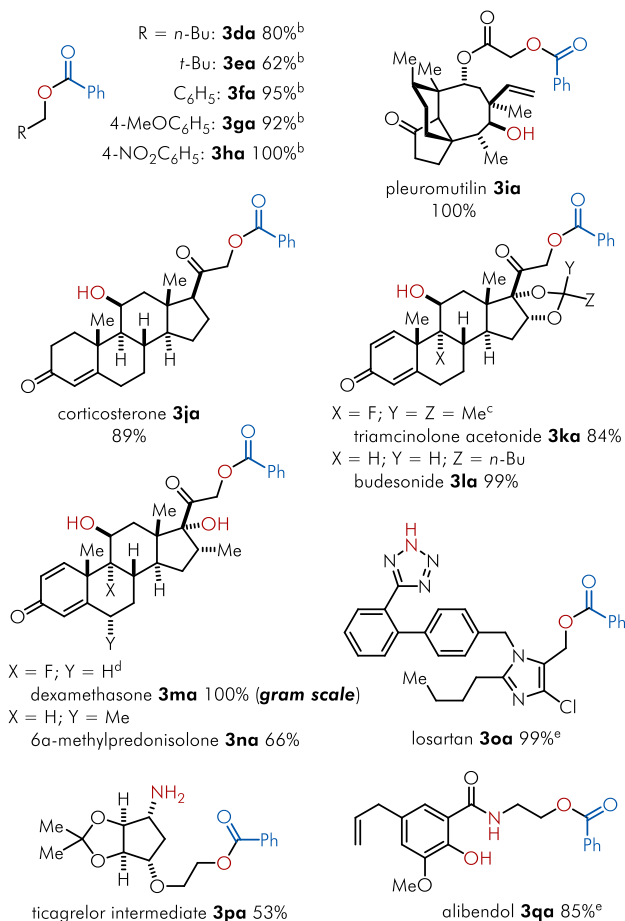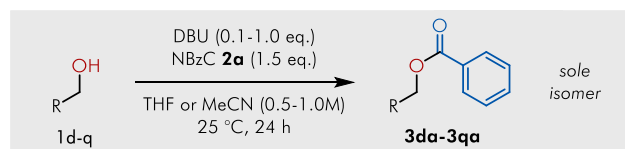**Table 1. Additive Screening of Benzoylation Reaction with NBzC 2a^a**

	R	additive	solvent	time/h	yield/%
1	1-Octyl	4-NO$_2$C$_6$H$_4$OH	CH$_2$Cl$_2$	24	0
2	1-Octyl	TFA	CH$_2$Cl$_2$	24	0
3	1-Octyl	CSA	CH$_2$Cl$_2$	24	32
4	1-Octyl	TfOH	CH$_2$Cl$_2$	24	40
5	1-Octyl	FeCl$_3$	CH$_2$Cl$_2$	24	17
6	1-Octyl	Sc(OTf)$_3$	CH$_2$Cl$_2$	24	0
7	1-Octyl	pyridine	THF	24	0
8	1-Octyl	2,6-lutidine	THF	24	0
9	1-Octyl	DMAP	THF	24	2
10	1-Octyl	imidazole	THF	24	0
11	1-Octyl	Et$_3$N	THF	24	0
12	1-Octyl	*i*-Pr$_2$EtN	THF	24	0
13	1-Octyl	DABCO	THF	24	0
14	1-Octyl	DBU	THF	12	100
15^b	1-Octyl	DBU (0.3 eq)	THF	24	100
16	2-Octyl	DBU	THF	24	1
17	*t*-Bu	DBU	THF	24	0

^{a}Conditions: ROH (0.50 mmol, 1.0 eq.), NBzC (0.75 mmol, 1.5 eq.), additive (0.50 mmol, 1.0 eq.), solvent (0.5M), 24 h, Yields determined by H NMR using internal standard. ^{b}A catalytic amount (0.3 eq) of DBU was used.

pureulomutilin **1i**, a peptidyl transferase inhibitor,[32] the primary hydroxy moiety was specifically benzoylated to yield a new benzoate-type prodrug **3ia** quantitatively even in the presence of enolizable aliphatic ester and ketone, which might cause side reactions under basic conditions. Further functional group compatibility was confirmed by the reactions of steroidal drugs such as corticosterone **1j**, triamcinolone acetonide **1k**, and budesonide **1l**, dexamethasone **1ma**, and, 6α-methylpredonisolone **1n**. The corresponding benzoate-type prodrugs (**3ka**–**3na**) were obtained in moderate to high yields (54–99%) without significant side reactions, despite the presence of acid- and/or base-labile functional groups, such as acetal, enone, 2-fluoroalcohol,[33] and/or 1,3-diol monoester.[7b] The utility of this primary alcohol-selective reaction was also demonstrated by using drugs or its precursor having other types of nucleophiles. Losartan (**3o**), an angiotensin II receptor blocker gave the corresponding prodrug **3oa** in 99% yield chemoselectively over tetrazole.[34] A precursor of ticagrelor (**3o**), which has a secondary amine, afforded benzoate **3pa** in 55% yield without any amide detected on the crude ^{1}H NMR. An antispasmodic, choleretic, and cholekinetic, alibendol **3q** delivered prodrug **3qa** in 85% yield chemospecifically in the presence of relatively hindered phenol and amide.

Having proven that the reaction is highly functional-group-tolerant as well as primary alcohol-selective, we next focused on establishing a new practical way to prepare a variety of NAroCs (**2a**–**2g**) including NBzC (Scheme 2). Although the preparation of highly elctron-deficient NAroC **3mc** requires the conventional NaH-using condition,[35] a safer alternative way for NAroCs was established by a Schotten-Baumann-like condition

Scheme 1. Primary Alcohol-Selective Benzoylation of Monols and Complex Drug Molecules


R = n-Bu: **3da** 80%[b]
t-Bu: **3ea** 62%[b]
C$_6$H$_5$: **3fa** 95%[b]
4-MeOC$_6$H$_5$: **3ga** 92%[b]
4-NO$_2$C$_6$H$_5$: **3ha** 100%[b]

pleuromutilin **3ia** 100%

corticosterone **3ja** 89%

X = F; Y = Z = Me[c]
triamcinolone acetonide **3ka** 84%
X = H; Y = H; Z = n-Bu
budesonide **3la** 99%

X = F; Y = H[d]
dexamethasone **3ma** 100% (**gram scale**)
X = H; Y = Me
6α-methylprednisolone **3na** 66%

losartan **3oa** 99%[e]

ticagrelor intermediate **3pa** 53%

alibendol **3qa** 85%[e]

[a]Isolated yields. See SI for reaction conditions. Isolated yield was shown. [b]Yields determined by crude ^{1}H NMR using internal standard. [c]MeCN was used instead of THF. [d]Carbazole was also quantitatively obtained. [e] 2.0 eq. of DBU was used.

with a phase-transfer catalyst. Minimizing side reactions, this protocol enabled multigram and multidecagram preparation of NAroCs (up to 24.0 g) after recrystallization (or hexane wash) of crude solids without the need for chromatography. It turned out that all these NAroCs **2a**-**2g** were easy-to-handle bench-stable solids. NAroCs **2b**–**2g** were applied to aroylate dexamethasone 3m to provide a wide range of electronically differentiated prodrugs (**3mb**–**3mg**) as sole regioisomers in moderate to high yields (59–99%).
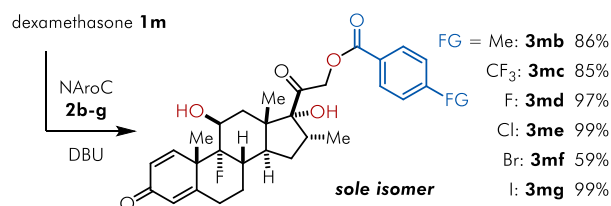
To gather insight into the role of DBU, we apply DBU to the Williamson reaction system, which generally gives the corresponding benzyl ether in high yield when alkoxide is involved.[36] After stirring a solution of **1a**, DBU, and benzyl bromide (1:1:1 mol ratio) in THF (0.5M) at 25 °C for 24 h, even trace amount of the corresponding ether was not detected on the crude ^{1}H NMR, suggesting that DBU would not deprotonate **1a** in the reaction system. This would be rationalized by the huge pKa

Scheme 2. Multigram and Multidecagram Scale Preparation of NAroC 2a-g[a]

$$\left(\begin{array}{c} X = H, CH_3, CF_3{}^{b} \\ F, Cl, Br, I \end{array}\right)$$

NAroC **2a-g** 91-100%
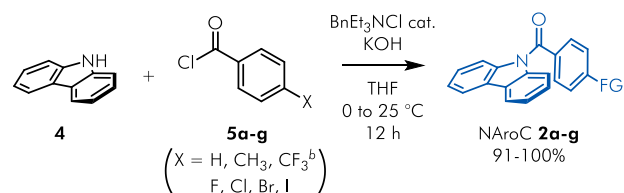
[a]Reaction condition: carbazole (10-100 mmol), number (15-150 mmol), BnEt3NCl (1.0-10 mmol), KOH (20-200 mmol), THF (20 mL), 12 h. Yields of isolated products. [b]NaH was used instead of BnEt3NCl and KOH.

Scheme 3. Primary Alcohol-Selective Aroylation of Dexamethasone 3ma[a]

dexamethasone **1m**

NAroC **2b-g**

DBU

FG = Me: **3mb** 86%
CF$_3$: **3mc** 85%
F: **3md** 97%
Cl: **3me** 99%
Br: **3mf** 59%
I: **3mg** 99%

sole isomer

[a]Reaction conditions: dexamethasone (0.10 mmol), NBC (0.15 mmol), DBU (0.010-0.030 mmol), THF (0.20 ml), 24 h, isolated yields.

gap between protonated DBU and alcohol in aprotic solvent (*e.g.* pKa in DMSO = 13.9 and ca. 30 respectively), which could not stabilize the generating alkoxide by hydrogen bonding. To gain further information on whether DBU reacts with NAroC, we next prepared a solution of DBU and **2a** (1:1 mol ratio) in THF-d$_8$ (0.05M). On the ^{1}H NMR spectrum after 24 h, we did not observe any possible species except for DBU and **2a**, such as *N*-benzoylamidine or *N*-benzoylamidinium,[37] indicating that DBU would not act as a nucleophilic catalyst[38] to NAroCs.

Based on all these observations, we propose the following catalytic cycle (Scheme 4). First, DBU and alcohol **1** makes a hydrogen bonding complex **A**. When the following addition reaction of **A** to NAroC **2** takes place, DBU acts as a general base[39] catalyst rather than a specific base or nucleophilic catalyst. The resulting tetrahedral intermediate **B** eliminates carbazolate and the following protonation delivers benzoate **3** and carbazole **4** along with the regeneration of DBU catalyst.

Scheme 4. Possible Reaction Mechanism
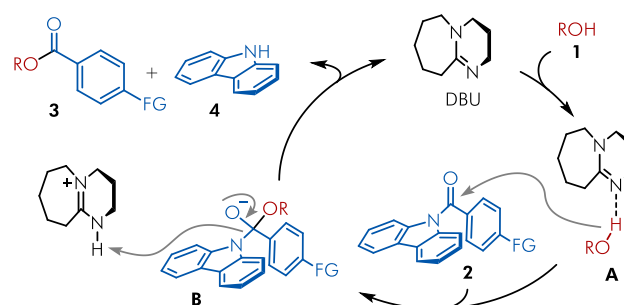
In conclusion, we have developed a highly primary alcohol-selective aroylation enabled by NAroC. DBU was the optimal alcohol activator most likely as a general base. The mild condition enables to supply underexplored prodrugs bearing a wide range of functionality and aroyl groups. Carbazole, the stoichiometric byproduct could be easily recovered, and a safer multidegagram preparation of NAroCs was also established. Since alcohol is one the most common moieties in complex drug molecules, we believe that the present aroylation method would accelerate drug discovery. Extension of this method to other acylation systems are currently underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional experimental procedures and analytical data (^{1}H, ^{19}F, ^{13}C NMR, melting point, IR, and specific optical rotation) for all new compounds (PDF)

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## Notes
The authors declare no competing financial interest.

REFERENCES
(1) Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Järvinen, T.; Savolainen, *Nat. Rev. Drug*. Discov. **2008**, *7*, 255–270.
(2) Rautio, J.; Meanwell, N. A.; Di, Li.; Hageman, M. J. *Nat. Rev. Drug. Discov*. **2018**, *17*, 559–587.
(3) Kleiman, A.; Tuckermann, J. P. *Mol. Cell. Endocrinol*. **2007**, *275*, 98–108.
(4) Horta, E.; Bongiorno, C.; Ezzeddine, M.; Neil, E. C. *Clin. Neurol. Neurosurg*. **2020**, *188*, 105566.
(5) Liu, Y.; Chen, Q.; Mou, C.; Pan, L.; Duan, X.; Chen, X.; Chen, H.; Zhao, Y.; Lu, Y.; Jin, Z.; Chi, Y. R. *Nat. Commun*. **2019**, *10*, 1675.
(6) see references in references 1 and 2.
(7) (a) Smith, M. B. Delocalized Chemical Bonding, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 8; John Wiley & Sons, Inc.: New Jersey, 2020; pp 33–103. (b) Wuts, P. G. M. Protection for the Hydroxyl Groups including 1,2- and 1,3-Diols, *Greene's Protective Groups in Organic Synthesis*, 5; John Wiley & Sons, Inc.: New Jersey, 2014; pp 17–471.
(8) For the importance of drug chemical stability, see: Croso, A. D; Pignataro, L; Belvisi, L; Gennari, C. *Chem. Eur. J.* **2019**, *25*, 14740–14757.
(9) For benzene substitution effect on pharmacological activity, see: Chen, H; Deng, S; Wang, Y; Albadari, N; Kumar, G; Ma, D; Li, W; White, S. W; Miller, D. D; Li, W. *J. Med. Chem.* **2020**, *63*, 827–846.
(10) For the rare example of benzoate-type prodrug: Palanki, M. S. S.; Akiyama, H.; Campochiaro, P.; Cao, J.; Chow, C. P.; Dellamary, L.; Doukas, J.; Fine, R.; Gritzen, C.; Hood, J. D.; Hu, S.; Kachi, S.; Kang, X.; Klebansky, B.; Kousba, A.; Lohse, D.; Mak, C. C.; Martin, M.; McPherson, A.; Pathak, V. P.; Renick, J.; Soll, R.; Umeda, N.; Yee, S.; Yokoi, K.; Zeng, B.; Zhu, H.; Noronha, N. *J. Med. Chem.* **2008**, *51*, 1546–1559
(11) Li, XF; Zong, MH; Zhao, GL; Yu, YG; Wu, H. *Biotechnol. Bioprocess Eng*. **2010**, *15*, 608–613.
(12) García, J.; Fernández, S.; Ferrero, M.; Sanghvi, Y. S.; Gotor, V. *Tetrahedron Lett*. **2004**, *45*, 1709–1712.
(13) Bizerra, A. M. C.; Montenegro, T. G. C.; Lemos, T. L. G.; de Oliveira, M. C. F.; de Mattos, M. C.; Lavandera, I.; Gotor-Fernández, V.; de Gonzalo, G.; Gotor, V. *Tetrahedron*, **2011**, *67*, 2858–2862.
(14) Ciuffereda, P; Alessandrini, L; Terraneo, G; Santaniello, E. *Tetrahedron Asymmetry*, **2003**, *14*, 3197–3201.
(15) Caddick, S.; McCarroll, A. J.; Sandham, D. A. *Tetrahedron*. **2001**, 57, 6305–6310.

(16) Ibe, K.; Hasegawa, Y.; Shibuno, M.; Shishido, T.; Sakai, Y.; Kosaki, Y.; Susa, K.; Okamoto, S. *Tetrahedron Lett.* **2014**, *55*, 7039–7042.

(17) (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. J. *J. Org. Chem.* **1993**, *58*, 3791–3793. (b) Baraldi, P.G.; Romagnoli R.; Del Carmen N. L.; Perrettie, M.; Paul-Clark, M. J.; Ferrario, M.; Govoni, M.; Benedini, F. Ongini, E. *J Med Chem*. **2004**, *47*, 711-719. (c) By following reference 17b, we attempted to obtain 21-*O*-predonisolone, but obtained a dibenzoyl predonisolone as the sole isomer in 40% yiled.

(18) Soll, R. S.; Seitz, S. P. *Tetrahedron Lett*. **1987,** *28*, 5457–5460.

(19) Gage, C.; Vogel, J.; Bendas, G.; Rothe, U; Schmidt, R. R. *Chem. Eur. J.* **2006**, *6*, 111–122.

(20) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5252–5253.

(21) Maki, T.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **1998**, *39*, 5601–5604.

(22) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996–1002.

(23) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420–2421.

(24) Lin, M.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 997–1000.

(25) Bandgar, B. P.; Kamble, V. T.; Sadavarte, V. S.; Uppalla, L. S. *Synlett.* **2002**, *5*, 735–738.

(26) Ritter, T.; Zarotti, P.; Carreria, E. M. *Org. Lett*. **2004**, *6*, 4371–4374.

(27) Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591–1592.

(28) Kim, D; Chamg, H. Kim, W. J. *J. Org. Chem.* **1985**, *50*, 1751–1752.

(29) Lee, J. I.; Park, S. J. *Bull. Korean Chem. Soc.* **2000**, *21*, 141–144.

(30) Bonesi, S. M.; Erra-Balsells, R. *J. Heterocyclic Chem.* **1991**, *28*, 1035–1038.

(31) Kang, B.; Yasuno, Y.; Okamura, H.; Sakai, A. Satoh, T.; Kuse, M.; Shinada, T. *N*-Acylcarbazole as a selective transamidation reagent *Bull. Chem. Soc. J.* [Online early access]. DOI: 10.1246/bcsj.20200116. Published Online: May 12, 2020. https://www.journal.csj.jp/doi/10.1246/bcsj.20200116 (accessed May, 12, 2020).

(32) Lolk, L.; Pøhlsgaard, J.; Jepsen, A.S.; Hansen, L. H.; Nielsen, H.; Steffansen, S. I.; Sparving, L.; Nielsen, A. B.; Vester, B.; Nielsen, P. *J. Med. Chem.* **2008**, *51*, 4957–4967.

(33) Chaabouni, M. M.; Baklouti, A. *J. Fluor. Chem.* **1990**, *47*, 155–162.

(34) Rajasekaran, A.; Thampi, P. P. *Eur. J. Med. Chem.* **2004**, *39*, 273–279.

(35) (a) Huang, P.; Chen, H. *Chem. Commun.* **2017**, *53*, 12584–12587. (b) Cai. S.; Zhi, H.; Li, J.; Gu, L.; Ni, Y.; Cheng, Z.; Wang, S.; Xiong, W.; Li, L.; An, Z.; Huang, W. *Adv. Mater.* **2017**, *29*, 1701244.

(36) Bevan, J. G. M.; Lourenço, E. C.; Chaves-Ferreira, M.; Rodrigues, J. A.; Ventura, M. R. *Eur. J. Org. Chem.* **2018**, 908–914.

(37) Zhang, X.; Waymouth, R. M. *ACS Macro Lett.* **2014**, *3*, 1024–1028.

(38) Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003–2006.

(39) Overberger, C. G.; Salamone, J. C.; Yaroslavsky, S. *J. Am. Chem. Soc.* 1967, 89, 24, 6231–6236.
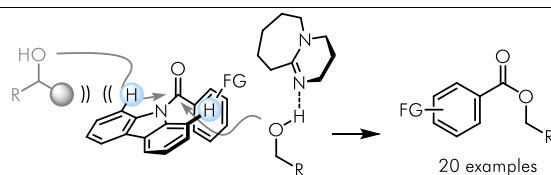
■ highly primary alcohol-selective ■ mild general base catalysis
■ broad scope ■ underexplored prodrugs