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Synthesis of Lactones via C−H Functionalization of Nonactivated C(sp^3)−H Bonds

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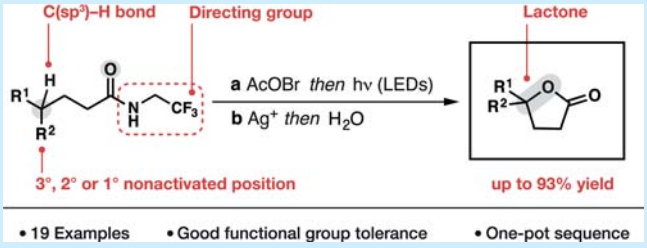
Supporting Information

ABSTRACT: An electron-deficient amide is utilized as a directing group to functionalize nonactivated C(sp^3)−H bonds through radical 1,5-hydrogen abstraction. The γ-bromoamides formed are subsequently converted to γ-lactones under mild conditions. The method described is not limited to tertiary and secondary positions but also allows functionalization of primary nonactivated sp^3-hybridized positions in a one-pot sequence. In addition, the broad functional group tolerance renders this method suitable for the late-stage introduction of γ-lactones into complex carbon frameworks.



Lactone rings occur as a common and widespread structural motif in natural and synthetic compounds. In particular, many fine chemicals, natural products, and pharmaceuticals comprise saturated γ-lactones. Naturally occurring lactones, such as γ-decalactone (**1**), often contribute to the aromas of various foods and fruits or exhibit interesting biological activities such as the neurotrophic sesquiterpene jiadifenolide (**2**) or the antibacterial peptidoglycan biosynthesis inhibitor avenaciolide (**3**) (Figure 1a).[1] Most methods for synthesizing saturated γ-lactones, such as halolactonization or intramolecular substitutions, depend on prefunctionalized γ-positions with either electrophilic or nucleophilic properties (Figure 1b).[2] In nature, however, in many cases such oxygen heterocycles are introduced by selective oxidation of scarcely functionalized carbon frameworks by powerful oxidases such as the heme and non-heme iron enzyme families.[3]

Since the pioneering observations of Hofmann, Löffler, and Freytag,[4] a variety of methods have been established to transform C−H bonds directly. New concepts enabling innate and directed C−H functionalizations with control over regio- and stereoselectivity are emerging, including transition-metal-catalyzed reactions.[5] Nevertheless, the extraordinary properties of nitrogen-centered radicals and the high selectivity of radical hydrogen abstractions still inspire scientists to develop novel methods for controlled oxidation in a variety of applications.[6] Since the 1960s, there have been reports that amidyl radicals can in principle be used to form γ-lactones via hydrogen abstraction.[7] Nevertheless, such a lactonization has not found application in synthesis. As Suárez stated in 2005,[8] this is due to the narrow scope, low chemical yields, and poor reproducibility of the procedures published. A method that allows the functionalization of nonactivated tertiary, secondary, and also primary C−H bonds is highly desirable but has not been available to date. Ideally, it would operate under mild conditions and tolerate a wide variety of functional groups. To find solutions for this challenge, we conducted a systematic investigation of the radical-mediated

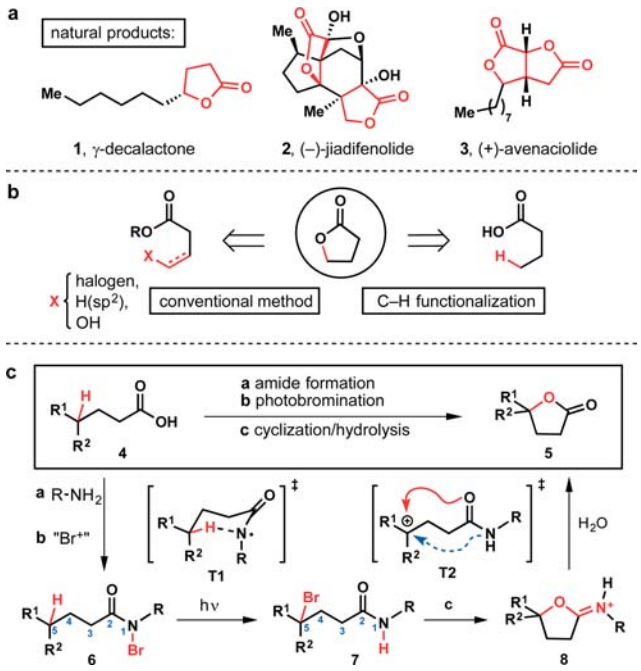


Figure 1. (a) Selection of natural products containing γ-lactones. (b) Retrosynthetic approaches toward γ-lactones. (c) Mechanistic description of lactone formation.

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synthesis of lactones utilizing amidyl-directed C−H functionalization. This strategy would follow the mechanism depicted in Figure 1c. Here carboxylic acid **4** is converted to the amide, followed by *N*-bromination to afford the labile *N*-bromo species **6**. Upon irradiation, this compound forms a nitrogen-centered radical, which can undergo 1,5-H abstraction via the six-membered transition state **T1**. Radical recombination gives rise to γ-bromoamide **7**, which then should allow cyclization to form iminium lactone **8** over the amide.[9] Hydrolysis then yields lactone **5**.

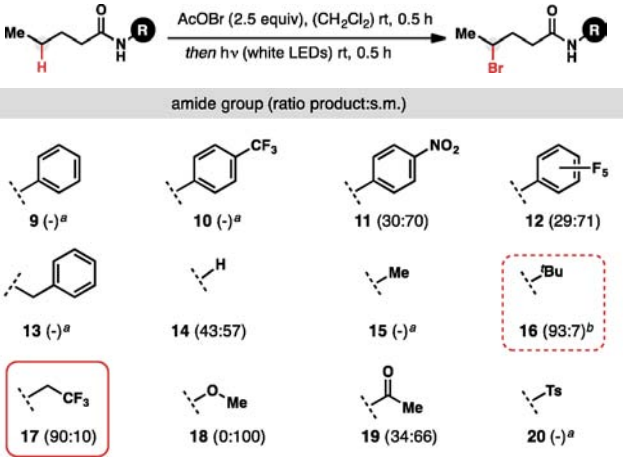
First, different substituents were screened for their aptitude to achieve the desired C−H functionalization on the test substrate pentanoic amide (Table 1). Acetyl hypobromite and white light-emitting diodes (LEDs) were used to generate the *N*-bromo species and initiate the radical reaction, respectively. It became evident that many substituents show either no γ-bromination (**9**, **10**, **13**, and **20**) or moderate ratios of product to starting material (**11**, **12**, **14**, and **19**). Very good results were obtained with *tert*-butyl amide **16** (93:7; Table 1). However, the *tert*-butyl amide underwent spontaneous cyclization to form the iminium lactone, which proved to be unreactive under a variety of hydrolysis methods, presumably because of the steric bulk of the *tert*-butyl group. Calculations and experiments have indicated that especially electron-deficient amidyl radicals tend to undergo hydrogen abstractions readily.[6a,10] Since the trifluoroethyl group has proven to be suitable for the carbamate-directed synthesis of 1,3-diols as demonstrated by the Baran group,[6b] we investigated the reaction with trifluoroethyl-substituted amide **17**. We were pleased to observe that in this case the hydrogen abstraction led to the formation of the C−H functionalized product in an excellent ratio (90:10) without formation of any side products. With a simple route to the γ-bromoamide established, we turned our attention to different cyclization methods and found that formation of the iminium lactone could be easily induced with the addition of silver(I) tetrafluoroborate under mild conditions.[11] However, attempts to isolate and purify the iminolactone after deprotonation with base were unsuccessful.[12] Instead, facile hydrolysis was achieved at room temperature by direct addition of water to the reaction mixture. This finding was unexpected in that *tert*-butyl iminolactones (**8**, R = *tert*-butyl; Figure 1) formed from *tert*-butyl amides could be hydrolyzed only under harsh conditions, such as refluxing sulfuric acid.[7c,13] In contrast, we were able to isolate the lactones under very mild conditions. This underscores the advantageous properties of the trifluoroethyl amide as a directing group, as it displays an optimal balance of electron deficiency, *O*-nucleophilicity, and hydrolyzability.

Next, we looked at a series of simple substrates to evaluate whether different aliphatic sp^3 positions could be functionalized. Starting from commercially available carboxylic acids, a series of γ-lactones were synthesized by conversion of the respective amides in a one-pot lactonization protocol (Table 2; for screening details, see Table S1). Notably, not only tertiary (**21**, **22**, and **23**) and secondary (**24**, **25**, and **26**), but also primary C(sp^3)−H bonds (**27**, **28**, and **29**) were found to be readily functionalized this way, giving rise to the respective γ-lactones in good to excellent yields. Besides compounds with various alkyl lengths, also spirocyclic structures (**23**) as well as α-substituted lactones (**25**, **27**, and **28**) are accessible.

To investigate the scope and the limitations of the reaction, a series of more complex structures were synthesized and converted to the respective lactones. Here the fully optimized protocol was utilized (Table S1). As depicted in Table 3, the lactone moiety could be introduced into a variety of structures with different functional groups such as ketones (**30**), protected amines (**31**), aryl units (**32**), and electron-deficient olefins (**33**). Complex polycyclic γ-lactones (**34**, **35**) and bislactones (**36**) were also synthesized. In several cases (**32b**, **33b**, **35b**, **36b**, and **37b**), the yield was improved by utilizing AgOAc instead of $AgBF_4$ to promote cyclization.

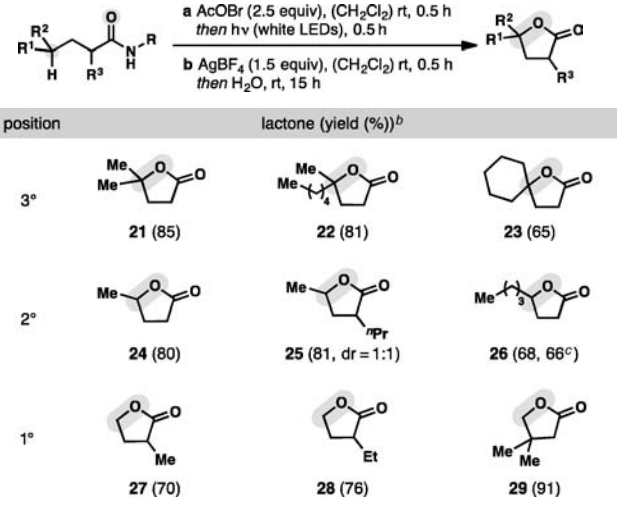
As with most C−H oxidation methods, electron-rich alkenes and enones do not tolerate the radical reaction step; in the case of an epoxide-containing substrate we investigated, γ-bromination was successful, but the cyclization conditions required were not compatible (see Table S2). Moreover, a limitation was found in the case of sterically hindered substrates: α-quaternary amides failed to undergo *N*-halogenation, while one substrate with a sterically very demanding γ-substituent failed to undergo H-abstraction. DFT calculations indicated that in this case the transition state energy was considerably higher than in the case of regular substrates (further discussion and mechanistic details

Table 1. Screening of N Substituents



[a]Complex product mixture; no γ-bromination was observed. [b]Cyclization product.

Table 2. Synthesis of Tertiary, Secondary, and Primary γ-Lactones[a]



[a]R = CH_2CF_3. [b]Determined using CH_2Br_2 as an internal standard. [c]Isolated yield.

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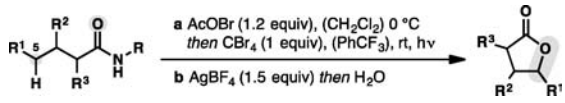
Table 3. Scope and Limitations[a]



entry	substrate	product	yield (%)[b]
1	30a	30b	49 (85 brsm)
2	31a	31b	46 (91 brsm)
3	32a	32b[c]	93
4	33a	33b[c]	75
5	34a	34b	26 (37 brsm)[e]
6	35a	35b[c]	65[d]
7	36a	36b[c]	37
8	37a	37b[c]	63
9	38a	38b	73 (96 brsm)
10	38a	38b	26 (67 brsm)

[a]R = CH_2CF_3; TCP = tetrachlorophthalimide. [b]Isolated yield. [c]AgOAc then AcOH, H_2O instead of $AgBF_4$ then H_2O for (2). [d]Determined using CH_2Br_2 as an internal standard. [e]No further defined product was isolated.

based on DFT calculations can be found in the Supporting Information).

After investigating the scope of the reaction, we were interested to see whether it would be possible to alter the regio- and chemoselectivity by incorporating specific structural features. Substrate **37a** with benzylic C−H bonds at the δ-position diverged from the usually favored transition state and gave rise to the six-membered lactone **37b**. This trend was also observed in the case of compound **38a**, where the γ-position was blocked by a quaternary center. Here, also a seven-membered transition state initially led to formation of the δ-bromoamide. However, upon cyclization the system yielded γ-lactone **38b**, presumably via a 1,2-methyl shift. It is important to note that spatially suitably arranged nucleophilic groups, such as an ester, can outcompete the amide in the cyclization, as shown in the conversion of ester **39a** to γ-lactone amide **39b**.

In conclusion, the first general method has been developed that allows the introduction of lactone rings by amide-directed C−H functionalization in good to excellent yields with unprecedented scope. Although nitrogen radical chemistry has been known since the age-old HLF reaction, this work features two major advances by employing the trifluoroethyl amide as a directing group: (1) the highly efficient hydrogen abstraction, which is not limited to tertiary and secondary sp^3 positions but is also suitable for the conversion of primary nonactivated methyl groups, and (2) the efficient cyclization and mild hydrolysis, which allow the direct and simple synthesis of γ-lactones in a one-pot fashion in the presence of a variety of functional groups. In total, 19 different substrates were converted successfully, showcasing highly predictable selectivity, good functional group tolerance, and broad scope for the functionalization of aliphatic C−H bonds. Since lactones are prominent structural features of many synthetic compounds and natural products, application of this C−H lactonization method will open up novel routes, including biomimetic late-stage C−H oxidations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03371.

Experimental procedures and spectral data for all new compounds and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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