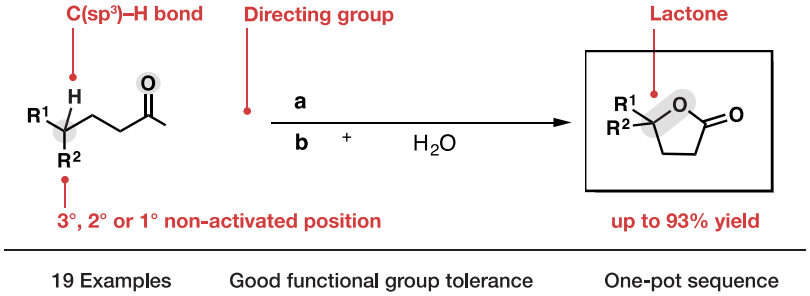
Synthesis of Lactones *via* C–H Functionalization of Non-Activated C(sp³)–H Bonds

Johannes Richers,[1‡] Michael Heilmann,[2‡] Markus Drees[1] and Konrad Tiefenbacher[2,3]*

[1] Technical University of Munich, Department Chemistry, Lichtenbergstraße 4, 85747 Garching, Germany.
[2] University of Basel, Department of Chemistry, St. Johanns-Ring 19, 4056 Basel, Switzerland
[3] ETH Zurich, Department of Biosystems Science and Engineering, Mattenstrasse 26, 4058 Basel, Switzerland.



ABSTRACT: An electron-deficient amide is utilized as directing group to functionalize non-activated C(sp³)–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 for functionalization of primary non-activated sp³-hybridized positions in a one-pot sequence. In addition, a broad functional group tolerance renders this method suitable for the late-stage introduction of γ-lactones to 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 aroma 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 directly transform C–H bonds. 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

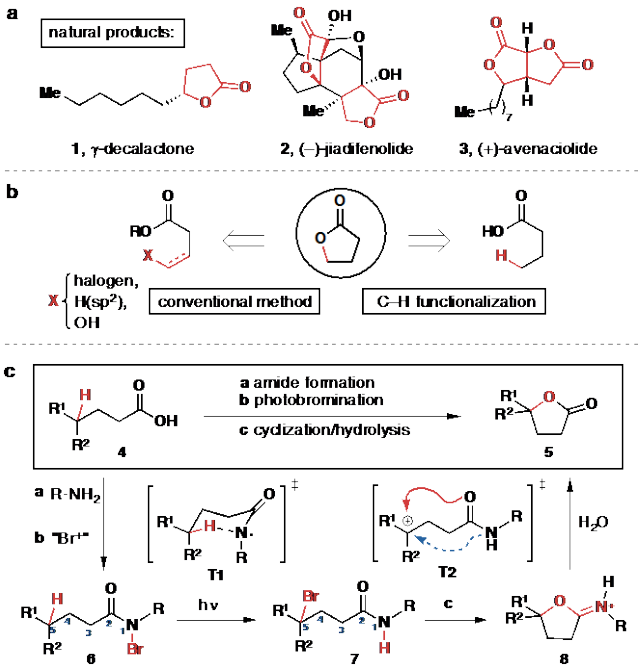


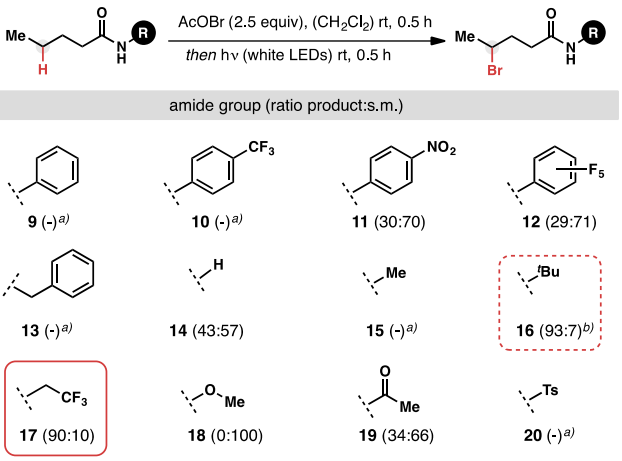
Figure 1. (**a**) Selection of natural products containing γ-lactones. (**b**) Retrosynthetic approaches towards γ-lactones. (**c**) Mechanistic description for the lactone formation.

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, the low chemical yields and poor reproducibility of the procedures published. A method that allows for the functionalization of non-activated tertiary, secondary and also primary C–H bonds is highly desirable but not available so far. Ideally, it would operate under mild conditions and tolerate a wide variety of functional groups. In order to find solutions for this challenge, we conducted a systematic investigation of the radical-mediated 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 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 the γ-bromoamide **7**, which then should allow for cyclization to form the 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 LED light 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 *t*-butyl amide **16** (93:7, Table 1). However, the *t*-butyl amide underwent spontaneous cyclization to the iminium lactone which proved to be unreactive under a variety of hydrolysis methods, presumably due to the steric bulk of the *t*-butyl group. Calculations and experiments have indicated that especially electron-deficient amidyl radicals tend to readily undergo hydrogen abstractions.[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 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] Attempts to isolate and purify the iminolactone after deprotonation with base, however, were unsuccessful.[12] Instead, facile hydrolysis was achieved at room temperature by directly adding water to the reaction mixture. This finding was unexpected in that *t*-butyl iminolactones (Figure 1, **8**, R = *t*-butyl), formed from *t*-butyl amides could only be hydrolyzed 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 directing group, as it displays an optimal balance of electron deficiency, *O*-nucleophilicity and hydrolyzability.

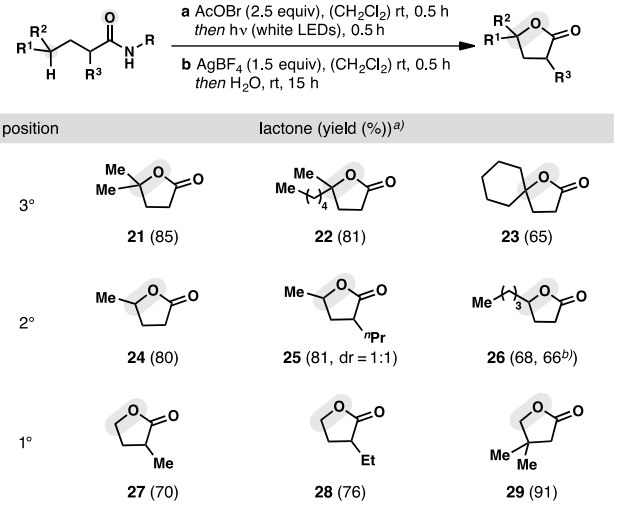
Table 1. Screening of *N*-Substituents.



a) complex product mixture, no γ-bromination observed. b) cyclization product

Next, we looked at a series of simple substrates to evaluate whether different aliphatic sp^3-positions can be functionalized. Starting from commercially available carboxylic acids, Table 2 shows a series of γ-lactones, which were synthesized by conversion of the respective amides in a one-pot lactonization protocol (for screening details, see Supporting Table S1). Notably, not only tertiary (**21**, **22**, **23**) and secondary (**24**, **25**, **26**), but also primary C(sp^3)–H bonds (**27**, **28**, **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**, **28**) are accessible.

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

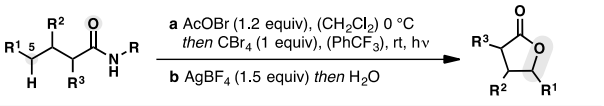


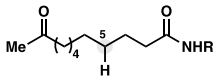
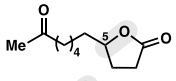
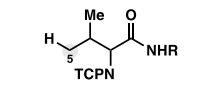
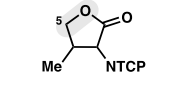
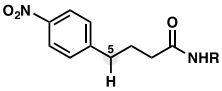
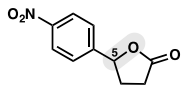
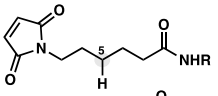
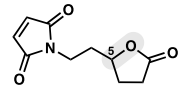
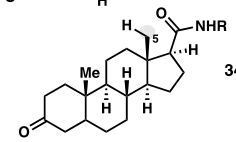
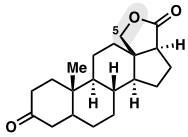
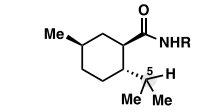
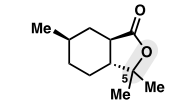
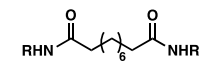
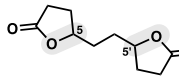
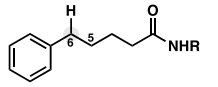
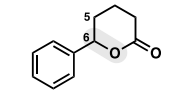
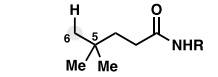
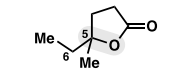
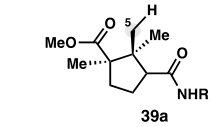
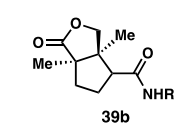
R = CH_2CF_3. a) determined with CH_2Br_2 as internal standard. b) isolated yield.

In order 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 (Supporting Table S1). As depicted in Table 3, the lactone moiety could be introduced to a variety of structures with different functional groups such as ketones (**30**), protected amines (**31**), aryl units (**32**), and electron deficient olefins (**33**). Also complex polycyclic γ-lactones (**34**, **35**) and bislactones (**36**) were synthesized. In several cases (**32b**, **33b**, **35b**, **36b**, **37b**), yields could be

improved by utilizing AgOAc instead of $AgBF_4$ to promote cyclization.

Table 3. Scope and Limitations.



entry	substrate		product		yield (%)[a]
1		**30a**		**30b**	49 (85 brsm)
2		**31a**		**31b**	46 (91 brsm)
3		**32a**		**32b**[b]	93
4		**33a**		**33b**[b]	75
5		**34a**		**34b**	26 (37 brsm)[d]
6		**35a**		**35b**[b]	65[c]
7		**36a**		**36b**[b]	37
8		**37a**		**37b**[b]	63
9		**38a**		**38b**	73 (96 brsm)
10		**38a**		**38b**	26 (67 brsm)
	39a		**39b**		

R = CH_2CF_3. **TCP** = Tetrachlorophtalimide. [a] isolated yield. [b] AgOAc *then* AcOH, H_2O instead of $AgBF_4$ *then* H_2O for 2). [c] determined with CH_2Br_2 asinternal standard.[d] no further defined product isolated.

As for most C–H oxidation methods, electron-rich alkenes and enones do not tolerate the radical reaction step; in case of an epoxide-containing substrate we investigated, γ-bromination was successful, but the cyclization conditions required were not compatible (see Supporting Table S2). Moreover, a limitation was found in 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 case of regular substrates (further discussion and mechanistic details based on DFT calculations can be found in the Supporting Information).

After having investigated the scope of the reaction, we were interested to see if it is possible to alter the regio- and chemoselectivity by incorporating specific structural features. Substrate **37a** with benzylic C–H bonds in 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 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* 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 for the introduction of lactone rings by amide directed C–H functionalization with good to excellent yields and 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 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 non-activated methyl groups. (2) The efficient cyclization and mild hydrolysis, which allows for the direct and simple synthesis of γ-lactones in a one-pot fashion in the presence of a variety of functional groups. In total, nineteen different substrates were converted successfully, showcasing a highly predictable selectivity, a good functional group tolerance and a 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.

Experimental procedures and spectral data for all new com-pounds and DFT calculations. (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: konrad.tiefenbacher@unibas.ch / tkonrad@ethz.ch

Author Contributions

‡ These authors contributed equally.

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