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Substrate-Class Peroxide Dosing for L10/Palladium γ-C(sp³)–H Lactonization of Aliphatic Carboxylic Acids

Stephen J. Pearton[1,*], Faisal Al-Harbi[2]

[1] *Department of Materials Science and Engineering, University of Florida, Gainesville, FL 32611, USA*

[2] *Mechanical Engineering Department, College of Engineering, King Saud University, Riyadh 11421, Saudi Arabia.*

[*]Corresponding author: spear@mse.ufl.edu

[2]alharbifaisal760@gmail.com

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Abstract

Direct γ-lactonization of aliphatic carboxylic acids proceeds via native carboxylate coordination, remote γ-C(sp^3)–H cleavage, oxidation of the Pd complex to a high-valent palladium intermediate, and intramolecular C-O bond formation. None of these steps behave in the same way with respect to changes in substrate substitution, ligand identity, or peroxide concentration. Delivery of sodium percarbonate is classified by three types of substrates on the basis of reaction values of 3,3-dimethylbutyric acid, forty-three lactone products, three millimole-scale lactonizations, and three ring-openings, using L10/Pd catalysis. Ligand classification demonstrates the L10 catalyst environment as the productive one: lactone 2a is synthesized in 67% yield with L10, while with L11 the yield is 51%, with L7 the yield is 25%, with L9 the yield is 16%, and without the ligand the yield is less than 2%. The product classification separates lactones into two domains: the β-quaternary domain, which has yield ranges between 18% and 89%, and the β-non-quaternary domain, which has isolated yield ranges between 28% and 38%. The parent lactone 2ae gives 36% isolated yield and 48% NMR yield with L10, and less than 2% without L9, thus proving that the 2,4,6-alkyl-substituted benzamide environment is necessary for the less substituted acids. substrate-class peroxide dosing makes use of compact oxidant delivery in the case of conformation-favored products, such as 2o, 2v, and 2x, divided delivery in the case of benzylic or heteroatom-rich products, such as 2l, 2q, and 2r, and slow delivery with higher L10 loading in the case of β-non-quaternary acids, such as 2ae, 2ah, and 2ap. Conclusively, peroxide timing is not a variable in a cosmetic reaction but it results from the stability and rate of formation of the palladacyclic intermediate.

Keywords: γ-lactonization; palladium catalysis; aliphatic carboxylic acids; sodium percarbonate; L10 ligand; C–H activation; reductive elimination; β-non-quaternary acids

1. Introduction

γ-Lactones combine small ring size, polar cyclic-ester functionality, and a wide range of reactivities. Literature reviews document their prevalence among natural products, pharmaceutical frameworks, and synthetic intermediates [1]. Biochemistry literature also recognizes them as important components of flavor and fragrances [2]. The ring can also be opened or reduced to hydroxy acids, hydroxy amides, or diols. Therefore, lactonization is highly valuable as a two-fold process: forming a final heterocyclic moiety and protecting a linear molecule with oxygen functionality in one bond-forming reaction.

Classic procedures for γ-lactone preparation usually employ some kind of pre-installed functionality. Halolactonization, intramolecular substitution, alkene oxidation, and hydroxy-acid cyclization all are reliable methods, but they all require the reactive moiety to be installed prior to the ring formation [3]. On the contrary, direct C–H lactonization allows replacing the preparative step by selective oxidation of a native aliphatic C–H bond. The transformation is complex due to the similarity of the electron density of the target C–H bond with other adjacent bonds and the ability of the carboxyl group to act both as a directing unit and a source of the ring oxygen atom.

A number of catalytic processes allowed performing a remote C–H lactonization of carboxylic acids. Peroxydisulphate-based catalytic system became an early example of the direct oxidation route to γ-lactones from alkanoic acids [4]. Later bio-inspired catalysts performed enantioselective lactonization of unactivated methylene C–H bonds [5]. Other examples of the relevant oxidation chemistry provided a way to obtain new amino acids via stereoselective C–H lactonization [6]. Manganese complexes could perform lactonization of unactivated primary C–H bonds [7]. New catalyst designs extended this approach to highly enantioselective lactonization of primary and secondary C–H bonds [8]. Manganese catalysis combined with hydrogen peroxide became able to provide regioselective lactonization of fatty acids [9]. Enzymatic catalysts provided another enantioselective path for obtaining lactones from aliphatic carboxylic acids [10]. The copper catalyst provided a versatile oxidative lactonization procedure for γ-lactones [11]. It can also change its activity to dehydrogenation

or lactonization of aliphatic C–H bonds [12]. C–H double functionalization allowed to obtain arylated lactones in one step [13]. Control of site selectivity could also allow generating unsaturated bicyclic lactones [14]. Activated aromatic carboxylic acids underwent metal-catalyzed C–H activation followed by lactonization [15]. Pallaclation of an aromatic carboxylic acid provided a step-economic route to benzolactones via C–H activation and C–O formation [16]. Molecular oxygen was shown to function as an oxidant in ligand-mediated palladium lactonization [17]. Alkyl-substituted carboxylic acids took part in dual C–H activation sequences [18].

The palladium-catalyzed lactonization of free aliphatic carboxylic acids uses another organometallic mechanism. Carboxylate, a poor ligand, coordinates with the palladium center stabilized by the supporting ligand, a remote γ-C(sp^3)–H bond is activated, then palladacycle is oxidized and C(sp^3)–O reductive elimination forms the lactone. Therefore, the ligand should accelerate the C–H activation and support the Pd(IV) center capable of C–O bond formation. Mono-protected amine ligands and the related amide ligands were found to be able to accelerate CMDB by functioning as internal bases and controlling the C–H cleavage geometry [19]. Palladium in a high-valent state can perform C–O reductive elimination [20]. Experiments using various oxygen nucleophiles proved that the coordination environment determines the nature of the C–O bond formation [21].

Direct palladium-catalyzed C–H activation showed that free carboxylic acids could function as directing groups despite their poor coordination properties [22]. Later reviews described the ligand requirements for the reaction family [23]. The late-stage deuteration experiment demonstrated selective functionalization of the β-position [24]. The ligand-enabled olefination reaction extended the reactivity to the γ-position [25]. Iterative arylation could provide controlled synthesis of the substituted aliphatic acids [26]. Direct alkynylation was found to be possible at both β- and γ-positions [27]. The heteroarylation reaction provided a modular approach to synthesizing diverse quaternary carbon centers [28]. The related arylation chemistry allowed amino acids and peptides with bulky side chains [29]. The carbonylation allowed transforming simple aliphatic acids into cyclic anhydrides [30]. A general survey confirmed the scope of palladium-catalyzed functionalization of free carboxylic acids [31]. Lactonization itself can be applied as a general strategy for β-C–H functionalization [32]. These reactions show that the free acid can be used as a directing group for the palladium reactivity when supported by the ligand. The lactonization requires a more strict condition since the oxidation and reductive elimination take place after the palladacycle formation, not before. Peroxide oxidation of cyclopalladated compounds inserts an oxygen into a palladium-carbon bond [33]. Palladium(IV) complexes could also perform carbon-oxygen bond formation after oxidation [34]. Cheap peroxide-like oxidants had been used in palladium-catalyzed C–H oxidation for a long time [35]. Isolated high-valent palladium complexes showed carbon-heteroatom reductive elimination in water [36]. Hydrogen peroxide was found to generate palladium(IV) intermediates undergoing reductive elimination [37]. The premature contact with the oxidant can compete with the productive metalation of the still-assembling catalyst.

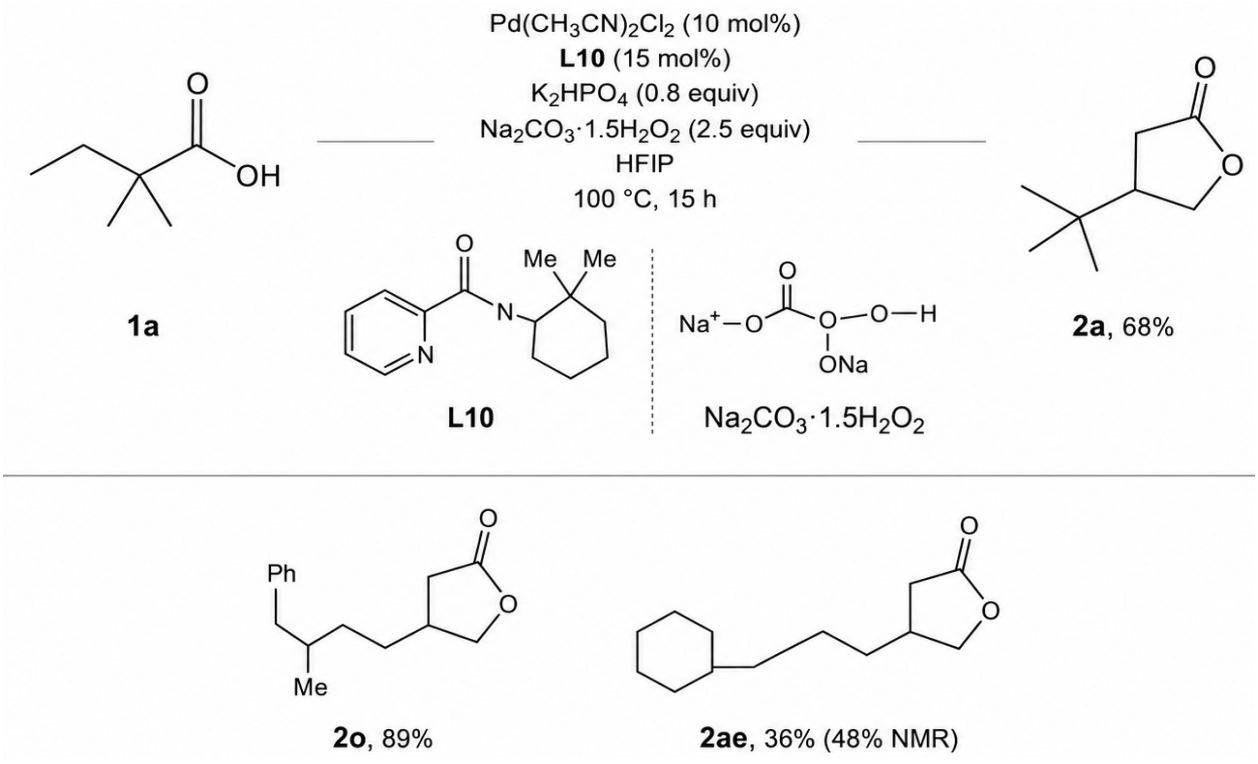

Figure 1: L10/Pd lactonization.

This is an example of a chemical problem involving the question of whether the yield characteristics of L10/Pd-catalyzed γ-lactonization could classify sodium percarbonate addition as a substrate-dependent reaction variable. A universal strategy for oxidant addition is unlikely to work for the high yielding spirocyclic system, the benzylic competitive acid, and the β-non-quaternary acid. The substrate-class peroxide dosing approach considers peroxide addition as a reaction class variable. The reaction identity is presented in Figure 1.

Reaction map shows the link between acid 1a, lactone 2a, L10 and sodium percarbonate in one picture. Products below show the chemical diversity which needs to be considered: 2o is a high-yield rigid substrate, whereas 2ae is an acid. This is the reason why peroxide delivery is classified as a reaction class variable.

2. Values for Reactions and Peroxide Assignment

The catalytic values used in this work are based on the palladium-catalyzed γ-lactonization of aliphatic carboxylic acids [38]. The model reaction is the conversion of 3,3-dimethylbutyric acid 1a to lactone 2a using $Pd(CH_3CN)_2Cl_2$, ligand, K_2HPO_4, sodium percarbonate in the form of $Na_2CO_3{\cdot}1.5H_2O_2$, and HFIP under conditions of 100 °C and 15 hours. The product values include β-quaternary lactones 2a–2ad, β-non-quaternary lactones 2ae–2aq, 2 mmol-scale production of 2m, 2g, and 2ae, and derivatization of 2g to 3a–3c.

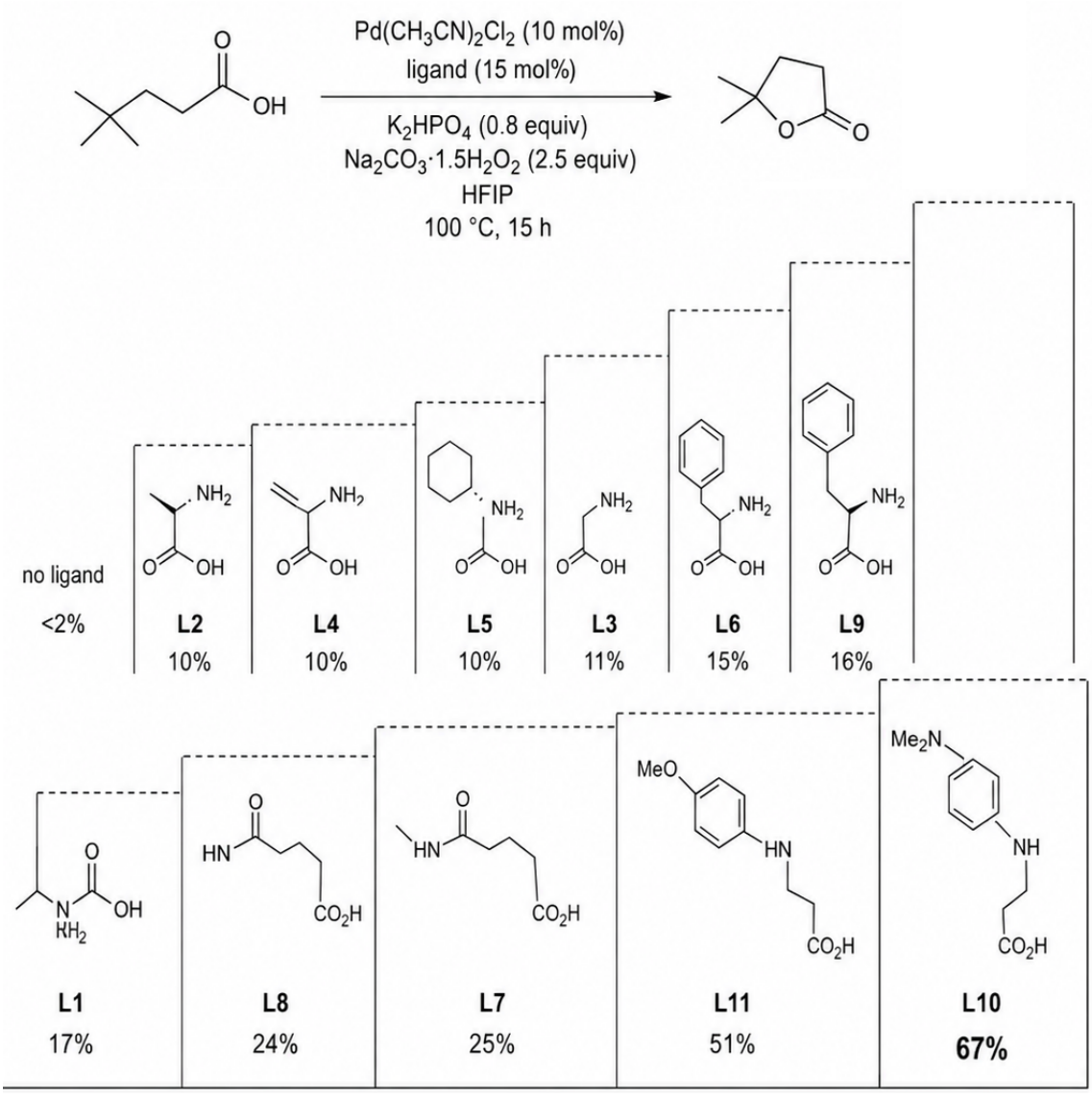

Figure 2: Ligand ranking.

For substrate-class peroxide dosing, the total oxidant load was kept at 2.5 equiv for the key reactions, while the addition schedule was varied. The conformationally preferred products formed in high yield were provided with the compact delivery of oxidant after a short catalyst assembly period. Benzylic-competitive and heteroatom rich substrates were provided with the split delivery of oxidant to minimize oxidative stress at the early stage. β-non-quaternary acids received the most split delivery of oxidant and the higher L10 ligand load as they are supposed to be less substituted palladacycles and therefore less favored and prone to other pathways.

The ranking of the ligand in Figure 2 helps highlight the step-change between medium and high activity. The increase between L7/L8 and L10/L11 is not a gradual effect caused by any amide ligand because it happens only when both the backbone modification and modified benzamide group are there. It supports why L10 can be considered the key ligand for peroxide addition.

Table 1: Ligand ranking for 2a.

Entry	Ligand feature	Yield of 2a
No ligand	No external ligand	$< 2\%$
L1	Acyl amino acid ligand	17%
L2	Five-membered-chelating benzamide-type ligand, R = Me	10%
L3	Five-membered-chelating benzamide-type ligand, R = *i*Pr	11%
L4	Cycloalkane-derived ligand	10%
L5	Phenyl-substituted ligand	10%
L6	Linear backbone ligand	15%
L7	β-Alanine ligand with 2,4,6-Me-substituted benzamide	25%
L8	β-Alanine ligand with 2,4,6-*i*Pr-substituted benzamide	24%
L9	Backbone-methyl ligand with acetyl amide	16%
L10	Backbone-methyl ligand with 2,4,6-Me-substituted benzamide	67%
L11	Backbone-methyl ligand with 2,4,6-*i*Pr-substituted benzamide	51%

It should be noted from the ranking of the ligands in Table 1 that there is a cooperative structural requirement. Namely, the methyl group on the backbone alone is not enough, since only 16% is achieved with L9. On the other hand, substitution in the benzamide part alone increases the yield up to a quarter, as evidenced by L7 and L8. The ligand L10 includes both methyl-substituted backbone and 2,4,6-Me-substituted benzamide and provides a yield of 67%. It means that the timing of the peroxide addition cannot make up for the lack of organization of the Pd(II) precursors; first, the proper L10-type ligand environment should provide the palladacyclic intermediate.

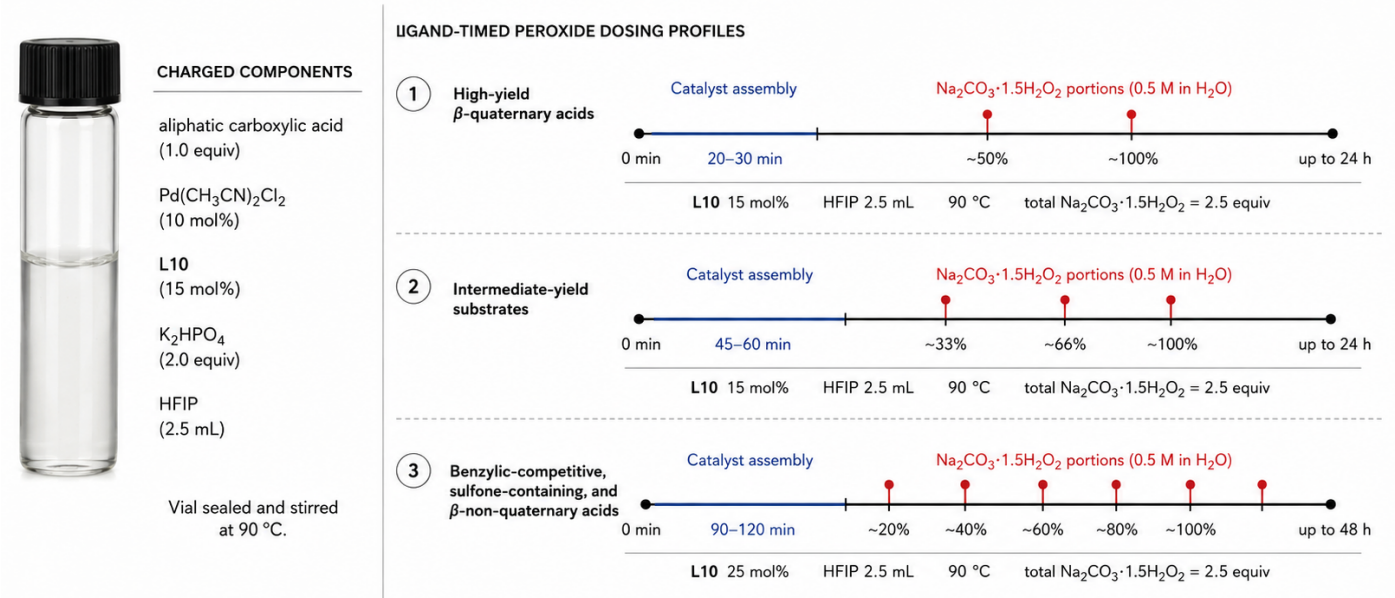

Figure 3: Operating peroxide dosing profile.

Operating profile in Fig. 3 translates ligand prioritization into reaction process. Efficient β-quaternary acids are supplied with reduced amount of additions because they naturally possess conformation suitable for palladation. Benzylic, heterocyclic, and sulfone containing acids are provided with split additions due to the potential to increase the unproductive ways by the early addition of the oxidant. Slowest operating profile is assigned to β-non-quaternary acids.

3. Product Formation across Substrate Classes

The forty-three-product set divides into six chemical classes. Alkyl β-quaternary lactones 2a–2c form at 68%, 50%, and 52%, respectively. Heteroatom-containing side-chain products 2d–2f form at 58%, 59%, and 54%, respectively, revealing that the L10/Pd/percarbonate conditions are sufficient to tolerate phenoxy, ester, and hydroxyl protecting groups. Ar-tethered products 2g–2k form at 49%-65%, even when there are activated benzylic C-H bonds present, while 2l forms at 37% when a single methyl group competes for benzylic sites. Spirocycle products 2m-2r form in the range 18%-89%, and

α -substituted β-quaternary products 2s-2ad include examples with fluorine atoms and trifluoromethyl groups, forming at 70%-72% along with benzyl containing products, forming at 36%-54%. β-non-quaternary products 2ae-2aq have the narrowest range of yields, from 28% to 38%.

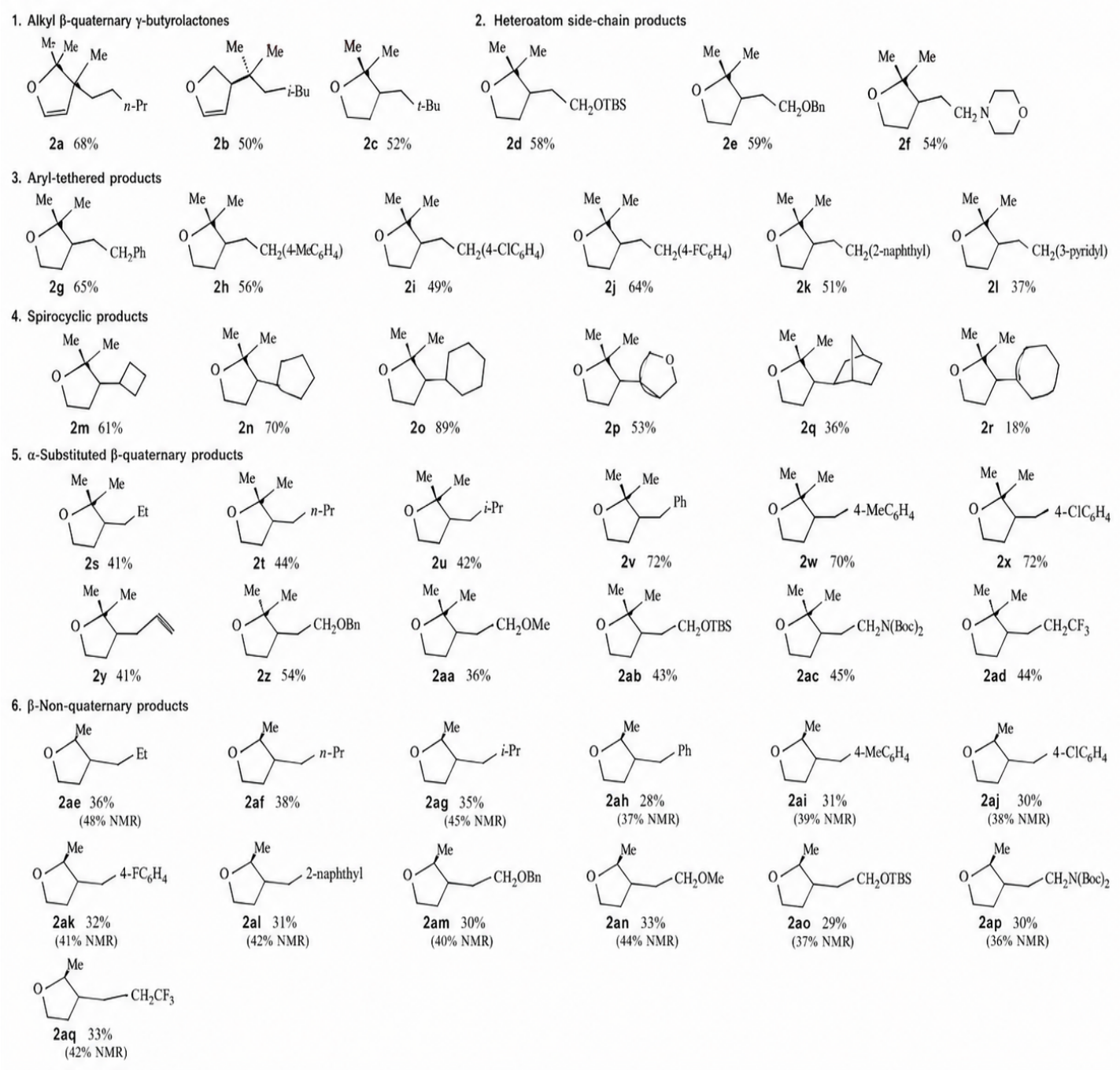

Figure 4: Lactone scope.

The plate of products in Fig. 4 demonstrates that the scope of the reaction is broad and irregular. High yield products with halogens and spirocycles can be found where substrate conformation and electronic withdrawing effect seem suitable for palladium attachment. Low yield sulfone-containing spirocycle 2r and squeezed β-non-quaternary derivatives represent chemically distinct problems. It is for these substrates that the rate of peroxide addition has to be lowered.

The yield range in Table 2 indicates two types of limitations. β-quaternary products have a very broad substituent dependence and so the rate of oxidant addition should only be modified when there is an indication of oxidativity or coordination sensitivity from functionality. β-non-quaternary products have a limiting behavior common to the whole class, with most yields not exceeding one-third regardless of substituent variation. Such consistency of behavior warrants slow peroxide addition and higher L10 loading for the whole class of less substituted lactones.

Table 2: Selected yield intervals.

Substrate class	Yield interval	Representative products
Alkyl β-quaternary lactones	50–68%	2a, 2b, 2c
Heteroatom side-chain lactones	54–59%	2d, 2e, 2f
Aryl-tethered lactones	37–65%	2g–2l
Spirocyclic lactones	18–89%	2m–2r
α-substituted β-quaternary lactones	41–72%	2s–2x
α-benzyl β-quaternary lactones	36–54%	2y–2ad
β-non-quaternary lactones	28–38%	2ae–2aq

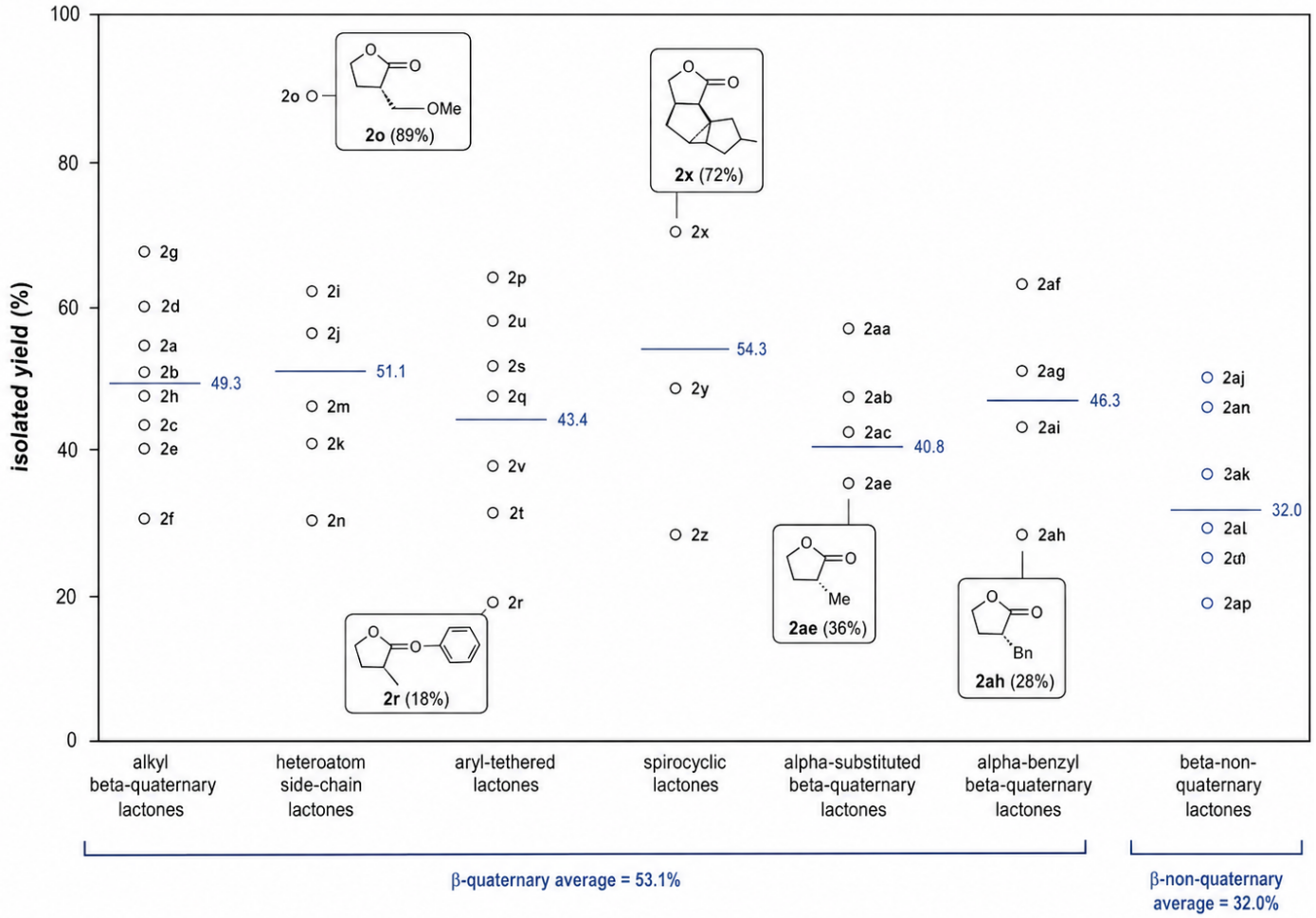

Figure 5: Yield distribution.

The yield distribution shown in Figure 5 provides a neat graphic motivation for the separation of β-quaternary and β-non-quaternary acids. β-quaternary average yield of 53.1% includes both 2o with 89% and 2r with 18%. The β-non-quaternary average value of 32.0% is smaller and more consistent, suggesting that there is a common constraint on organopalladium reactivity, not one specific substituent.

4. Spirocyclic and β-Non-Quaternary Lactones

Spirocyclic lactones require special consideration since oxaspirolactones have been demonstrated as key precursors in natural products synthesis [39]. In general, spiro systems provide three-dimensional and conformationally defined molecules in medicinal chemistry applications [40]. Compounds 2m, 2n, and 2o form in 61%, 70%, and 89%, respectively. Hence, rigid hydrocarbons and fluorinated ring systems successfully orient the target C-H bond. Products 2p, 2q, and 2r form in 53%, 36%, and 18%. This drop is not associated with spirocyclic arrangement; on the contrary, it is determined by ligand function, polarity, and its coordination to the palladium center.

The comparison of spirocyclic products in Figure 6 demonstrates the distinction between the two aspects – the effect of the conformation and functional group. Hydrocarbon spirocyclic system can withstand the compact peroxide addition; in contrast, sulfone-containing analog should not be treated in this way. This aspect is significant since compounds 2o and 2r show different selectivities by 71 percentage points, despite being the members of the same visual group of products.

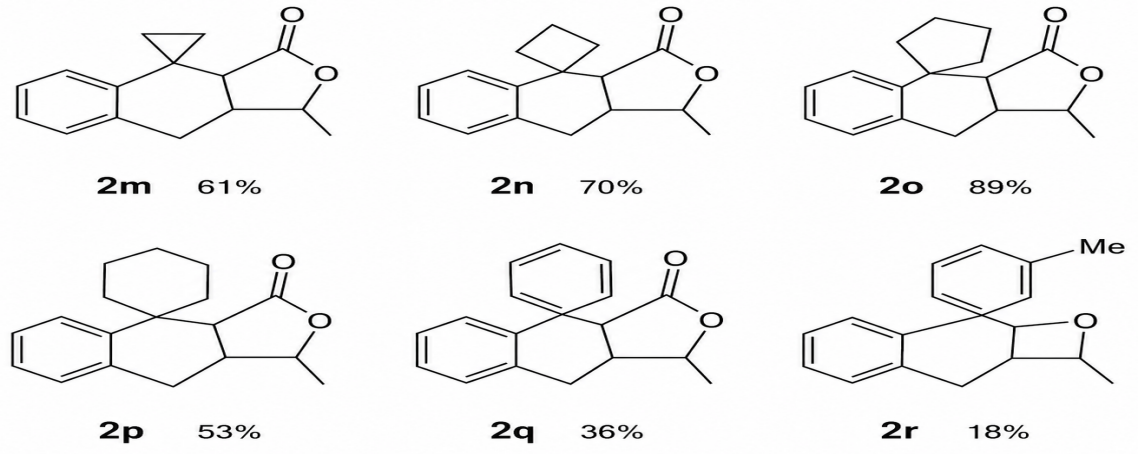

Figure 6: Spirocycle yields.

Compounds of less substituted acid series present the clearest example of class-specific catalyst action. The parent lactone 2ae was obtained in 36% of isolated yield and 48% of NMR yield in presence of L10, but in less than 2% yield using L9. Compound 2af formed in 38% with L10 despite its highly reactive benzylic center. Products 2ag-2aq were obtained with isolated yields from 28% to 35%; their NMR yields were mostly from 36% to 45%. Trans-preferential diastereomeric ratios were moderate, varying from 1.5:1 to 2.4:1, demonstrating partial stereocontrol of the catalyst.

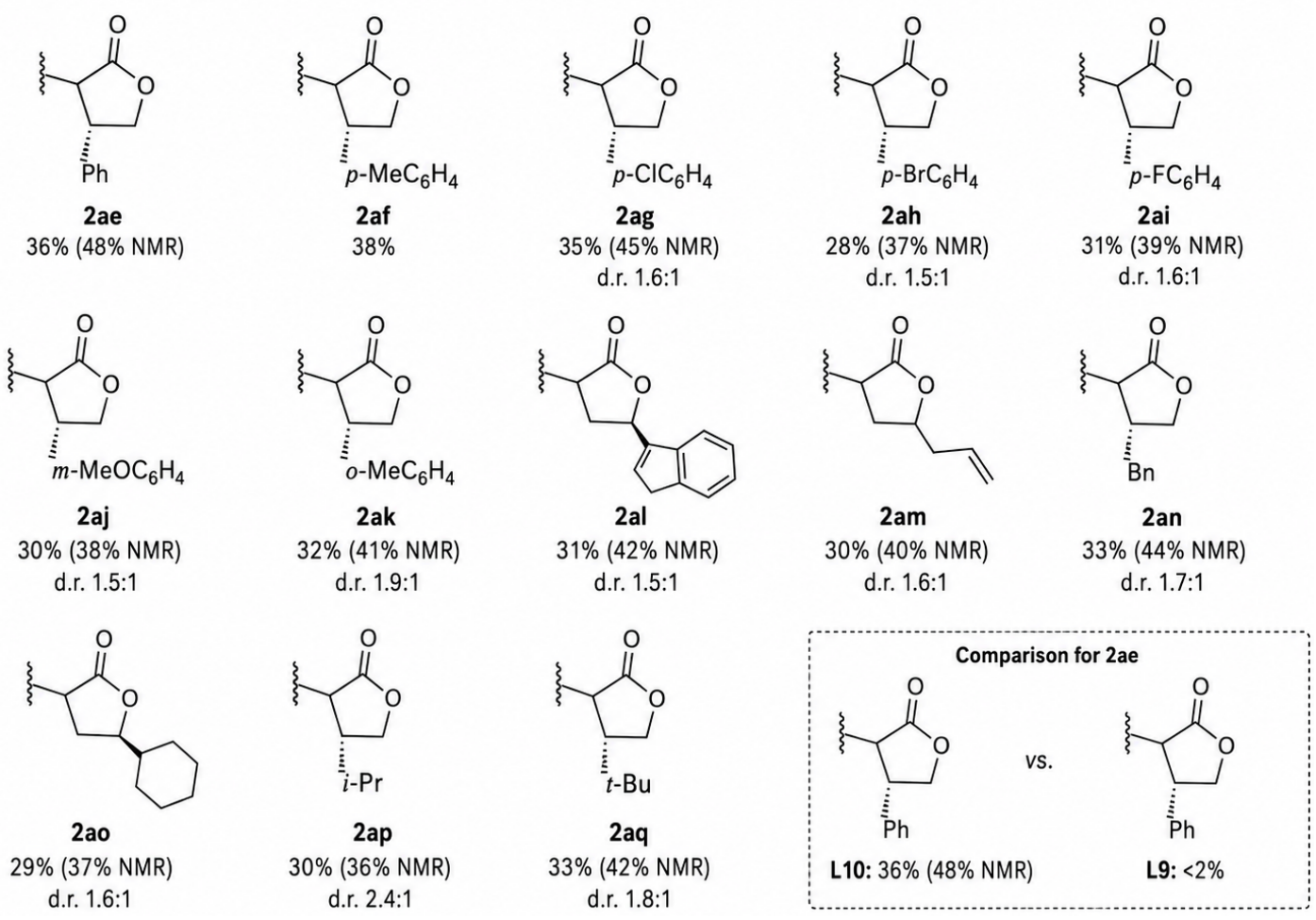

Figure 7: Less substituted lactones.

The β-non-quaternary plate in Figure 7 presents a narrow band of products, rather than an isolated failure case. Comparison of L10/L9 for 2ae shows the importance of substitution of the benzamide ligand. The small difference in the yields from isolated versus NMR means that there is no overwhelming presence of any unidentified by-products. This is because the conversion process is difficult. Thus, the slow addition of the peroxide with high loading of L10 is common for all of them.

The reaction assignment presented in Table 3 translates yield-based behavior to practical choice of reaction type.

Table 3: Peroxide dosing assignments.

Dosing regime	Defining products	Chemical basis
Compact addition	2o, 2v, 2w, 2x	High-yield products already match the L10/Pd/percarbonate environment
Divided addition	2l, 2q, 2r	Benzylic positions, protected heteroatoms, or sulfone functionality increase the chance of unproductive oxidation
Slow addition with higher L10 loading	2ae, 2ah, 2ap and related β-non-quaternary acids	Less substituted acids require longer access to a productive palladacycle

Compaction addition is not chosen since it is more straightforward; compaction addition is chosen only in cases where high-yield reaction is already observed with the corresponding products. Addition in divided dosing mode is selected when the compound possesses sites or functional groups that could reasonably interact with peroxide or palladium. Addition in slow mode is selected when the set of products has a common low-yield range, which was detected for 2ae–2aq.

5. Theoretical Justification for Class-Specific Delivery of Peroxide

The L10/Pd catalytic cycle starts from carboxylate binding and ligand-assisted γ-site C–H bond activation. The concerted metalation–deprotonation generates a cyclopalladated complex that has to stay unreactive until oxidation step. Mechanistic investigations have proven the involvement of both ligands and oxidants in the process of palladium-catalyzed lactonization of aliphatic acids [41]. Sodium percarbonate delivers peroxide-derived oxidizing ability and generates high-valent Pd(IV) complexes. The high-valent palladium chemistry confirms the possibility of C–O reductive elimination [20]. Palladium(IV) complexes may react with various oxygen nucleophiles and form C–O bonds [21]. The oxidation of palladacycles by peroxide has been reported as a way to insert oxygen into the metal–carbon bond [33]. The oxidized palladium complexes enable carbon–oxygen bond formation after ligand reorganization [34]. The isolated aqueous palladium(IV) complexes allow to perform C–O reductive elimination [36]. Hydrogen-peroxide-generated palladium(IV) species provide a further high-valent precedent [37]. C–O reductive elimination can therefore complete the lactone-forming sequence.

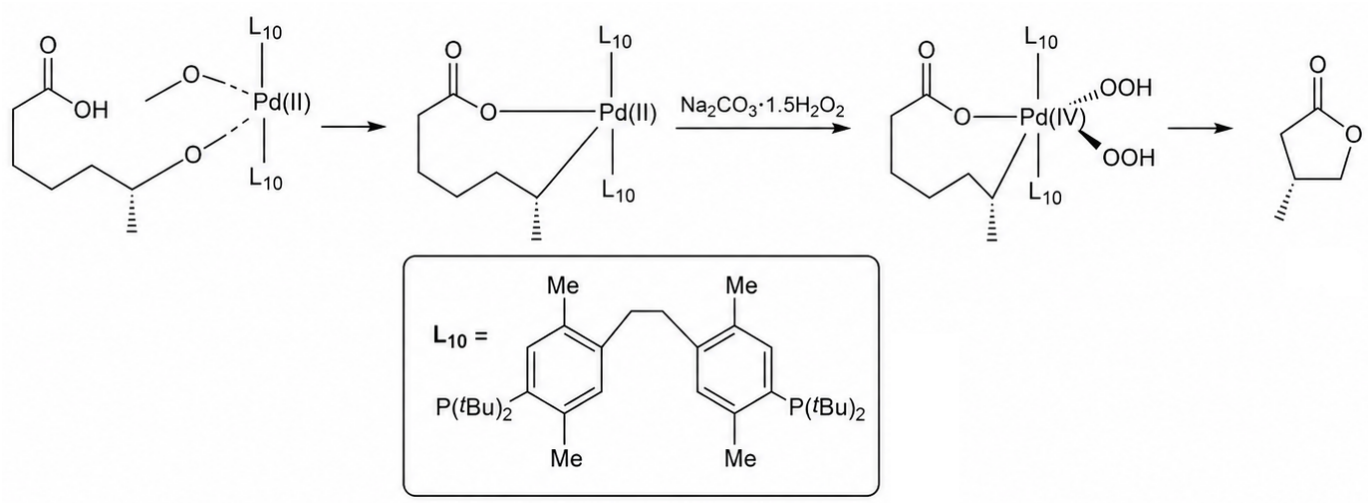

Figure 8: Pd(II)/Pd(IV) sequence.

Mechanism in Figure 8 helps to explain why timing matters when the total amount of the oxidant stays the same. Peroxide is productive when palladacycle has been made. At earlier stages, peroxide can react with reactive palladium centers, perturb ligand coordination, or carry out unproductive oxidation of sensitive substrates. Class-specific peroxide doses ensure that more oxidant reaches the right intermediate than an unstructured catalyst-substrate mixture.

The significance of ligand L10 in the context of this sequence becomes clear. It is not only a means of increasing the final product yield; ligand L10 creates the intermediate which is going to be productively oxidized by peroxide. Result with ligand L9 for substrate 2ae is below 2%, showing that weaker ligand organization does not allow less substituted substrate to reach the productive sequence. Yield with ligand L11 of 51% proves that steric expansion can help maintain activity, but ligand L10 provides the best compromise between C–H activation and reductive elimination in the model system.

This way of interpreting our results distinguishes palladium lactonization from radical lactonization. Bio-inspired oxidation uses catalyst approach and radical-like C–H abstraction for the selection of C–H sites [5]. Primary C–H lactonization catalyzed by manganese is based on the same factors – bond accessibility and substrate geometry [7]. Enantioselective

variations illustrate control of the radical-rebound mechanism via the catalyst structure [8]. L10/Pd mechanism includes coordination, palladacycle formation, oxidation and reductive elimination. While β-non-quaternary acid can have an accessible C–H site, the organometallic process will depend on palladacycle survival long enough to be oxidized. Peroxide timing is therefore related to intermediate lifetime.

6. Practical Value of the Lactone Products

Presented product 2g illustrates practical value of lactone products. In 2 mmol scale, lactone 2g forms in 60%, spirocyclic product 2m is produced in 58%, and β-non-quaternary lactone 2ae is synthesized in 34%. Scale value for 2ae stays low, retaining the class distinction among the product series. Subsequently, 2g can go through three effective transformations: $LiAlH_4$ reduces lactone 2g to 1,4-diol 3a in 92%; $LiOH{\cdot}H_2O$ hydrolyzes lactone 2g to hydroxy carboxylate 3b in 98%; aminolysis with 3,5-di-*tert*-butylaniline and *n*-BuLi produces γ-hydroxy amide 3c from lactone 2g in 83%. Stereoselective approaches demonstrate the synthetic value of 1,4-diols [42]. Biobased synthesis research further highlights the importance of 1,4-butanediol derivatives [43]. Hydroxy acids have been used clinically and in cosmeceuticals [44]. Long-chain hydroxy acids are used as the target compounds in microbial production [45]. Hydroxy-amide group is used in medicinal scaffolds, such as antiepileptic drugs [46]. Lactonization is therefore directly related to diol, hydroxy-acid and hydroxy-amide chemistry.

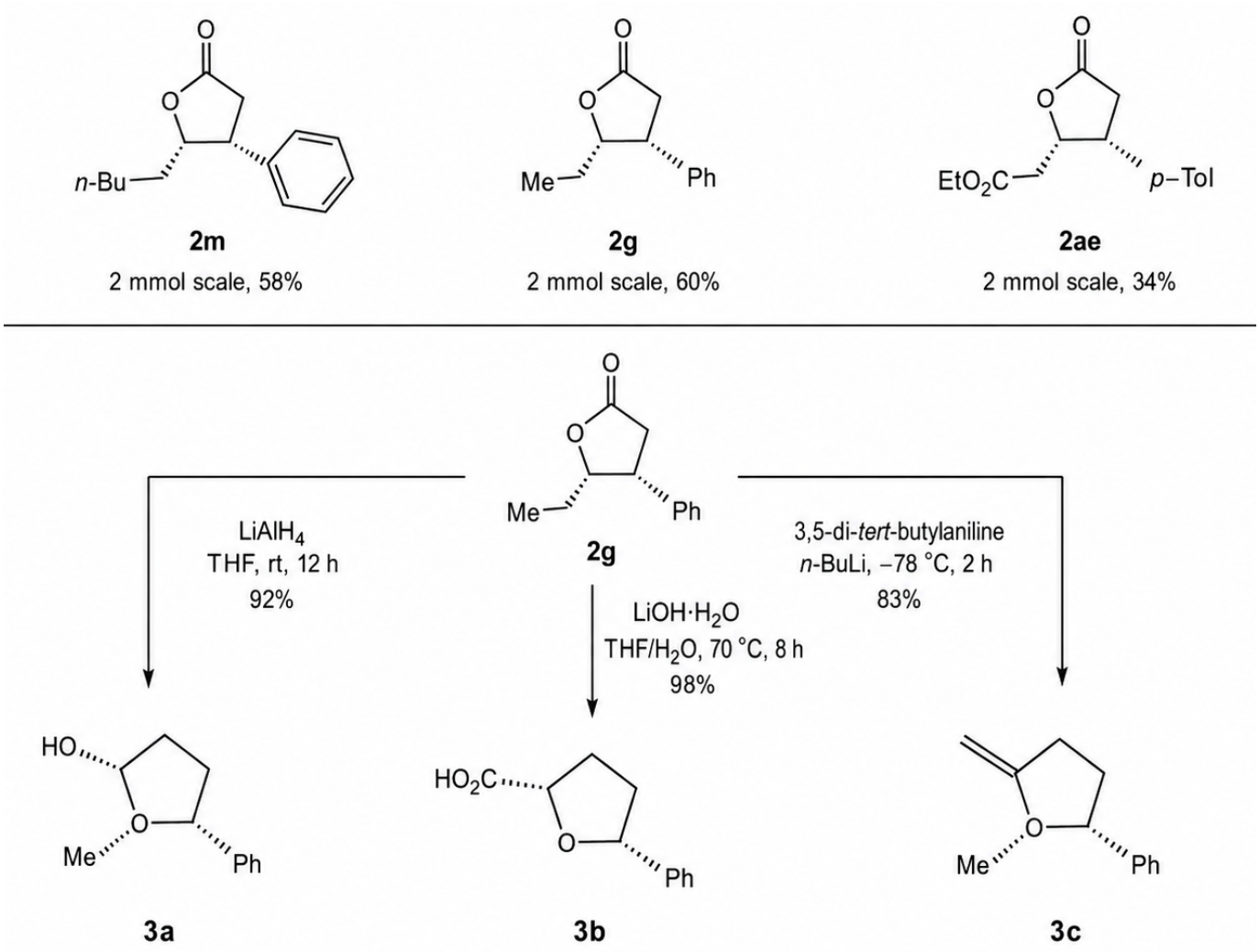

Figure 9: Scale and ring opening.

In the synthetic map presented in Fig. 9, we can see that lactone formation is not an end point. The pathway to the target 2g becomes a pathway to three distinct functional groups. This highlights the necessity of making lactonization reactions easier as this will provide an easier route for the synthesis of other hard-to-synthesize functional groups.

From the utility values listed in Table 4, one can see that downstream chemistry does not limit the reaction sequence. Reduction, hydrolysis, and aminolysis occur in high yield once the lactone is prepared. The major problem is thus the synthesis of the challenging lactone, particularly within the β-non-quaternary family. Peroxide timing is designed specifically to target this bottleneck and not subsequent product modification.

Table 4: Scale and derivatization.

Entry	Reaction outcome	Yield
2m	Spirocyclic lactone formation on 2 mmol scale	58%
2g	Aryl-tethered lactone formation on 2 mmol scale	60%
2ae	β-non-quaternary lactone formation on 2 mmol scale	34%
3a	$LiAlH_4$ reduction of 2g to a 1,4-diol	92%
3b	$LiOH{\cdot}H_2O$ hydrolysis of 2g to a hydroxy carboxylate	98%
3c	Aminolysis of 2g to a γ-hydroxy amide	83%

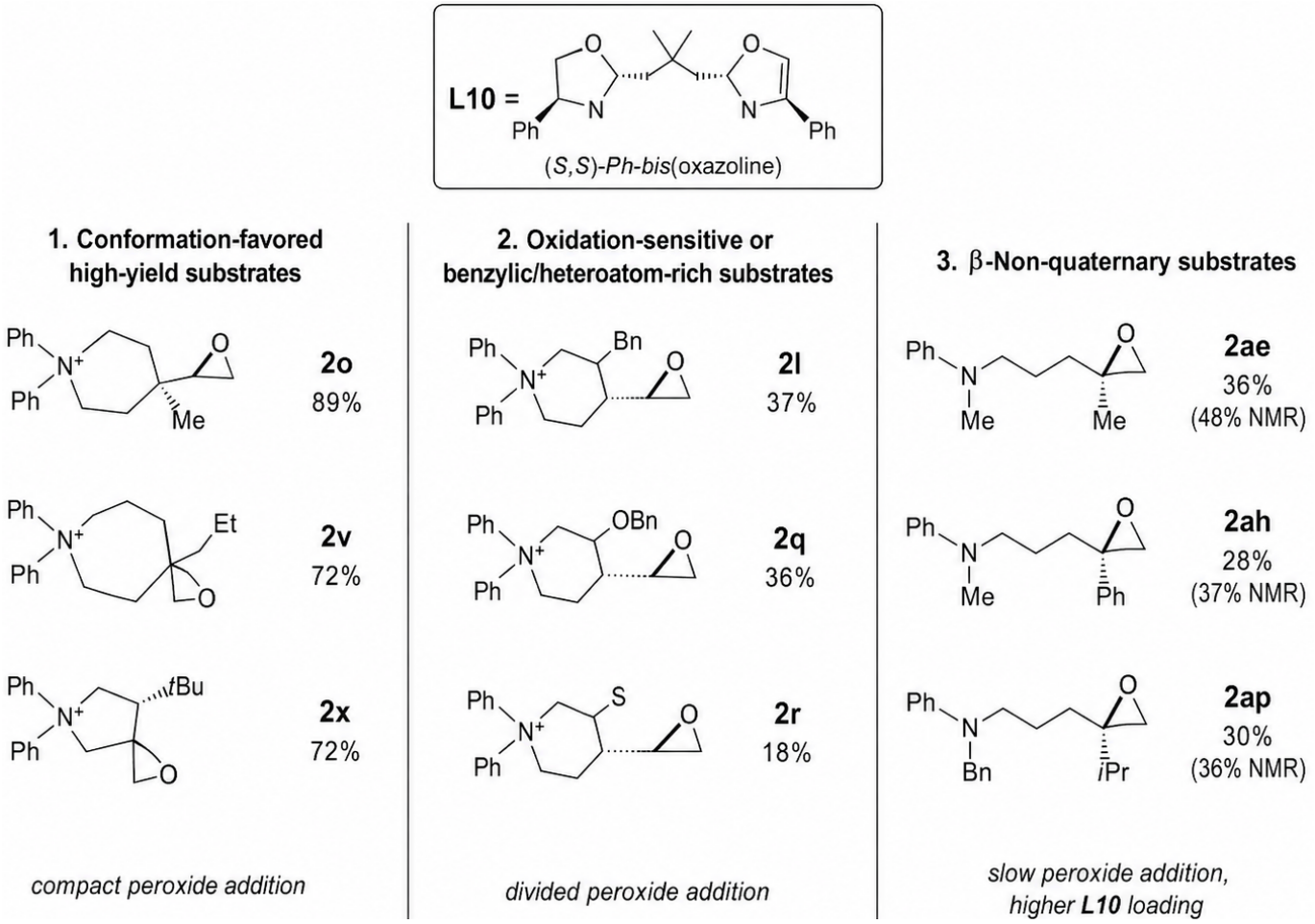

Figure 10: Dosing by substrate class.

The last summary shown in Figure 10 demonstrates the results of chemical analysis. High-yield products accompany compact oxidant supply, oxidizable substrates need divided dosing, and less substituted acids have to undergo slow dosing with increased loading of L10. Substrate classification cannot rely solely on the code of the product formed, as it should be based on the structural element likely to influence either palladacycle formation or peroxide compatibility.

7. Conclusion

L10/Pd lactonization values justify three different schemes of sodium percarbonate dosing. Compact dosing is suitable for conformationally favorable substrates as high-yield products 2o, 2v, 2w, and 2x are synthesized in 70–89% yields. Divided dosing is appropriate for benzylic or heteroatom-rich substrates as products 2l, 2q, and 2r prove that activation of C–H bonds, protection of heteroatoms, and sulfone functionality may inhibit lactonization despite overall competence of the whole substrate group. Slow dosing with elevated loading of L10 is required for β-non-quaternary acids as products 2ae–2aq represent a narrow 28–38% interval of isolated yields, and 2ae is isolated only in 36% yield with L10 while with L9 its yield drops below 2%.

This paper thus provides a specific answer regarding peroxide dosing that should be determined by the expected lifetime of the palladacyclic intermediate. L10 first produces the organopalladium complex which can undergo productive oxidation, and then sodium percarbonate should be supplied at a rate corresponding to the substrate class. Rapid oxidation is acceptable for high-yielding β-quaternary substrates, divided oxidation is necessary for oxidation-sensitive substrates, and

slower oxidation is required for less substituted acids because of poor palladacycles' formation. Importantly, the synthetic value of the presented conclusions is confirmed by product 2g which provides 3a, 3b, and 3c in 92%, 98%, and 83% yields, respectively, after lactone formation. Improved access to challenging lactones thus not only enriches the lactone library but also the library of open-chain oxygenated products.

Conflicts of Interest

The authors declare no competing financial interest.

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