Macrolactonization Driven by Supramolecular Interactions.

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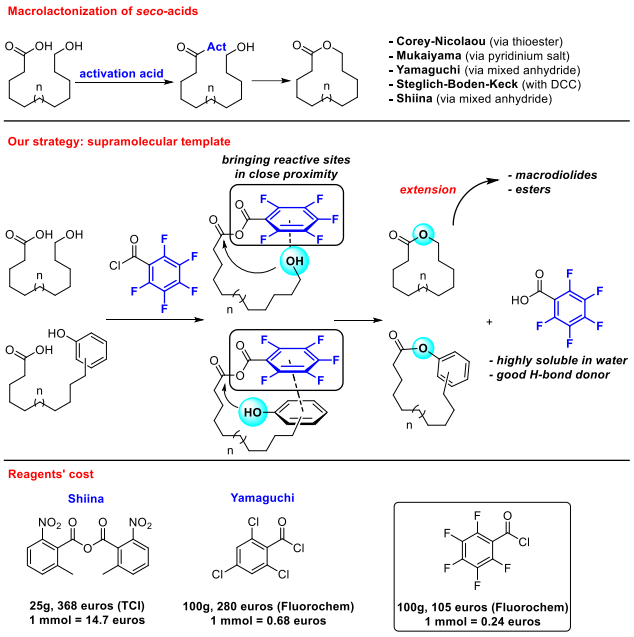
Supporting Information Placeholder

ABSTRACT: Macrolactones constitute a privileged class of natural and synthetic products with a broad range of applications in the fine chemicals and pharmaceutical industry. Despite all the progresses made towards their synthesis, notably from *seco*-acids, a macrolactonization promoter system that is effective, selective, flexible, readily available, and, insofar as possible, compatible with manifold functional groups is still lacking. Herein, we describe an alternative strategy relying on a speculated supramolecular template to enable a convenient access to macrolactones, macrodiolides and esters with a versatility that had not been reached with classic methods.

Macrolactones are encountered in a broad range of natural products, notably marine macrolides, pharmaceuticals, cosmetics and agrochemicals.[1] They are one the foremost pillars of the flavor and fragrance industry with compounds such as Exaltolide® (Firmenich) and Musc T® (Takasago) that are prevalent in our everyday lives.[1c] In light of their industrial relevance and the challenges associated with their synthesis, the design of efficient and inventive strategies to access macrolactones has sparked relentless efforts in the synthetic community and the interest in this field is not likely to wane.[2] Though the methods devised for macrolactonizations are numerous, they remain substrate-dependent and the quest for a user-friendly system applicable to a vast array of substrates is as compelling as ever. One of the most common approaches involves the macrocyclization of *seco*-acids (Scheme 1). In the seventies, a groundbreaking discovery by Yamaguchi revealed that the stoichiometric activation of the carboxylic acid, via the formation of a mixed anhydride, could be used as a driving force to promote macrocyclizations.[3] This approach was further improved by Shiina with the development of the 2-methyl-6-nitrobenzoic anhydride (MNBA) reagent and related compounds.[4] Other classic examples based on the same concept include Corey-Nicolaou,[5] Steglich-Keck-Boden[6] and Mukaiyama macrolactonizations.[7] However, most of these methods are fraught with distinctive drawbacks that can limit their appeal. To cite but a few examples, they can require highly diluted reactions and a sophisticated slow addition procedure to prevent oligomerizations. Moreover, their use is often accompanied by the formation of several side-products, which can make the purification of the targeted product cumbersome and are potentially toxic, without forgetting to mention their cost-effectiveness as they must be used in stoichiometric amounts. Those issues might become even more critical given

Scheme 1. Approaches towards the Macrolactonization of *Seco*-acids.

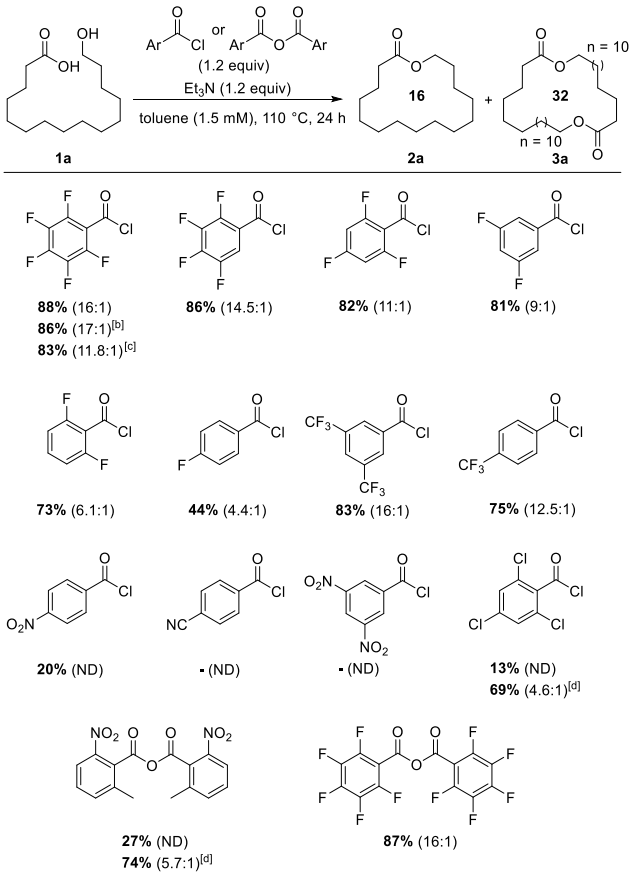


that macrolactonizations usually take place in the last steps of a total synthesis, where they are performed on a small scale and with unpredictable outcomes. To answer these various challenges, synthetic chemists have mainly focused on two alternative strategies, namely the development of catalytic systems featuring transition metals, Brønsted and Lewis acids in order to limit the formation of side products,[2h,8] and the use of pre-organized substrates relying in general on non-covalent interactions to facilitate and control the macrocyclization process.[2g] However, these variants have their own limitations, such as a narrow substrate scope or the requirement for additional synthetic steps to introduce the reactive functional groups. In this context, we wished to combine the best aspects of the various approaches to achieve a general method for macrolactonizations. Based on their respective efficacy, we reasoned that using a supramolecular template combined with the formation of a mixed anhydride featuring pentafluorobenzoyl chloride as an activating agent might allow a convenient and optimal access to macrolactones. This type of electron-poor receptor can be suitable for numerous non-covalent interactions such as π-π interactions via a charge-transfer complex and overlooked π-anion and π-lone pair (lp)

interactions.[9] The latter was particularly of interest as we hypothesized that such interaction could bring both reactive sites in close proximity, removing the need for slow reagent addition.[10-12] Surprisingly, such interactions have hardly been used in synthesis, which might be explained by the lack of understanding regarding their true nature and the controversy related to their directionality.[13] To the best of our knowledge, the only major application of those interactions was reported by Collins' group to aid the pre-organization in ring-closing metathesis.[14,15] Another major advantage of this approach would be the potential extension to less reactive and underexplored phenol derivatives via π-π interactions. Pentafluorobenzoyl chloride is also much less expensive than Yamaguchi's and Shiina's reagents, and the highly water-soluble byproduct (pentafluorobenzoic acid) can be easily removed by aqueous treatment, counterbalancing the fact that a stoichiometric amount of pentafluorobenzoyl chloride had to be used. With respect to our strategy, one might argue that, if the lone pair of the alcohol is involved in such non-covalent interactions, its nucleophilicity might be reduced, but this problem could be remedied by the excellent H-bond donating ability of pentafluorobenzoic acid that could activate the mixed anhydride[16] and favor the nucleophilic addition. Herein, we describe the development of a simple and efficient protocol to access not only macrolactones but also macrodiolides and esters from aliphatic alcohols and phenols with excellent functional group tolerance.

In our initial studies, we investigated the reactivity of **1a** to provide access to Exaltolide® (**2a**) by screening a large variety of benzoyl chlorides and benzoic anhydrides in toluene (Table 1). For practical reasons, we set the reaction time at 24 h to facilitate the comparison between the various sources of activating agent. To test our initial assumption, we employed pentafluorobenzoyl chloride as an activating agent and triethylamine as a base, which gratifyingly delivered the targeted product in an excellent yield of 88% along with a high selectivity with respect to the macrodiolide **3a** (ratio 16:1). To our delight, NMR spectra of the crude product did not show any traces of the pentafluorobenzoic acid (see the Supporting Information for details). As anticipated, reducing the number of fluorine atoms on the benzoyl chloride reagent, which should in theory weaken the interaction between the alcohol and the arene, led to a corresponding decrease in selectivity. Interestingly, 3,5-bis(trifluoromethyl)benzoyl chloride gave a selectivity similar to pentafluorobenzoyl chloride with a slightly lower yield (83%). However, the resulting benzoic acid byproduct proved not to be soluble in water, which led us to discard this option. On the other hand, in the presence of electron- withdrawing groups other than fluorine, notably with Yamaguchi's reagent, little or no product was observed, emphasizing the critical role of fluorine for smooth reactivity. Additionally, the reaction was conducted in the presence Shiina's reagent, which showed a poor outcome. Pentafluorobenzoic anhydride gave identical results as pentafluorobenzoyl chloride. A careful monitoring of the reaction allowed us to determine that the reaction was reaching its full conversion within 2 h. Moreover, the transformation could be achieved at room temperature (48 h), but at the expense of the selectivity. Of note, the macrolactonization did not require the use of a distilled solvent as neither the selectivity nor the yield were affected in these conditions. Unfortunately, we did not circumvent the high dilution, which is required to avoid a significant drop in yield because of the formation of oligomers. We also performed a large survey of bases and solvents, without success in terms of

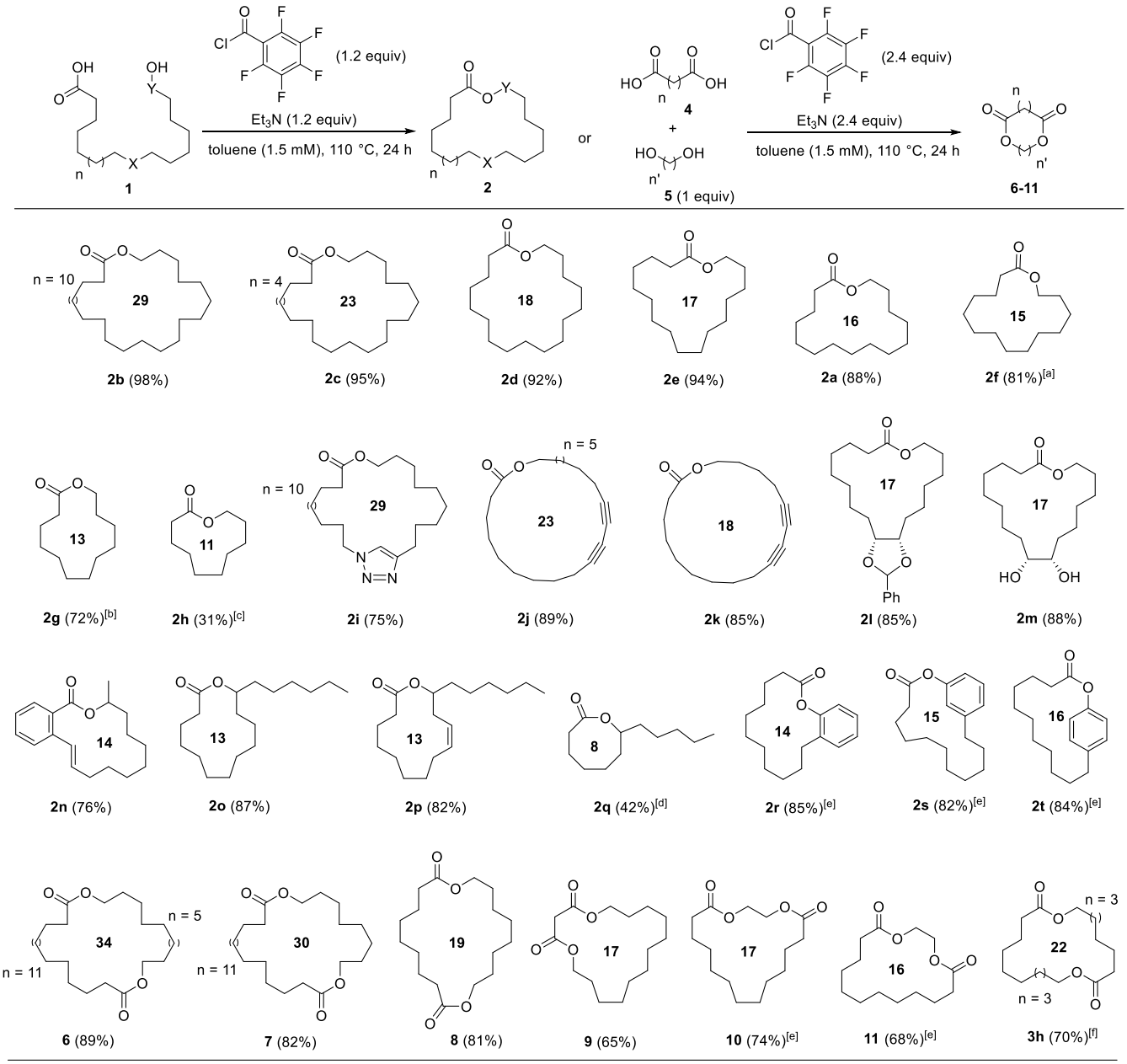
Table 1. Optimization of the Macrolactonization of **1a**.[a]



[a] The yields given are the isolated yields for **2a**. The ratios were determined by ^{1}H NMR using *para*-anisaldehyde as an external standard. [b] Reaction conducted with toluene not distilled. [c] Reaction conducted at room temperature for 48 h. [d] Reaction performed in the presence of pentafluorobenzoic acid (1 equiv).

efficiency and selectivity (see the Supporting Information for details). Predictably, the utilization of coordinating solvents (THF and MeCN), which might compete with the alcohol for the electron-poor host receptor, tends to diminish the selectivity (10.4:1 and 11.7:1, respectively). Regarding our hypothesis that pentafluorobenzoic acid could activate the mixed anhydride, we evaluated the the reactivity of Yamaguchi's and Shiina's reagents in the presence of pentafluorobenzoic acid and, while the selectivity was moderate, the conversion of the substrate to the products was no longer an issue.With these optimized conditions in hand, we began to explore the scope of the reaction using simple all-carbon linkers (**2a-2h**, Scheme 2). The macrolactonization was particularly effective for large ring sizes (from 17- to 29-membered rings **2b-2e**, yields up to 98%), without observing the formation of the corresponding macrodiolides. On the other hand, the proportion of macrodiolide increased with smaller ring sizes (**2f-2h**). While the yields remained good for 13- and 15-membered rings (72% and 81%, respectively), the ratio between macrolactone and macrodiolide attained 1 to 1 with 10-hydroxydecanoic acid **1h**, providing **2h** in a low yield of 31%. Then, we evaluated the reactivity of *seco*-acids incorporating various functional groups. In summary, the reaction proved to be compatible with triazole, strained 1,3-butadiyne, alkene and diol (protected or not) moieties to afford the targeted macrolactones in yields ranging from 65% to 89%. Using this method allowed us to access notably the framework of resorcylic lactones (**2n**) in 76% yield.[17] In addition, the reaction could be applied to secondary alcohols and even challenging 8-membered rings

Scheme 2. Reaction Scope for the Formation of Macrolactones and Macrodiolides.



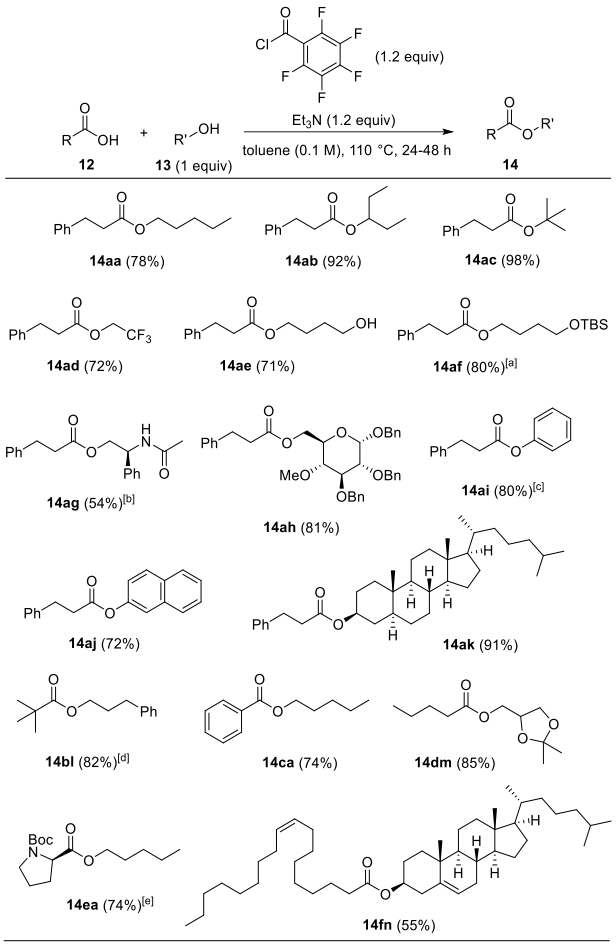
[a] Ratio macrolactone/macrodiolide 8:1 (separable by flash column chromatography). [b] Ratio macrolactone/macrodiolide 8:1 (separable by flash column chromatography). Ratio macrolactone/macrodiolide 1:1 (separable by flash column chromatography). [d] Reaction conducted at 50 °C. [e] Reaction conducted for 48 h. [f] Reaction conditions: *seco*-acid **1h** (1 equiv), pentafluorobenzoyl chloride (1.2 equiv) and triethylamine (2.4 equiv) in toluene (2 mM).

such as **2q** could be obtained in a moderate yield (42%) by employing this method.[18] Satisfactorily, the transformation was not limited to aliphatic alcohols, but could also be extended to phenols,[19] delivering the desired products, notably *meta*-and *para*-cyclophanes in good yields (82 to 85%), creating a new avenue for the synthesis of these compounds that have many applications in materials science and supramolecular chemistry.[20] Nevertheless, the reaction with phenols proved to be slower had to be carried for 48h to reach full conversion. Finally, we turned our attention to the preparation of macrodiolides, which are widespread scaffolds in medicinal chemistry.[21] Their synthesis is obviously not as trivial as the precedent case since two chemical events (esterification then macrolactonization) are involved when starting from *seco*-acids or diacids.[22] While Yamaguchi's approach is known to be incompatible with the formation of these types of compounds,[22b] we were pleased to find that 16- to 34-membered macrodiolides could be rapidly afforded in good to excellent yields (up to 89%). Besides, two compounds with major industrial applications, Musc T® and Zenolide® (**10** and **11**), could be generated in a single step within 48 h in 74% and 68% yields. Head-to-tail dimerizations are also achievable, as exemplified by **3h** (70%), provided that the concentration is slightly increased.

To further determine the potential of our method, we investigated intermolecular esterifications (Scheme 3). Once more, this procedure showcased a striking functional group tolerance. The reaction proved to be compatible with primary as well as secondary and tertiary alcohols (up to 98%). In a similar manner, primary, secondary and tertiary carboxylic acids exhibited the same efficiency. Moreover, we succeeded to

accomplish the mono-acetylation of 1,4-butanediol (**14ae**) in a good yield (71%). Even a poorly nucleophilic alcohol, trifluoroethanol, could be employed to deliver the corresponding ester **14ad** in 72% yield. Less reactive aryl alcohols such as phenol and naphthol could also be subjected to the reaction conditions to provide the desired products in 80% and 72%, respectively, in 48 h. Of note, substrates bearing acid-sensitive functional groups (TBS, Boc and acetal) were well-tolerated. Finally, compounds of interest such as amino alcohols (**14ag**), amino acids (**14ba**), carbohydrates (**14ah**), steroids (**14ak**) and fatty acids (**14em**) underwent smooth esterifications with yields ranging from 54% to 91%.

Scheme 3. Reaction Scope for Intermolecular Esterifications.



[a] The yield was determined by ^{1}H NMR using *para*-anisaldehyde as an external standard as the silyl group was cleaved on silica gel to give **14ae**. [b] Reaction conducted at 80 °C. [c] Phenol (2 equiv). [d] Alcohol **13l** (0.8 equiv). [e] Alcohol **13a** (1.5 equiv).

In summary, we have discovered an efficient and user-friendly protocol to achieve macrolactonizations of interest to a variety of applications in our society. This transformation, which featured the formation of a mixed anhydride based on the utilization of an inexpensive activating agent (pentafluorobenzoyl chloride), displayed a remarkable efficacy and functional group versatility, while overcoming most of the common limitations associated with such processes. For instance, this unique method could be equally applied to intramolecular macrolactonizations of *seco*-acids or to the intermolecular formation of macrodiolides and even esters. Mechanistic investigations to shed light on its function are on-going and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/

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Notes

The authors declare no competing financial interests.

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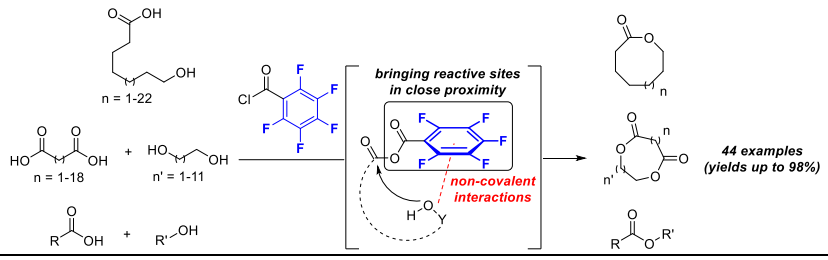
n = 1-22
n = 1-18
n' = 1-11
bringing reactive sites
in close proximity
non-covalent
interactions
44 examples
(yields up to 98%)