TRANSFORMATIONS OF OXYGEN FUNCTIONAL GROUPS IN ORGANIC MOLECULES MEDIATED BY MOLECULAR IODINE OR/AND *N*-HALO COMPOUNDS

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Doctoral Dissertation
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PRETVORBE KISIKOVIH FUNKCIONALNIH SKUPIN V ORGANSKIH MOLEKULAH OB PRISOTNOSTI MOLEKULARNEGA JODA ALI/IN *N*-HALO SPOJIN

Doktorska disertacija

Supervisor: Prof. Dr. Stojan Stavber

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Not everything that can be counted counts, and not everything that counts can be counted.
– Dr. Albert Einstein

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Abstract

The increasing demand for the sustainable world and consequently for environmentally friendlier technology in the last decades is a driving force towards the exploration of greener methodologies in the field of organic chemistry. In this context, the purpose of this dissertation lays in the development of effective and metal-free catalytic approaches for significant and established reactions, such as dehydrative C—C coupling, esterification and aldol condensation. Accordingly, the goal of the presented research was to explore and exploit the capabilities of certain halogen compounds as metal-free mediators in transformations of some oxygen functional groups in organic molecules.

Firstly, a method for direct dehydrative C–C coupling between benzylic alcohols and phenyl-substituted alkenes was developed, using molecular iodine as an ecologically acceptable metal-free catalyst, which presumably acts as a Lewis acid. The method allows solvent-free reaction conditions as well as the scale-up, furnishing polysubstituted olefins in high yields and thereby confirming the synthetic applicability of the presented methodology. Furthermore, the reaction pathway was proposed, suggesting the involvement of a carbocation intermediate. Finally, the possibility of the direct coupling between tertiary and secondary benzyl alcohols was examined and confirmed.

Further on, methodology for direct esterification of carboxylic acids and alcohols was developed, using a convenient, easily-handled, low-priced bench-top mediator – *N*-bromosuccinimide (NBS). The approach includes mild neat reaction conditions and relatively low temperatures (70 °C), providing comprehensive esterification of substituted benzoic acids as well as of mono-, di- and tri-carboxy alkyl derivatives. In addition, the efficacy of the method was elaborated also on more complex structural backbones of bile acids, such as cholic acid and dehydrocholic acid. The method is metal-free and proved to be air- and moisture-tolerant, allowing for a simple synthetic and isolation procedure as well as for the scale-up of aromatic and alkyl esters with yields up to 100%. In addition, a protocol for the catalyst recycling has been suggested.

Finally, the esterification protocol was furtherly upgraded by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a widely available, inexpensive, and metal-free precatalyst. The method allows the use of an even broader scope of carboxylic acids than the *N*-bromosuccinimide mediator, while maintaining all other advantages of the NBS-mediated reaction system. Moreover, the reaction pathway for esterification was proposed and a scale-up of certain industrially important derivatives performed. Lastly, to show a general ability of DBDMH acting as the activator of the carbonyl functionality, the methodology was expanded also on the aldol condensation of aldehydes.

Povzetek

V zadnjih desetletjih je naraščajoče povpraševanje po trajnostnem svetu in posledično po okolju prijaznejših tehnologijah postalo gonilna sila za razvoj zelenih metodologij na področju organske kemije. V tem kontekstu je bil namen disertacije razviti učinkovite in nekovinske katalitske pristope za pomembne in uveljavljene transformacije, kot so dehidracijsko pripajanje s tvorbo nove vezi ogljik–ogljik, esterifikacija in aldolna kondenzacija, cilj predstavljene raziskave pa je bil preučiti in izkoristiti možnosti uporabe določenih halogenskih spojin v vlogi nekovinskih mediatorjev pri transformacijah nekaterih kisikovih funkcionalnih skupin v organskih molekulah.

V prvem koraku sem razvila metodo za direktno dehidracijsko pripajanje benzilnih alkoholov in fenil-substituiranih alkenov, ki vključuje uporabo molekularnega joda kot ekološko sprejemljivega nekovinskega katalizatorja, ki najverjetneje deluje kot Lewisova kislina. Razvit sistem omogoča vodenje reakcij pod reakcijskimi pogoji brez uporabe topil, poleg tega pa omogoča sintezo polisubstituiranih olefinov v visokih izkoristkih in s tem potrjuje sintetsko uporabnost predstavljene metodologije. V nadaljevanju smo predlagali reakcijsko pot, ki predvideva nastanek karbokationskega intermediata, preučili in potrdili pa smo tudi možnost neposrednega spajanja med terciarnimi in sekundarnimi benzilnimi alkoholi.

V nadaljevanju sem predstavila novo metodo direktne kondenzacije karboksilnih kislin in alkoholov v prisotnosti *N*-bromosukcinimida (NBS) - priročnega in cenovno ugodnega mediatorja, ki omogoča enostavno rokovanje. Pristop vključuje mile reakcijske pogoje in relativno nizke temperature (70 °C) ter nudi možnosti esterifikacije širokega spektra substituiranih benzojskih kislin ter mono-, di- in trikarboksi alkil derivatov. Učinkovitost metode sem poleg tega prikazala tudi na kompleksnejših strukturnih ogrodjih žolčnih kislin, kot sta npr. holna in dehidroholna kislina. Metoda ne vključuje uporabe kovin in je tolerantna na zrak ter vlago, poleg tega pa omogoča enostaven postopek sinteze in izolacije ter pripravo aromatskih kot tudi alkilnih estrov na večji skali z izkoristki do 100%. Predlagan je tudi postopek reciklaže mediatorja.

V zadnjem delu sem metodo esterifikacije nadgradila z uporabo širše dostopnega ter cenovno ugodnejšega nekovinskega prekatalizatorja 1,3-dibromo-5,5-dimetilhidantoina (DBDMH), ki v primerjavi z *N*-bromosukcinimidom omogoča esterifikacijo širšega nabora karboksilnih kislin, pri tem pa ohranja vse prednosti reakcijskega sistema z uporabo NBS. Sintezo nekaterih industrijsko pomembnih derivatov sem nato izvedla tudi na večji skali ter podala predlog reakcijskega mehanizma. Na samem koncu sem metodologijo razširila še na aldolno kondenzacijo aldehidov z namenom, da bi s tem pokazala, da DBDMH lahko deluje kot splošen aktivator karbonilne skupine.

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Abbreviations

BC	Before Christ
BOP	(Benzotriazole-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate
CDI	carbonyldiimidazole
CSA	10-Camphorsulfonic acid
DBDMH	1,3-dibromo-5,5-dimethylhydantoin
DBSA	*p*-dodecylbenzenesulfonic acid
DCC	*N,N'*-dicyclohexylcarbodiimide
DFT	Density functional theory
DME	1,2-Dimethoxyethane
DMSO	Dimethyl sulfoxide
DMT-MM	(4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DPAT	Diphenylammonium triflate
ESI	Electrospray ionization
GDP	Gross domestic product
GGA	Generalized gradient approximation
HCRC	Highly concentrated reaction conditions
HR-MS	High Resolution Mass Spectroscopy
IBX	2-iodoxybenzoic acid
IUPAC	International Union of Pure and Applied Chemistry
LB	Lewis base
LDA	Lithium diisopropylamide
LICA	Lithium N-isopropylcyclohexylamide
LIHMDS	Lithium hexamethyldisilazane
LITMP	Lithium 2,2,6,6-tetramethylpiperidide
NBS	*N*-bromosuccinimide
n-BuLi	*n*-Butyllithium
NIS	*N*-iodosuccinimide
NISac	*N*-iodisaccharin
NMR	Nuclear magnetic resonance
NXSs	*N*-halosuccinimides
PAFR	Phenolsulfonic acid formaldehyde resin
PAW	Projector-augmented-wave
PBE	Perdew-Burke-Ernzerhof
PFPAT	Pentafluorophenylammonium triflate
SFRC	Solvent-free reaction conditions
TfOH	Trifluoromethanesulfonic acid
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
TsOH	*p*-toluenesulfonic acid
US-PP	Ultra-Soft Pseudopotential

UV/VIS . . . Ultraviolet-visible spectroscopy
XB . . . Halogen bond

Chapter 1

Introduction

1.1 Definition of the Problem

From the early beginnings around 1000 BC, civilizations have used technologies to raise the quality of life by extracting metals from ores, making pottery and glazes, rendering fat into soap, fermenting beer and wine, extracting chemicals from plants for medicine and perfume, making glass and making alloys like bronze and brass. Nowadays, as the world population is growing toward 8 billion, there is an ever-increasing demand for better food and agrochemicals, better materials, higher amount of medicines and fuel, more manufactured goods, such as clothes and machinery, and last but not least, better access to clean water and fresh air. The progress and development of science, including chemistry, has been encouraged by these needs for the last 200 years and has taken the path of creativity, innovation and discovery. Nonetheless, chemists have followed this path without fully understanding the impacts of chemicals on human health and the environment. Therefore, they have not entirely predicted the consequences of their creations, discoveries and methods or processes they have used to get to these innovations. In recent years, while the knowledge expanded significantly, providing us with understanding of the aftereffects on the molecular level, the growing environmental awareness pushed chemists to question their practice and led them to conscious minimization of the consequences by following the green chemistry principles [1]. The 12 principles were defined in 1998 by Paul T. Anastas [2] and represent the heart of green chemistry's *modus operandi* [3]:

1. waste prevention instead of remediation
2. atom efficiency
3. less hazardous/toxic chemicals
4. safer products by design
5. innocuous solvents and auxiliaries
6. energy efficiency by design
7. preferably renewable materials
8. shorter synthesis – avoiding derivatization
9. catalytic rather than stoichiometric reagents
10. designing products for degradation
11. analytical methodologies for pollution prevention
12. inherently safer processes.

The increasing acceptance of green chemistry in academic and industrial community over the last decades has been resulting in a movement to design a safer, healthier and more sustainable world [4]. On September 25th, 2015, United Nations adopted a set of 17 goals to end poverty, protect the planet and ensure prosperity for all as part of a new sustainable development agenda. The goals and targets will stimulate action over the next fifteen years in areas of critical importance for humanity and environment [5]. In this context, the discovery and development of chemical transformations and catalysis that will not be harmful to the environment will play an increasingly important role in sustainable development of organic chemistry.

1.2 Catalysis

A key purpose of green chemistry is the minimization or preferably the elimination of waste in the manufacture of chemicals and associated products with the motto: "prevention is better than cure". This calls for a change of paradigm in the concept of efficiency in organic synthesis from one that is focused on yield to waste minimization [3]. Together with the rise of green chemistry in the last two decades, *catalysis* has been intensely applied in pharmaceutical and fine chemical industries with the aim of minimizing the enormous amounts of waste generated by the use of stoichiometric inorganic reagents. Catalysts are used in 80% of all chemical industrial processes, and create annual global sales of about 1500 billion dollars, contributing directly or indirectly to approximately 35% of the world's GDP [6]. The term *catalyst* is defined as a substance that changes the velocity of a reaction without itself being changed in the process. It lowers the activation energy of the reaction but in doing so it remains unaltered. This means that in principle at least, it can be used in small quantities and reused indefinitely, so that in net effect it does not generate any waste material.

Catalysis depends on changes in the reaction *kinetics*. While thermodynamics works as a signpost to show the way to the most stable products, the kinetics determines the relative rates of the many competitive pathways available for the reactants. By lowering the activation energy, catalysts open alternative mechanistic routes with lower activation energy barriers than those of the noncatalyzed reactions and can therefore be exploited to make metastable products from catalytic processes in a fast and selective way. Due to the availability of new pathways, catalyzed reactions can be conducted at much faster rates and lower temperatures than noncatalyzed reactions. However, a catalyst can only *shorten the time* needed to achieve thermodynamic equilibrium, but cannot shift the position of that equilibrium and therefore cannot catalyze a thermodynamically unfavorable reaction [7].

Depending on whether the catalysts are in the same physical phase as the substrate or not, we can divide them into two major groups: homogeneous and heterogeneous catalysts [8]. Enzymes are usually considered as a third group, but can be viewed as a special kind of the heterogeneous catalysis. In *heterogeneous catalysis* the phase of the catalyst differs from the phase of the reactants and the catalysis typically takes place on the surface of the catalyst. The key step in this type of catalysis is the process of *adsorption*, by which a reactant (gas or solution) binds to the surface of the catalyst (solid or liquid). The majority of heterogeneous catalysts are in the solid phase and since only specific locations on their surface (*active sites)* exhibit catalytic activity, the larger surface area-to-mass ratio of the catalyst results in higher reaction rates. This ratio can be expressed by the specific surface area [m^2/g], which is defined as the total surface area of a material per unit of mass. Increasing the specific surface area of a catalyst can be attained by high material porosity or by reducing the particle size to nanoscale. Since heterogeneous catalysts are in a different

phase than the reaction mixture, they can usually easily be separated from the reactants and products and recycled for their further use. From an industrial perspective this is an important property, as heterogeneous catalysts are usually expensive (noble metals) and biotoxic [9].

Homogeneous catalysts are generally relatively small molecules that are dissolved in the same solution as the reactants and products. The significant advantages of homogenous catalysis over heterogeneous catalysis are high diffusivity and heat transfer under proper stirring, as all reactants and catalysts are in one phase. In heterogeneous catalysis, diffusivity might be an issue for catalysts with a low surface area, while heat transfer might be problematic due to the different heat capacities of reactants and catalysts. Moreover, molecular catalysts are often easier to study, since the active sites on the catalytic molecules are usually well-defined and can be synthesized or modified with atomic-scale accuracy. Due to the easier fine-tuning of the steric and electronic properties of the homogenous catalyst and easier mechanism studies, the selectivity is generally also higher relative to heterogeneous catalysis. However, while the only limitation regarding the operation temperature in heterogeneous catalysis is posed by catalyst stability under harsh conditions, the homogeneous catalysis usually requires lower temperatures due to the presence of a solvent, except if a reaction is carried out under high pressure. In such cases, the temperature height is limited by catalyst stability [1].

1.2.1 Molecular Iodine

As one of the members in halogen group, iodine is an important micronutrient element, essential for growth of humans and animals. The goiter-preventing effects of seaweeds due to the iodine content were known to the legendary Chinese emperor Shen-Nung as early as around 3000 BC. Nevertheless, iodine was not officially recognized as a new element until the nineteenth century in the time of Napoleonic wars, when the British Royal Navy blocked the ports and the import of raw materials for gunpowder to France was suddenly hampered. French chemists were therefore looking for alternative sources of potassium nitrate which served as an oxidant. In 1811, Bernard Courtois, French chemist born to a manufacturer of saltpetre (potassium nitrate), accidentally extracted the ashes of brown algae *Laminaria* with excessive amount of concentrated sulfuric acid resulting in the formation of a vapour with a blue-violet colour, after which iodine was named [10].

Molecular iodine (I_2) is an easy-to-handle solid, soluble in many organic solvents and 16% of it is utilized in industrial catalysis. Unlike the heavy metals, iodine is an environmentally friendly and a relatively inexpensive element (in the last 10 years its bulk price was 20–100 $/kg, which is orders of magnitude cheaper than Pt, Pd or Os) [11]. Because it possesses an oxidative as well as a weak electrophilic character it can be used as an antiseptic and deodorant, but at the same time it is also employed both as a stoichiometric reagent and as a catalyst [11-18] in numerous organic transformations [19, 20]. It is water-tolerant and exhibits high catalytic activity in dilute solutions, under highly concentrated reaction conditions (HCRC) as well as under solvent-free reaction conditions (SFRC). SFRC are particularly important and appreciated from the green-chemical standpoint, as they contribute to waste minimization, cost efficiency and reduction of heath-risks [21].

While molecular iodine is soluble in many organic solvents, it is only slightly soluble in water. However, in the presence of dissolved iodides, solubility in water may be significantly increased due to the formation of triiodide ions (I_3^-) [12]. Another of the iodine remarkable features is the formation of polyiodides, which assemble when iodine associates with iodides or triiodides [22]. In addition to polyiodides, iodine is also capable of complexing oxygen

functional groups [12] and this distinctive property inspired our methodology of iodine-catalysed dehydrative condensation of alcohols and alkenes, presented in Chapter 3.

1.2.1.1 Iodine and Halogen Bond

Since halogen-bond donation has successfully been applied in different chemistry areas in the last few years, iodine has once again recurred as a promising catalyst in organic synthesis. It is assumed that this noncovalent interaction could also be accounted for the catalytic effect of molecular iodine.

The noncovalent interactions given by halogen atoms in haloorganic compounds can be divided into two main groups. In the first group, the halogen atoms act as electron density donor sites (*Lewis base*) toward electron-deficient partners as hydrogen atoms or metal cations. This interaction can be easily understood in terms of the high electronegativity of halogen atoms resulting in a high electron density at their surface. In the second class, halogen atoms act as electron density acceptor sites (*Lewis acid*) and attractively interact with electron donors. This latter interaction is known as the *halogen bond* (XB) [23]. According to the International Union of Pure and Applied Chemistry (IUPAC), a halogen bond occurs, when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity [24].

At first sight, the halogen bonding phenomenon may be puzzling, since halogen atoms themselves are usually viewed as having partial negative charges. The contradiction of them giving noncovalent interactions with a negative portion of another molecule can be rationalized by the presence of a region of positive electrostatic potential, the so-called σ-hole [25], on the outermost portion of the halogen surface, centred on the R—X axis. The atomic radius along the covalent bond is smaller than in the perpendicular direction as an outcome of this anisotropic distribution of the electron density. Accordingly, halogen atoms have a double character. When they interact with electron density acceptor sites through electron density donation from their nonbonding orbitals (negative belt), they act as Lewis bases. When they accept electron density into the σ hole from Lewis bases, they act as Lewis acids (Figure 1.1) [10].

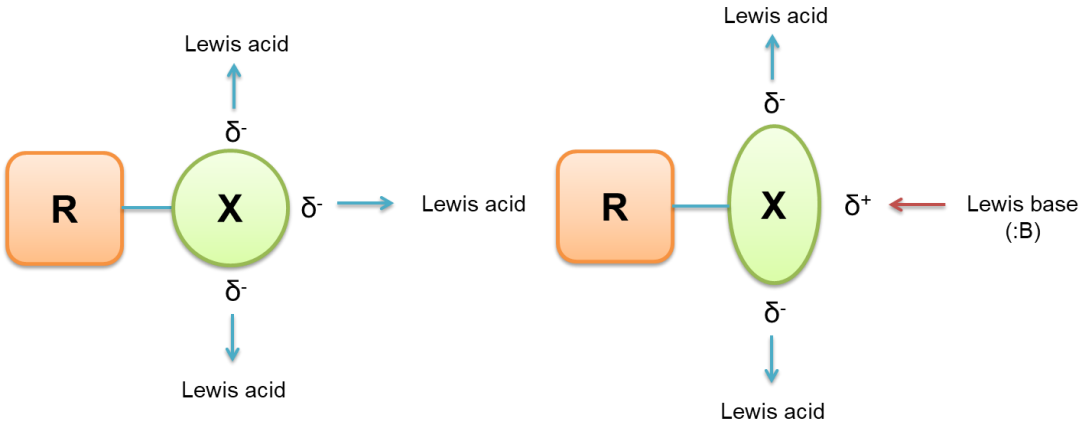


Figure 1.1: Illustration of the covalent R–X bond, the electron density distribution on the X atom and the resulting attractive interaction with Lewis acids and Lewis bases [10].

Halogen bonding can also be depicted as presented in Figure 1.2, where :B is the Lewis base (B = N, O, S, Se, … or I^-, Br^-, Cl^-, F^- …). X is a halogen atom, which can be part of a dihalogen, e.g. Cl_2, Br_2, I_2, or it may be a substituent on some other molecule, often

organic (R = C, Halogen, N …). The strength of the interaction increases with the polarizability of X going from chlorine to bromine to iodine [26]. Fluorine atom can work as a halogen donor only when attached to particularly strong electron-withdrawing groups [27]. Well known electrophilic fluorinating reagents $CF_3C(O)OF$ and $(CF_3SO_2)_2NF$ are very typical examples. If the electron-withdrawing group is sufficiently strong, then there may even be no negative belt on its lateral sides, as there is in F_2. Instead it may have a positive electrostatic potential on its entire surface [27]. The attractive nature of XB results in shortening of the interatomic distance of participating atoms (X and B) for 35–10% relative to the sum of van der Waals radii of involved atoms, while the R—X covalent bond is elongated. The stronger the interaction, the shorter the X···B distance and closer to 180° the angle between the covalent and noncovalent bonds in the R—X···B system [10].

Figure 1.2: Schematic depiction of halogen bonding.

Both n and π electrons can be involved in XB formation and usually the latter give weaker interactions than the former due to the minor localization of electron density in π clouds compared to lone pairs. Increased electron density on the donor site results in stronger interactions; therefore, anions are usually better XB acceptors than neutral species. The XB interaction energies range from 5-180 kJ/mol, from the weak Cl···Cl interaction between chlorocarbons to the extremely strong $I^-\cdots I_2$ interaction in I_3^- [28]. Iodine is a better halogen bonding donor than lighter halogens, its electron density acceptor ability increases with the increased electron-withdrawing ability of the atom bound to it. The general order is X—I > C(sp)—I > C(sp^2)—I > C(sp^3)—I (X=halogen) [10].

Halogen bond is similar to hydrogen bond, the main similarity being the role of the positive site (electron density acceptor, Lewis acid, electrophile) played by the halogen and hydrogen atoms, respectively; the inherent difference is that atoms of the XVII and I groups are involved. XB can be in fact considered as a hydrophobic analogue of HB as halogen-bonded adducts are, in nearly all cases, much more lipophilic than the structurally analogous corresponding hydrogen-bonded adducts [29, 30]. Halogen-bonding based on neutral fluorinated Lewis acids in particular may be considered as a *hydrophobic "sister interaction" to hydrogen bonding* [31, 32]. This hydrophobic character may be significant for certain targeted applications of noncovalent interactions, which are based on low polarity, e.g. their use in very apolar solvents. Besides hydrophobicity, halogen bond features high *directionality* of the interaction, resulting in bond angle R–X · · · LB ≈ 180° because at more obtuse angles the repulsion between the lone pair electrons of the halogen and that of the Lewis base occurs [29, 33, 34].

The next difference is *tunability*, which is considerably broader in case of halogen bonding relative to hydrogen-bonding, since four different halogen atom types are available: F, Cl, Br and I. As already mentioned, each of them forms halogen bonds of different strength, which allows design of the Lewis acid relative to its purpose or specific application needs. In most cases, strong halogen bonding is desired, and thus iodine-based halogen-bond donors are mainly used, but sometimes a better match of orbital sizes with the substrate molecule may be needed, which can be tuned by choosing the appropriate halogen atom type [30]. Moreover, lighter halogens are also sterically less demanding and this can sometimes be essential whether a bioactive compound would fit into the protein binding site or not. Also, the halogen-bond strength may be tuned by changing the electronegativity [29, 33] and polarizability [34] of the substituent R. Generally, an increased electronegativity will result in stronger Lewis acidity.

The third difference lays in *the electronic nature of the interacting atom* [30]. As hydrogen and iodine lay on the opposite sides of the periodic system, their orbital size and softness is inherently different. Consequently, hydrogen-bonding and halogen-bonding are suitable for different groups of Lewis bases. For example, halogen-bonding-based receptors bind with bromide, iodide and also chloride anion, but it exhibits minimal interaction with *p*-toluenesulfonate, nitrate, and bisulfate. On the other hand, analogous hydrogen-bonding-based receptors make measurable interaction with such oxoanions [35]. In addition, unlike in the case of hydrogen-bonding, halogen-bonding adducts feature low solvent dependency [36].

Halogen bonds are a key factor in crystal engineering for the preparation of porous materials as well as in design of solid-state materials with desired optical, conducting and magnetic properties [29]. Besides, XB are also crucial in preparation of supramolecular soft matters (halogen bonded liquid crystals, polymers, gels) and nanomaterials. In solar cell technology XB help to prevent the undesired charge accumulation on the perovskite surface, thereby improving the solar cell performance. In addition, halogen bonds are important in drug design, since they may be decisive, whether the drug will activate/deactivate the enzyme because of their attractive interaction or not. Bearing in mind the analogies between hydrogen bonds and halogen bonds, many researches started to investigate the possibility to use XB donor molecules in organic catalysis. However, it soon became clear that the main advantages of XB bonding may in fact lay rather in its distinctive nature relative to hydrogen bonding: directionality, tunability, hydrophobicity and variable size of the donor atom [29].

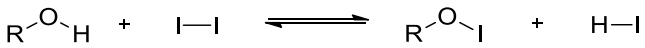
Considering all this, iodine has all the characteristics to act as a very good halogen bond donor. Many contributions have been published, using iodine as an accelerator of organic reactions [11]. Although many of them imply that Lewis acidity is the cause of the iodine catalytic activity, the exact modes of action of I_2 are still not completely understood.

1.2.1.2 Mechanisms in Iodine Catalysis

Notwithstanding the importance of iodine as a catalyst in organic synthesis, the exact mode of action is still not completely understood, as mentioned above, and the nature of the actual catalytic species in iodine-catalysed reactions is therefore still under discussion, especially for the reactions, performed in the presence of protic solvents [12]. In general, three different mechanistic models have been proposed with the aim of explaining the catalytic effect of molecular iodine [37]:

1. *"Hidden" Brønsted acid catalysis by HI*

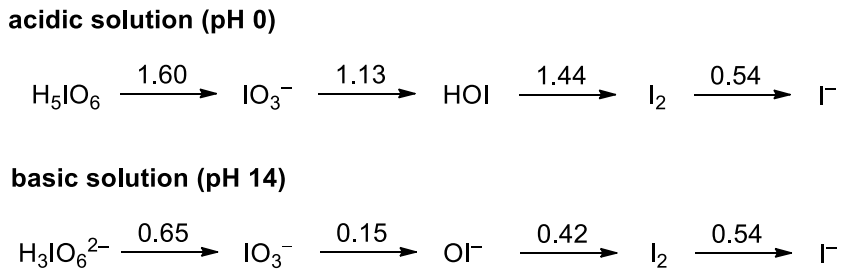
Catalytic effect of molecular iodine may be attributed to a decomposition of the precatalyst I_2 and the formation of HI in aqueous or alcoholic reaction media, as shown in Equation 1.1 [37].



(1.1)

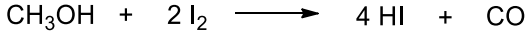
According to the Latimer diagrams (Scheme 1.1), in *basic* aqueous solutions iodine readily disproportionates to iodide and hypoiodite as well as other iodine–oxygen species [38], while in acidic solutions around pH 0, iodine is stable against disproportionation. For neutral solutions around pH 7, which are probably closest to most experimental conditions, where iodine is used in substoichiometric amounts in the absence of any other additive, a very unfavorable equilibrium constant of 2.0×10^{-13} has been determined for the reaction between water and iodine (Equation 1.1, R=H) [39]. HI is the most acidic decomposition species of molecular iodine and is thereby typically considered as the hidden Brønsted acid catalyst [19]. Among the different acids that could be formed in these decomposition

reactions and subsequent reactions of the intermediates, HI should be by far the strongest acid in aqueous solution [39]: pKa(HI) ≈ −10 [40], pKa(HOI)=+10.6 [41], pKa(HIO_3) ≈ +0.2 [42], and pKa(H_5IO_6)=+3.3 [43]. Water is typically only present in very small concentrations as an impurity in dried solvents. Together with the unfavorable thermodynamics of the reaction, this renders an aqueous decomposition by traces of water less probable explanation of the catalytic effect, even though some cases are known in which hypoiodic acid acts as the active catalyst [44-46].



Scheme 1.1: Latimer diagrams, summarizing the standard potentials (in V) for iodine at pH 0 and 14.

However, similar reactions could be taken into consideration, when iodine is mixed with alcohols instead of water (Equation 1.1, R ≠ H). The intermediate organic hypoiodides are generally unstable and are prone to subsequent conversion into the corresponding carbonyl compounds [47-49]. An alternative explanation of HI formation is a slow reaction of iodine with methanol in the gas phase to form HI and CO (Equation 1.2) [50]. Based on this, HI catalysis is often suggested, when alcohol solutions of iodine are used [19, 51-54]. However, as theoretically every other nucleophile could also release HI by attacking molecular iodine in nucleophilic substitution reaction, this makes mechanism disposition even more complex.



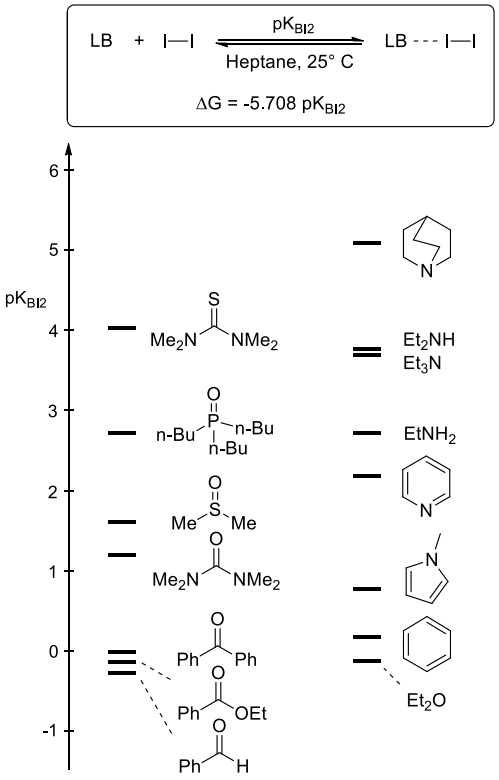
(1.2)

2. Lewis acid/halogen-bond catalysis by iodine

The first report on the halogen bond involving iodine molecule is mentioned already in 1863, when Guthrie confirmed the 1:1 stoichiometry of the $NH_3\cdots I_2$ complex, previously discovered by Colin in 1814 [55]. Its crystal structure implies a shortened N–I (2.27 Å) and elongated I–I (2.83 Å) bond [56], which strongly suggests an attractive interaction between the dihalogen (iodine) and the Lewis base (NH_3). Almost 100 years after Guthrie confirmed the $NH_3\cdots I_2$ complex [57], the association constants (K_a) between I_2 and arenes were obtained along with quantum mechanical studies of these interactions which set the fundamentals for all experimental and theoretical studies that have been performed in the following years.

The distinctive characteristic of iodine of making different colors in various solvents is also known from as early as 1890s (for instance, purple in CCl_4 or $CHCl_3$, red in benzene or toluene, and brown in alcohols and ethers). As a result of the numerous investigations and reports of such iodine complexation with different organic molecules, many association constants have been determined for combining iodine with different Lewis bases [58, 59]. These values provided a foundation for a comprehensive Lewis basicity scale, which includes a plethora of complexation reactions of molecular iodine with Lewis bases [60, 61]. These complexes generally exhibit relatively weak interactions (for typical organic electrophiles such as aldehydes, esters, or ketones around 0–5 $kJmol^{-1}$, which corresponds to $0<pK_{BI2}<1$), which might in spite of that be sufficiently strong for the exhibition of the catalytic effect; however, there are also some examples of stronger interactions, where

pK_{BI2}=5.22 and $\Delta G = -29.8$ kJmol^{-1}, such as for example in case of quinuclidine (Scheme 1.2) [60]. As a result of iodine halogen-bond characteristics and since many Lewis acids are generally proved to be effective catalysts for a variety of iodine-catalyzed transformations, halogen-bond phenomenon can be considered as a possible justification of iodine catalytic properties.



Scheme 1.2: Graphical representation of pK_{BI2} values for selected Lewis bases in heptane [37, 62].

3. Catalysis by iodonium (I^+) ions

The reason for iodine catalysis may also reside in splitting of the iodine-iodine bond, which can be either homolytic or heterolytic. Homolytic cleavage could take place under oxidative conditions, for example in the presence of oxygen or organic peroxides, while heterolytic cleavage requires the presence of Lewis bases. In the absence of strong Lewis bases, the heterolytic cleavage is highly unlikely (K = 1.8 x $10^{-10,}$ Equation 1.3) and even though the K for formation of I^+ and polyhalogen I^{3-} is considerably higher (Equation 1.4), the reaction is thermodynamically still very unfavorable [63, 64].

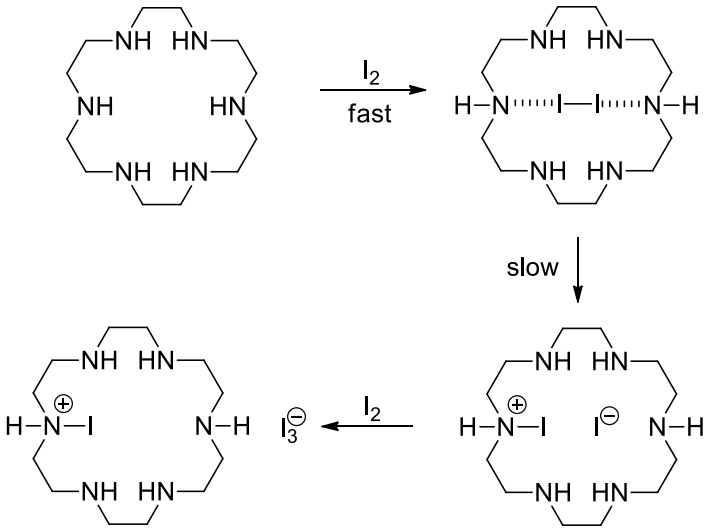
$$I_2 \underset{}{\overset{K = 1.8 \times 10^{-10}}{\rightleftharpoons}} I^{\oplus} + I^{\ominus} \qquad (1.3)$$

$$2\,I_2 \underset{}{\overset{K = 1.8 \times 10^{-5}}{\rightleftharpoons}} I^{\oplus} + I_3^{\ominus} \qquad (1.4)$$

On the contrary, excessive amounts of Lewis base in polar solvents can result in splitting of the I–I bond and formation of charged particles [65-68], including polyhalogen ions, well-known species, which find use in various chemical fields. However, since in the context of development of green methodologies iodine is often used as a mild, environmentally friendly

catalyst without the need of an inert atmosphere [12, 13, 19, 69-71], the impact of air oxygen is usually not inspected, which makes a homolytic cleavage of I–I bond another alternative as a possible cause of iodine catalytic activity [72-77].

An experimental investigation of iodine splitting has been performed with macrocyclic crown ethers [78-83]. In the case of cyclic ethers, such as 18-crown-6, stable halogen-bonded complexes with iodine were formed (ΔG=–5 kJmol^{-1}), but in the case of analogous aza-derivatives, the scenario is more complicated, as firstly, halogen-bonded complex is formed rapidly, which is followed by a slower cleavage of iodine-iodine bond, yielding I_3^- anion, which could be detected by UV/VIS spectroscopy (Scheme 1.3) [82]. Experimentally determined activation parameters enable calculation of an activation free energy of 90–100 kJmol^{-1} for I–I bond splitting at 258 °C.



Scheme 1.3: Iodine splitting in the case of aza-18-crown-6 [37, 82].

In the same way *N*-iodoimides promote such an effect in the solid state, where halogen-bonded cocrystal transforms into charged particles [84]. While complexation of *N*-iodosuccinimide (NIS) and dimethylaminopyridine (Py-NMe$_2$) results in a cocrystal with a "close-to-neutral" structure, analogous complex with *N*-iodosaccharin (NISac) gives a "close-to-ionic"structure − salt. It was demonstrated that the solid state organization within the crystal structure plays a crucial role in the actual charge delocalization within these systems and that the crystalline environment exhibits a strong influence on the position of iodine atom (Figure 1.3).

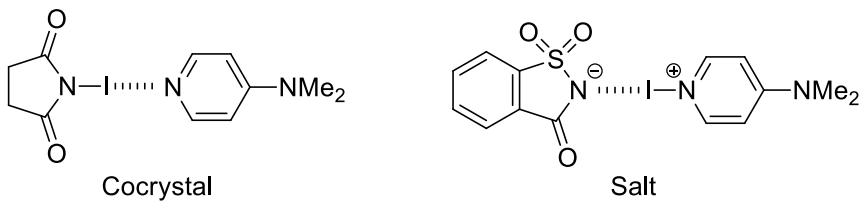
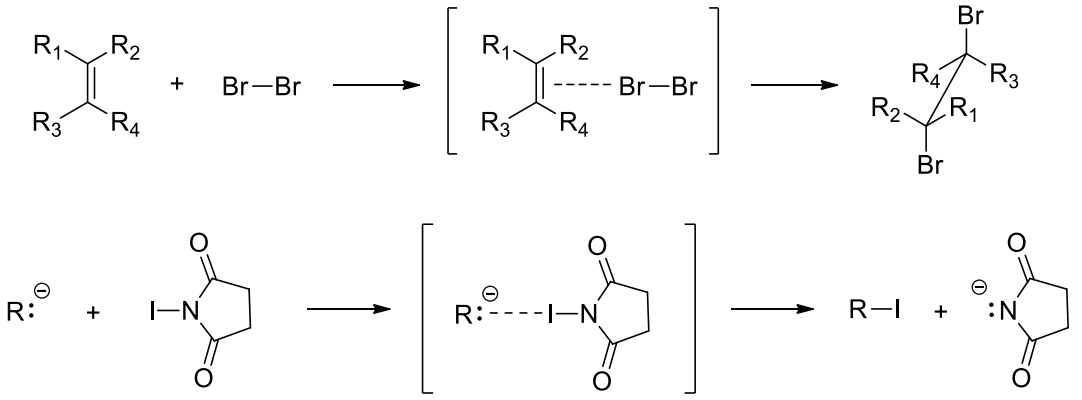


Figure 1.3: Illustration of the difference between the cocrystal structure in the complex NIS • Py-NMe$_2$ (left) and salt structure in the complex NISac • Py-NMe$_2$ [84].

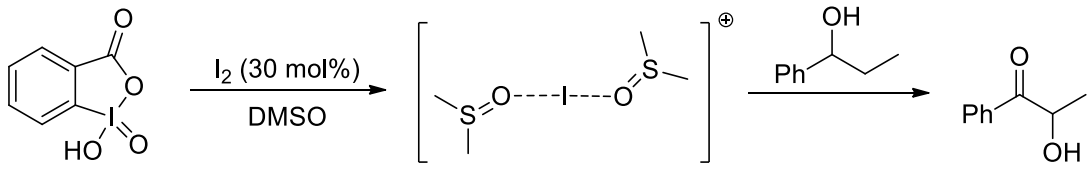
In general, if the interaction between Lewis base (LB) and R−X reaches a certain critical strength, halonium (X^+) transfer will take place, with the R−X bond being broken and a new X−LB bond being formed. In this case, the halogen-bonding adduct is not a stable thermodynamic minimum, but rather a prereactive complex. Like the majority of

noncovalent interactions, halogen bonding may therefore also be interpreted as the "frozen" transition state of covalent bond formation (and cleavage) [30]. Since the official definition of halogen bonding does not define the necessity of stability of the halogen-bonding adduct, the reactions with halonium transfer may be regarded to take place *via* the so-called "transient" or non-stationary halogen-bonding. Two typical examples of such halogenation reactions are the bromination of alkenes and iodination of substrates with *N*-iodosuccinimide (Scheme 1.4).



Scheme 1.4: Bromination of alkenes and iodination with NIS as general examples of transient halogen-bonding [85].

Beside the regular use of halogen(I) compounds as electrophilic stoichiometric reagents, iodonium ions have lately been proposed as the active catalytic species in the oxidation of secondary alcohols in the presence of catalytic amounts of iodine and stoichiometric amounts of 2-iodoxybenzoic acid (IBX) in DMSO (Scheme 1.5) [85]. The above discussed iodine splitting in the presence of Lewis bases together with the numerous applications of iodine (I) compounds in organic transformations suggest the catalysis by iodonium ions as another alternative for the molecular iodine catalytic behavior.



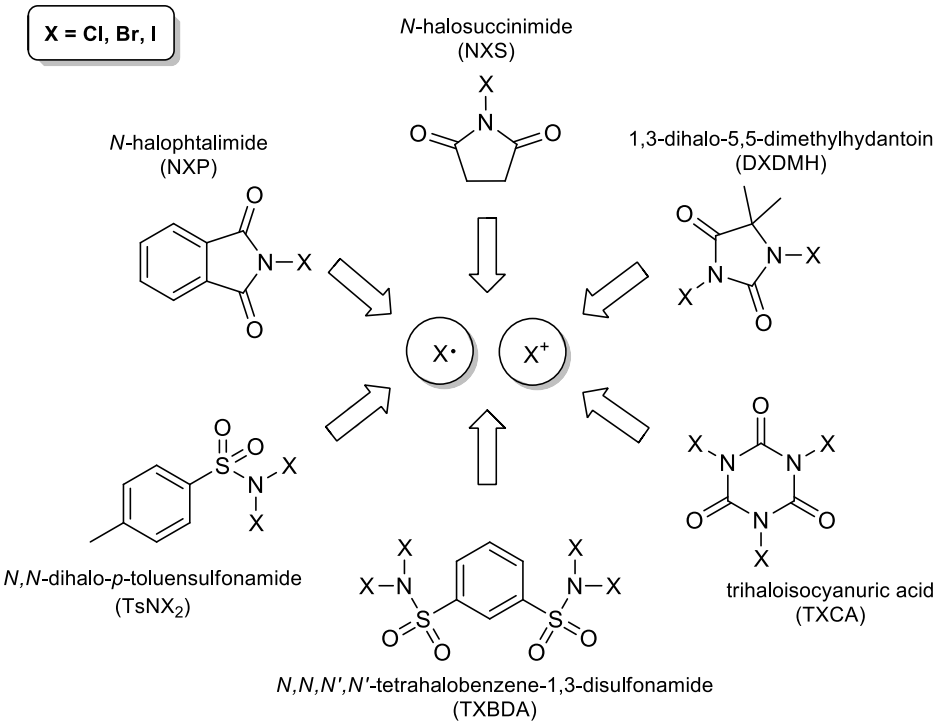
Scheme 1.5: Example of iodonium ion as the catalytic species in iodine catalysis [85].

1.2.2 *N*-Halamines

N-halamines were first mentioned as early as 1927, when they were defined as halogen derivatives of nitrogen. They can have either inorganic or organic character, while their common point is the ability to store halogen atoms in N−X covalent bonds [86]. Since the halogens are bonded to the nitrogen in their strong oxidative state (+1), *N*-halamines exhibit a strong antibacterial activity and can be exploited as effective disinfectants against various pathogens in a variety of applications: water treatment, air purification, textile products, dyes, paints, medical and healthcare products and even food processing [87, 88]. [23] Their long-term stability in aqueous solution and dry storage, metal-free character, high durability, regenerability, lower corrosion than free halogens, low handling and environmental risk together with their low cost [89-91] makes them attractive also from the synthetic perspective in a form of *N*-halo reagents. Their distinctive chemical properties

derive from the great lability of the N–X bond bearing an electron-withdrawing group on the nitrogen atom (e.g. carbonyl and sulfonyl), which enables their versatile use in organic synthesis, especially as sources of halenium ions (X^+) and halogen radicals ($X^\bullet$) [92]. Their potential as activators of organic molecules or as reagents in reactions of halogenation, oxidation, protection and deprotection as well as in the formation of C–X, C–O and C=O bonds has been recognized and discussed in several publications [93, 94]. Based on their structure, *N*-halamines can be classified into three different types: amine *N*-halamines, amide *N*-halamines and imide *N*-halamines. The effects of electron withdrawal and electron donation of each functional group type influence their stability in the following order: amine *N*-halamines > amide *N*-halamines > imide *N*-halamines (according to the dissociation constants in reaction of hydrolysis) [95]. McKee's group theoretically studied the stability of *N*-halamines in chloro derivatives. The results were surprising, since the longest N—Cl bond was found to be the strongest one. Based on this, it was concluded that the greater ionic character of the bond due to the increased polarity in the (imide N—Cl bond) is responsible for the shorter bond length but at the same time results in faster hydrolysis [96, 97].

From another perspective, *N*-halamines can be grouped into cyclic and acyclic. Both groups show good antibacterial activity, but acyclic are more unstable and are therefore more easily decomposed in the presence of water, light and heat. Consequently, cyclic *N*-halamines are more suitable for long-term disinfection, while acyclic are more convenient, if powerful and rapid disinfection is needed.



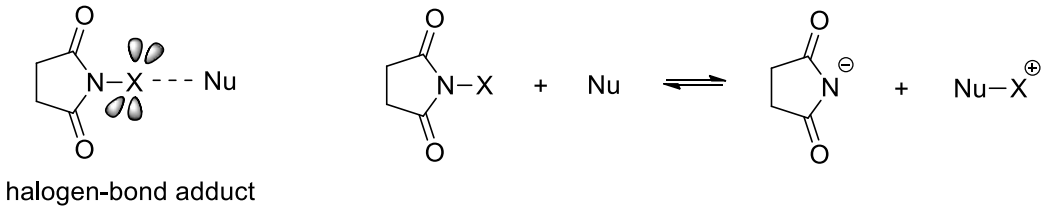
Scheme 1.6: Regularly utilized *N*-halo reagents as sources of halenium ions and halogen radicals [92].

Among the vast number of *N*-halo reagents, the most widely utilized are *N*-haloamides, *N*-haloimides (especially *N*-halosuccinimides), trihaloisocyanuric acids, *N*,*N*-dihalosulfonamides, and 1,3-dihalo-5,5-dimethylhydantoins (Scheme 1.6) [92]. Our research was focused mainly on use of *N*-halosuccinimides and dibromantin (1,3-dibromo-5,5-dimethylhydantoin) as stable, readily accessible and low-priced representatives of

N-halo reagents. Due to their availability, higher stability and low price relative to other *N*-halo reagents, NXSs as well as dibromantin have become established bromination reagents, since they stand as an effective, selective and convenient alternative to the hazardous molecular bromine. In addition, they have lately been attracting attention also as possible non-metal catalysts for comprehensive transformations in organic synthesis. Their catalytic/cocatalytic activity in oxidation reactions, condensation and protection reactions has been reviewed recently [98], but to the best of our knowledge, their use in esterification reaction has not been published yet.

1.2.2.1 *N*-Halosuccinimides

N-halosuccinimides (NXSs) are undoubtedly the most extensively studied group of *N*-halo compounds. Besides their wide use in halogenation chemistry, they can also be used in reactions of hydroxyhalogenation, oxidation, rearrangement, protection and deprotection [93, 94]. As already mentioned above (Chapter 1.2.1.2 Mechanisms in iodine catalysis), *N*-halosuccinimides as commonly used halogenation reagents supposedly act as halogen-bond donors in "transient" halogen-bonding [30]. During the halogenation reaction, the R—X bond is therefore broken and the halogen-bond donor is consumed. The activation of *N*-halosuccinimides by the addition of Lewis base in halogenation reactions was reported in several publications [99]. However, regarding the mechanism of action, it is very unlikely that halogen-bonding adduct (Scheme 1.7, left) is the activated species, since the only electrophilic center would then be blocked by the nucleophile. In other words, the lobe of the N—X σ* orbital in extension of the N—X bond would be blocked by the Lewis base and would prevent the subsequent reaction of halogenation. Therefore, the transfer of halonium ion to the Lewis base, which then takes over the role of the halogenating reagent, is a more probable scenario (Scheme 1.7, right) [30].



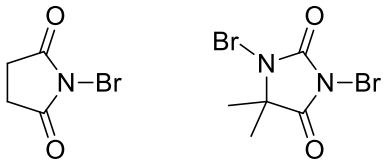
Scheme 1.7: Left: Halogen-bonding adduct of NXS and Lewis base. Right: Activation of NXS by Lewis base [30].

In a similar fashion, the *in situ* formation of the halonium ion (X^+) can be exploited also in the catalysis, where the X^+ acts as a Lewis acid in activation of various substrates. Catalytic quantities of electrophilic halogen-containing compounds can form an attractive interaction with moieties owning Lewis-basic properties and consequently activate them. In spite of its similarities to hydrogen-bonding catalysis, it features an important advantage of a broader substrate pool. The substrate scope in the case of hydrogen-bond catalysis is limited and constricted only to the "hard" Lewis bases, as the hydrogen bonding takes place only through a "hard" hydrogen atom. This prevents hydrogen-bonding catalysis to reach the significance of transition-metal-based catalysis in organic synthesis, owing to the fact that transition-metal catalysis offers more versatility, due to the availability of a variety of metal centers with different "hard" and "soft" characters [100]. On the other hand, halogen-bonding catalysis can offer a more flexible substitute for transition-metal catalysis, due to the availability of different halogen atom centers with a different size of orbitals, polarizability and oxidation states. Halogen-bonding catalysis is still in its early

stage of development, but its emerging applications in organocatalysis emphasize its importance in organic synthesis.

1.2.2.2 1,3-Dibromo-5,5-dimethylhydantoin (dibromantin)

Dibromantin, a structural relative to NXSs (Figure 1.4), is a bromine derivative of 1,3-dihalo-5,5-dimethylhydantoin, which is an even cheaper commercially available brominating reagent than NBS, widely used as drinking water disinfectant, bleaching agent in paper industry and as a deodorant [101, 102]. Besides its lower cost (in 2019 the price DBDMH according to the Sigma Aldrich catalogue is 78% of the NBS price), the bromine content in DBDMH is doubled relative to NBS and from the synthetic standpoint this makes it an even more attractive alternative to NBS. Interestingly, in spite of its wide use in halogenating chemistry, its catalytic potential has not been extensively explored yet [98], but its features as a halogen bond donor have already been recognized [103].



NBS DBDMH

Figure 1.4: Structures of NBS (representative of *N*-halosuccinimides) and DBDMH.

1.3 Dehydrative C–C Coupling

Among the vast amount of various reaction classes, the carbon-carbon (C−C) bond formation is presumably one of the most significant transformations for constructing molecular diversity in organic synthesis. A direct alkylation of hydrocarbons is an important tool, widely used in petrochemical as well as in pharmaceutical industry. Therefore, these transformations have been scientifically intriguing from their very beginning and various methodologies have been developed in this field. For instance, R.F. Heck, E. Negishi in A. Suzuki made a revolutionary breakthrough in organic synthesis by developing the palladium catalyzed C−C coupling, which won the Nobel prize in 2010 [104].

A general approach in C−C bond formation includes the coupling of an electrophile C−X (X = halogen atom, triflate, tosilate, mesylate, etc.) with a reactive nucleophile, most commonly in the form of an organometallic compound C−M (M = Mg, Zn, Sn, etc.) Nevertheless, due to the toxicity, moisture sensitivity and poor functional group tolerance of the organometallics, this approach is among the less favorable and a more atom-economic alternative of coupling C−X with an inactivated substrate (C−H) in the presence of a transition-metal catalyst was therefore developed and thoroughly surveyed [105]. Still, as the electrophilic C−X substrates may sometimes not be commercially available and additional synthetic steps are therefore needed for their preparation, a significant amount of waste material is formed at the end of the synthetic path, culminating in resource- and time-consuming purification. Consequently, the development of C−C coupling strategies, where construction of complex biologically significant backbones can be achieved with high atom economy by using low-priced and harmless precursors, is of great significance from the sustainability standpoint [106]. As a result, aryl alcohols, tautomerizable heterocycles and phenols, represented by C−OH, have lately attracted attention as proelectrophiles [107-114], since they can act as convenient, environmentally friendlier, low-cost and widely

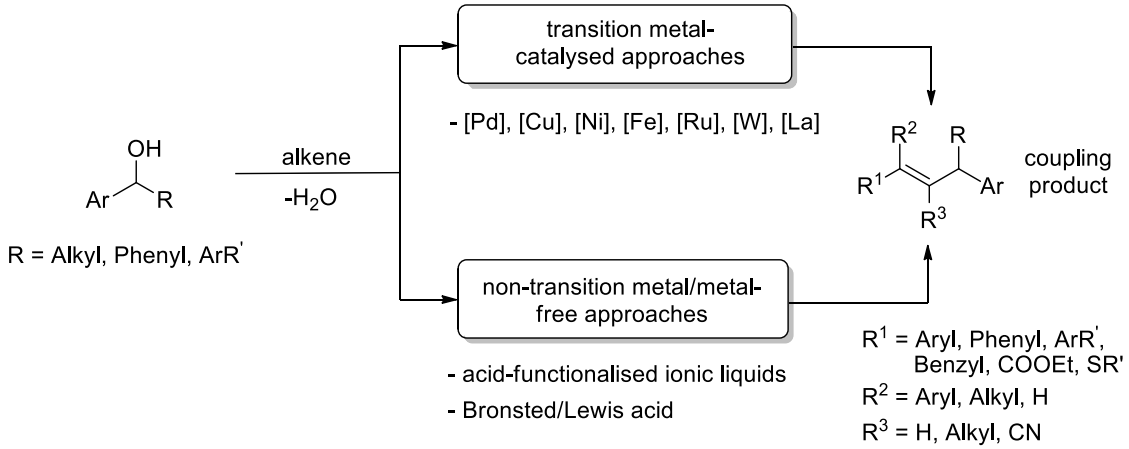
available substitutes for C−X compounds. With this in mind, a direct reaction between the C–OH functionality and the C–H bond would mean an ideal transformation, since unlike in the case of the wasteful prefunctionalization of C−X, water would be formed as the only by-product.

Both alcohols as well as alkenes are widely available feedstock, which are commonly used in industrial processes [115]. In this context, dehydrative coupling reaction stands as a perspective and economical methodology toward newly formed C−C bonds, yielding products, which can act as excellent templates in further synthetic modification. Regarding the type of the catalyst, dehydrative coupling can be generally classed into two different strategies: *transition metal-catalysed approaches* and *transition-metal-free approaches* [106]. On the other side, relative to the type of the newly formed C−C bond, these transformations can be divided into several categories:

a) C_{sp}^3 – C_{sp} bond formation: coupling of C_{sp}^3 – OH with alkynes (C_{sp} – H)
b) C_{sp}^3 – C_{sp}^2 bond formation: coupling of C_{sp}^3 – OH with alkenes and arenes/heteroarenes (C_{sp}^2 – H)
c) C_{sp}^3 – C_{sp}^3 bond formation: coupling of C_{sp}^3 – OH with 1,3-dicarbonyl compounds (C_{sp}^3 – H)
d) C_{sp}^2 – C_{sp} bond formation: coupling of C_{sp}^2 – OH with alkynes (C_{sp} – H)
e) C_{sp}^2 – C_{sp}^2 bond formation: coupling of C_{sp}^2 – OH with arenes (C_{sp}^2 – H)

Since the reaction system, developed in our laboratory and presented herein (Chapter 4) belongs to the group b), further discussion will be focused mainly on the methods regarding the reactions between alcohols and alkenes (C_{sp}^3 – C_{sp}^2 bond formation). The majority of known methods related to the coupling of olefins/enol acetates and alcohols is based on the use of metal catalysts, especially the ones including transition metals (e.g. Cu [116, 117], Fe [118-121], Ni [122], Ru [115], Pd [123-125], W [126], La [127]) and weak metals (e.g. Bi [128, 129], In [121, 129] and Ga [121]) (Scheme 1.8). On the other hand, the metal-free approaches include:

a) classic Brønsted acid/base catalysis (e.g. HCl [130], trifluoromethanesulfonic acid – TfOH [131], *p*-toluenesulfonic acid – TsOH [132] and *n*-BuLi [133]),
b) solid-supported acids (e.g. policresulen/SiO_2 [134] and $NaHSO_4$/ SiO_2) [135], and
c) acid-functionalised ionic liquids [136-138].



Scheme 1.8: Methodologies in carbon-carbon coupling between alcohols and alkenes.

In the majority of the above-presented methods, the catalyst acts as a Brønsted/Lewis acid, activating the alcohol molecule by abstracting the hydroxyl group. In this way, electron-withdrawing intermediate (carbocation) is formed, which is then attacked by

electron-rich π bond of alkene or enol acetate. This is followed by proton abstraction, and finally, product formation. Regarding the geometric selectivity, the newly formed products are in most cases *E*-isomers; nevertheless, in certain cases, where the R^1 and R^2 groups of an asymmetric alkene are of similar steric abundance, the *E*- and *Z*-isomers are formed in ratio 1 : 1 [118]. Some of the proposed mechanisms suggest the formation of ether, which further reacts to the C−C coupling product [116, 131, 132, 135-137]. Although the known methods are efficient, the metals are toxic and less favourable from the green-chemical perspective. The non-metal catalysis is therefore preferred, if possible. Nevertheless, the aggressiveness of Brønsted acid/base may result in poor reaction selectivity and demands neutralization after use. On the other side, ionic liquids are considered a green alternative due to their ability to simultaneously act as a catalyst and solvent, but their drawbacks, such as high price, difficult preparation and toxicity, cannot be neglected [139]. The coupling between alcohols and alkenes have mainly been performed in cancerogenic and environmentally nonfriendly halogenated solvents (e.g. dichloroethane, dibromoethane, dichloromethane, chlorobenzene), which is another impetus for the development of sustainable approaches toward dehydrative C−C coupling.

1.4 Esterification

The esterification reaction is still one of the principal research subjects in the organic chemistry field, since the ester moiety is a crucial part in many organic material compounds, active pharmaceutical ingredients and natural products [140]. Esterification is therefore frequently an irreplaceable reaction step during the synthesis of drugs, cosmetics, plasticizers, perfumes, flavour chemicals, fine chemicals, solvents and chiral auxiliaries [141]. While an enormous amount of methods is available for ester preparation, the importance of ester synthesis in the green-chemical as well as industrial aspect acts as a driving force, which intrigues the scientists to investigate and look for new approaches in esterification reaction.

Carboxylic acids are most frequently utilized as the key starting material and in this regard, the esterification methodologies can be classified into two groups: the reactions, where the carboxylic acid acts as an *electrophile*, and the one, where it takes a role of a *nucleophile* [142]. Since the methodology for esterification, developed in our laboratory, belongs to the first group, the focus of the literature survey regarding the publications on different esterification approaches and further discussion on their behalf is placed on the synthesis of carboxylic esters using carboxylic acids as electrophiles. If the carboxylic acid plays a role of an electrophile, the most typical and traditional method is Fischer esterification, where carboxylic acid reacts with an access of alcohol in the presence of catalytic amounts of sulfuric acid (H_2SO_4) and the water formed during the reaction is removed by Dean-Stark apparatus [143-145]. Another alternative includes the use of stoichiometric amounts of condensation reagents like *N*,*N*'-dicyclohexylcarbodiimide (DCC) [146], Mukaiyama condensation reagent [147], Ph_3P [148-151] and its derivatives, (benzotriazole-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) [152], carbonyldiimidazole (CDI) [153, 154], (4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) [155], etc. (Figure 1.5).

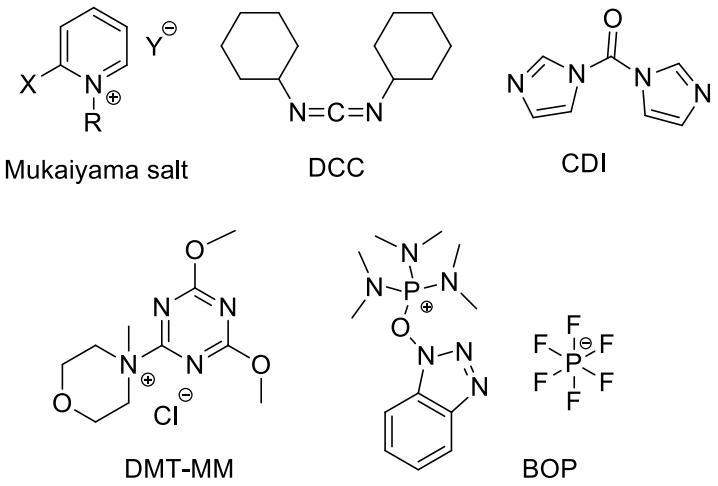
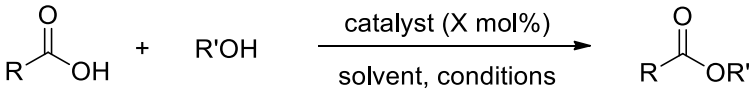


Figure 1.5: Structures of some significant condensation reagents for ester preparation.

However, from the sustainability standpoint, the more environmentally friendly approach involves the *catalytic* amounts of reagents without the need for excessive amounts of reactants. In Table 1.1, selected examples of progresses in esterification catalysis using equimolar (or nearly equimolar) amounts of carboxylic acid and alcohol are listed for the period of the last two decades [142].

Table 1.1: Representative progresses for catalytic approach in ester synthesis.



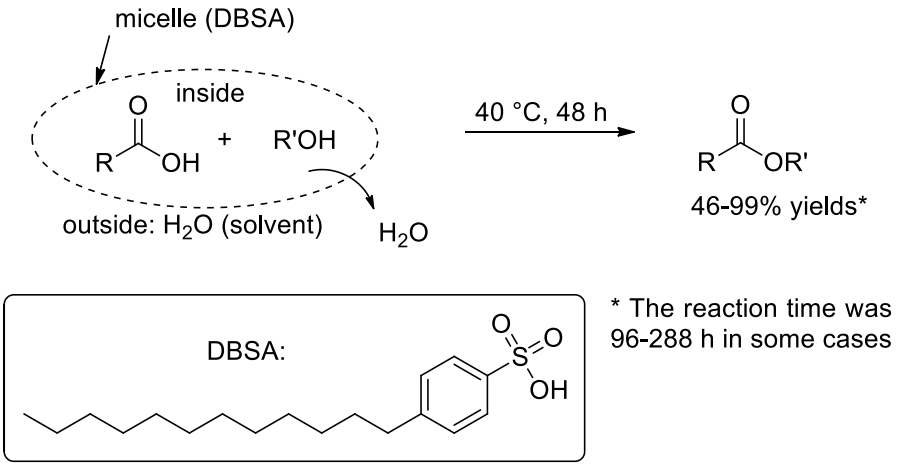
Entry	Publ. year	Catalyst (X mol%)	Solvent	Conditions	Ref.
1	2000	Hafnium(*IV*) salts (0.1-1.0 mol%))	toluene	Reflux, 5-36 h	[156]
2	2000	Diphenylammonium triflate (DPAT) (1-10 mol%)	toluene	80 °C, 4-48 h	[157]
3	2002	Fluoroalkyldistannoxane (5 mol%)	FC-72	150 °C, 10-16 h	[158]
4	2003	$HClO_4$-SiO_2 (1 mol%)	solvent-free	80 °C, 3.5-20 h	[159]
5	2003	Ti_4^+-mont (2 mol%)	solvent-free	110-150 °C, 3-6 h	[160]
6	2005	Bulky diarylammonium arenesulfonates (1-10 mol%)	Heptane or solvent-free	r.t.-115 °C, 1-72 h	[161]
7	2005	$Zn(ClO_4)_2 \cdot 6H_2O$	solvent-free	80-100 °C, 6-48 h	[162]
8	2006	Pentafluorophenylammonium triflate (PFPAT) (1 mol%)	toluene	80 °C, 2-48 h	[163]

9	2008	*p*-toluenesulfonic acid (TsOH) or 10-camphorsulfonic acid (CSA) (5 mol%)	solvent-free	60-80 °C, 3-48 h	[164]
10	2009	Phosphorofluoridic acid (5 mol%)	solvent-free	100 °C, 6 h	[165]
11	2012	*N*,*N*-diarylammonium pyrosulfates (5 mol%)	water	60-80 °C, 6-47 h	[166]
12	2013	TfOH (0.2-1 mol%)	Solkane 365mfc	80 °C, 18-48 h	[167]
13	2013	2-oleamido-5-nitropyridinium *p*-toluenesulfonate (1-10 mol%)	isooctane	r.t.-reflux, 5-144 h	[168]
14	2017	Zirconocene complex (1 mol%)	solvent-free	80-100 °C, 12 h	[169]
15	2018	*L*-leucine (5 mol%)	solvent-free	80 °C, 12-24 h	[170]

Another interesting approach for esterification of carboxylic acids is performed in water in the presence of a surfactant-type catalyst (*p*-dodecylbenzenesulfonic acid, DBSA) [171-173]. The role of the catalyst is to generate *micelles*, in which the reaction between carboxylic acid and alcohol takes place. The distinctive feature of micelles is their ability to release the water, liberated during the reaction, and thereby driving the equilibrium toward the ester formation. The method is particularly effective for long-chained carboxylic acids and alcohols due to their increased hydrophobicity (Scheme 1.9).

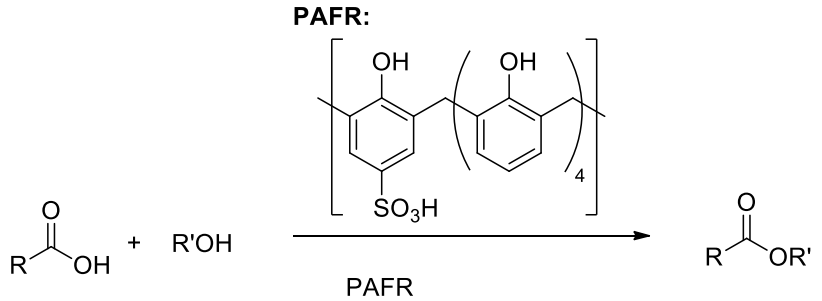
Furthermore, *solid catalysts* can be considered as another convenient alternative for ester preparation, either in the form of functionalized resins or solid supported catalysts. Their advantage is that they can easily be regenerated by filtration and reused without considerable loss of the catalytic activity. For example, porous phenolsulfonic acid formaldehyde resin (PAFR) prepared form 4-hydroxybenzenesulfonic acid and formaldehyde has been utilized (Scheme 1.10) [174, 175] as well as some solid-supported sulfonic acid catalysts:

- polystyrene-supported sulfonic acid catalyst [176],
- SBA-15-functionalized propylsulfonic acid catalyst [177],
- *p*-sulfonic acid calix[*n*]arenes catalyst [178],
- *β*-cyclodextrin-derived carbonaceous catalyst [179], and
- sulfonated hyperbranched poly(aryleneoxindole) acid catalyst [180].



Scheme 1.9: DBSA-catalyzed esterification of carboxylic acids (1 equiv.) and alcohols (2 equiv.) in water [142].

Finally, during the last years, *flow chemical methods* appeared as an effective tool in esterification reaction. For example, PAFR [174, 175] or silica, bearing terminal sulfonic acid moiety [181, 182] were employed as a catalytic component in the flow system.



Solvent-free conditions:	1 eq	1.2-5 eq	0.7 mol%	50 °C, 12 h	91-95% yields
Solvent-free conditions:	1 eq	5 eq	3 mol%	80 °C, 48 h	80-92% yields

Scheme 1.10: Condensation, catalyzed by porous phenolsulfonic acid formaldehyde resin (PAFR) [142].

On the other side, the synthesis of carboxylic esters using carboxylic acids as nucleophiles encompasses the following techniques [142]:

- nucleophilic reactions of carboxylate ion intermediates (the use of bases and ionic liquids, electrochemical reduction methods, the use of electrophile equivalents),
- esterification *via* the functionalization of C–H bond (for example in the presence of $Pd(OAc)_2$, CF_3SO_3H and *N*,*N*-dimethylacetamide under O_2) [183],
- the use of metal catalysts and organocatalysts for the addition of carboxylic acids on C–C multiple bonds (for example with [Ru] [184], [Au] [185], [Cu] [186], [In] [187], [Fe] [188], TfOH [189], etc.).

Even though the direct condensation of carboxylic acids and alcohols is conventionally conducted under acidic *or* basic reaction conditions [141], acidic conditions are generally more popular, since catalysis with base activators often results in hydrolysis of ester products, when the reaction mixture is subjected to aqueous workup. Especially Lewis acids

are increasingly gaining popularity in organic catalysis, as they are milder than Brønsted acids. However, most of the methods have some disadvantages regarding chemical sustainability or application limitations, such as toxic halogenated solvents, metal catalysts, aggressive reagents, limited substrate scope, low yields, high temperatures and the need for additional activators or stoichiometric dosages of reagents. Ergo, in spite of various effective methodologies, investigation and discovery of new routes for direct esterification of carboxylic acids and alcohols remains an attractive research topic.

1.5 Aldol Condensation

Aldol reaction is one of the most important organic reactions described as early as in 19th century [190]. The impetus for continuous development of this important approach for C−C bond formation has been forged in all fields of chemical synthesis, especially in the synthesis of biologically significant compounds [191]. For example, the synthetic challenges regarding the macrolide antibiotics like erythromycines (Figure 1.6) have provided the motivation for the development of significant synthetic tools, such as aldol reaction [192].

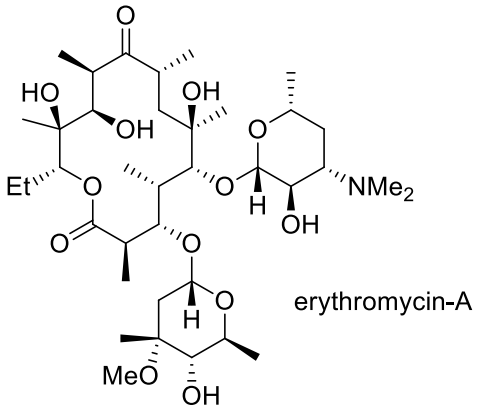


Figure 1.6: Structure of macrolide antibiotic erythromycin-A [192].

In its classical meaning, the term "aldol reaction" refers to a reaction between two organic molecules with a carbonyl functional group and is restricted to aldehydes and ketones. At least one of them must be enolizable, which means that it must have at least one α-positioned acidic proton. The enolizable carbonyl compound therefore acts as a nucleophile, while the carbonyl active compound takes the role of an electrophilic component. When the nucleophile and electrophile are different, the reaction is called a *crossed aldol reaction*; on the contrary, when the nucleophile and electrophile are the same, the reaction is called an *aldol dimerization* [193]. However, in a more advanced sense of the term "aldol reaction", this concept may be employed to any enolizable carbonyl compound (e.g. carboxylic esters, amides and carboxylates) that reacts with aldehydes or ketones. Even though the primary products are always β-hydroxycarbonyl compounds (*aldol addition*), they can further undergo an elimination of water to yield α,β-unsaturated compounds (*aldol condensation*), which are important building blocks in organic synthesis, especially due to their reactivity as substrates in 1,2- and 1,4-nucleophilic addition reactions [194]. These products have been recognized as potentially bioactive compounds [195] and are widely used in perfume industry [196]. For example, some important aldol products are 2-benzylideneheptanal (jasmine odor), 2-methyl-3-(4-isopropylphenyl)propanal (cyclamen odor), and 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)butanol (sandalwood odor) (Figure 1.7) [197]. In the biofuel industry, aldol condensation is a significant reaction during biomass conversion, since it enables a facile removal of oxygen by dehydration, which

assists in the transformation of biomass to liquid hydrocarbons. In such a way, this type of reaction is used to upgrade bio-derived carbonyl compounds into jet and diesel fuels or lubricants by subsequent hydrogenation [198]. Additionally, products of the aldol condensation and of the subsequent reactions are excellent solvents for the paint industry [199].

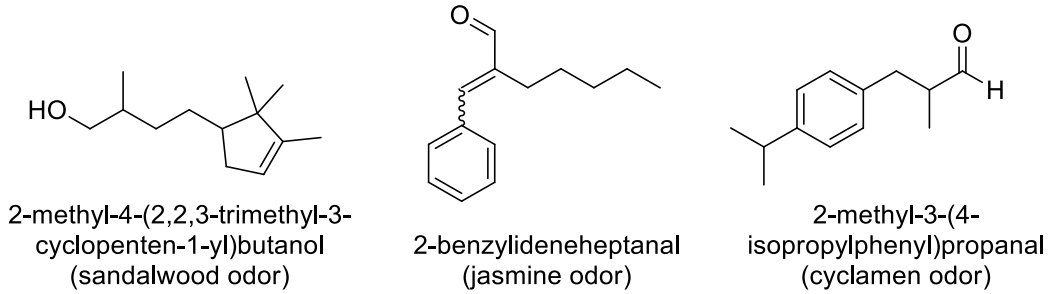
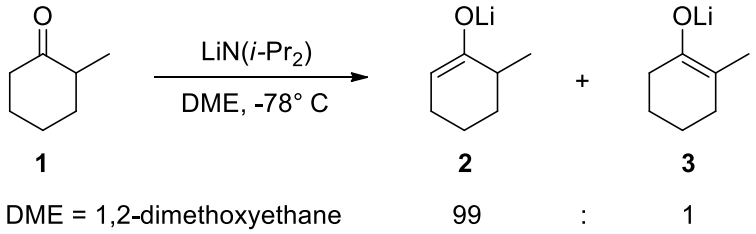


Figure 1.7: Structures of some important aldol products, used in the manufacture of fragrances.

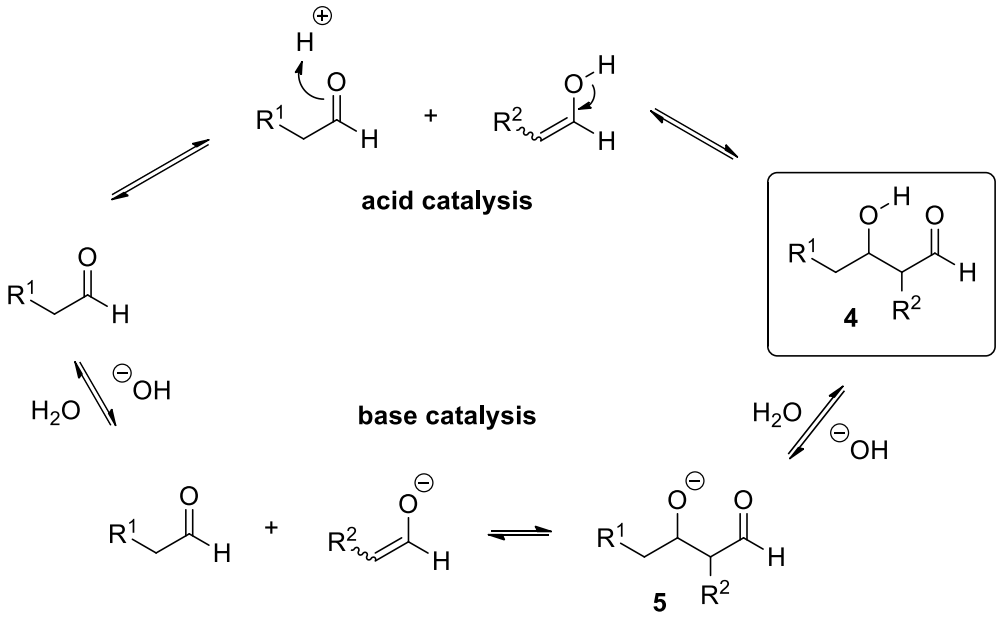
Traditionally [200-202], the aldol reaction is run in protic solvents and can be mediated either by acid or base. Under these conditions, the reaction is thermodynamically controlled and reversible, with the nucleophilic enol or enolate inevitably formed in the presence of electrophilic aldehyde or ketone. On the other hand, the modern approaches for aldol reaction, which appeared in the 1970s, comprise the irreversible formation of ''preformed enolates'', which are added to aldehydes or ketones. The most appropriate reagents for the preparation of enolates from the corresponding carbonyl compounds were found to be the lithium diisopropylamide (LDA) [193] and related bases, such as for example lithium *N*-isopropylcyclohexylamide (LICA) [203], lithium hexamethyl disilazane (LIHMDS) [204] and lithium 2,2,6,6-tetramethylpiperidide (LITMP) [205], due to their distinctive properties of soluble, strong and non-nucleophilic bases, which enable an irreversible reaction with controlled regiochemistry and without the nucleophilic attack on the carbonyl group (Scheme 1.11).



Scheme 1.11: Regioselectivity of enolate formation in the presence of LDA [193].

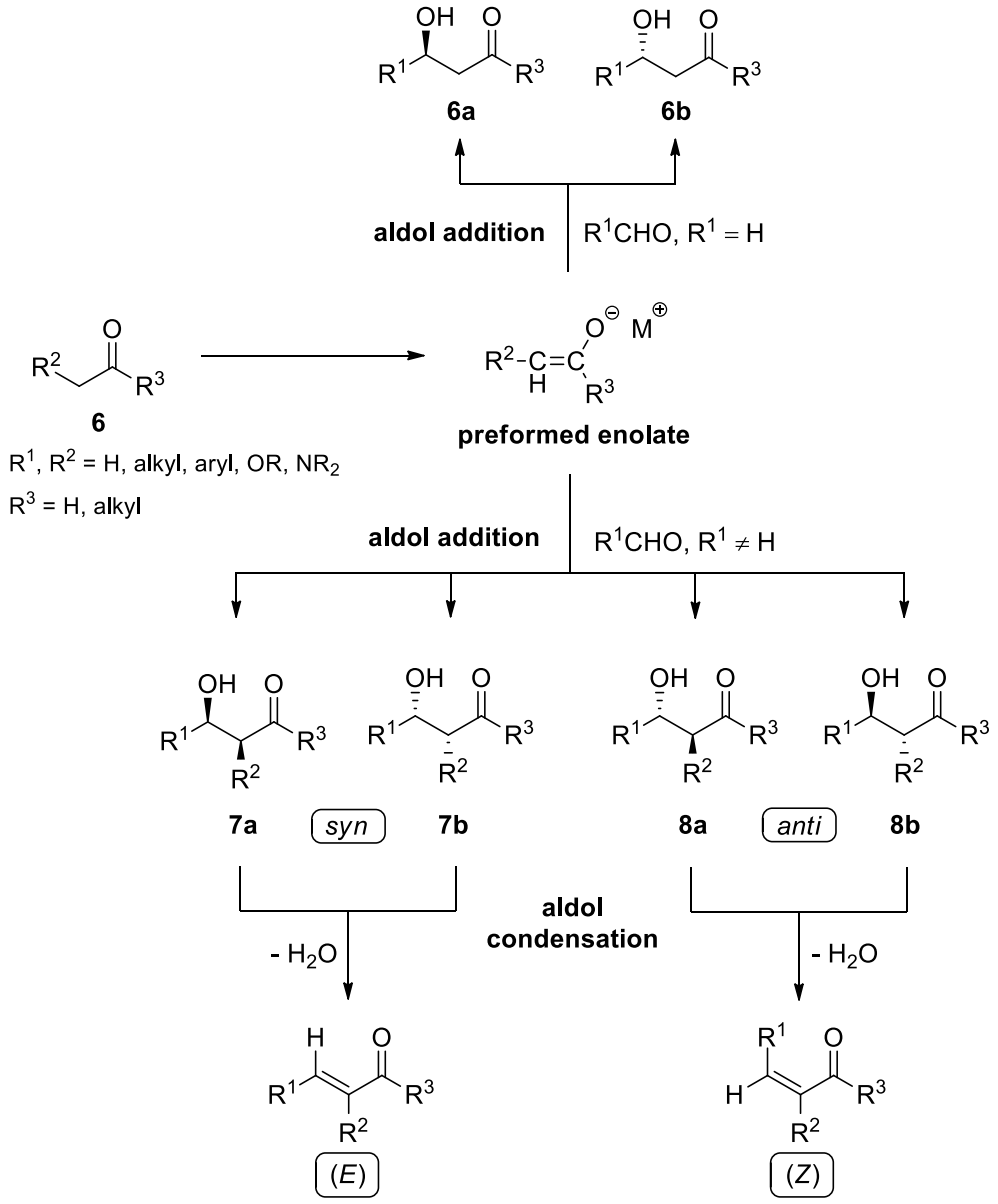
The reversibility of the aldol addition in the case of traditional acid/base catalysis could be a significant problem. The aldol product (Scheme 1.12, **4**) is substantially stabilized by the newly formed OH bond regardless of the type of catalysis (acid or base) and the relative energies between an aldehyde (or enolate) and the aldolate **5** show a marginally exergonic reaction [206, 207]. Moreover, an additional driving force of the reaction in the case of preformed enolates in non-protic solvents is the chelation of the counter-ion in aldolates [208]. A general guideline for protic solvents is that in the case of a reaction aldehyde-aldehyde, the reaction equilibrium for aldol addition is moved towards the product formation, while in the case of ketone-ketone reaction, it is moved toward the starting materials. Accordingly, if a solubility is not prevented by the length of the alkyl chain, self-

addition of enolizable aldehydes can be readily achieved in water. On the other hand, in the case of ketones, the aldol condensation is more often applied, since the enolizable self-addition gives only small amounts of the aldol product due to the unfavourable equilibrium described above. The subsequent water-elimination step moves the equilibrium toward the products, increasing the reaction yield.



Scheme 1.12: Mechanism of acid and base catalyzed aldol addition [193].

One of the major problems regarding the aldol condensation is related to the selectivity. A general stereochemical pattern is shown in Scheme 1.13 [193]. When a carbonyl compound **6** is transformed into "preformed" enolate, which subsequently reacts with an aldehyde, four different stereoisomers (**7a**, **7b**, **8a** and **8b**) can be formed. While **7a** and **7b** (**8a** and **8b**) are enantiomers, **7** and **8** form a diastereomeric pair. However, if neither enolate nor aldehyde is a chiral molecule, reaction results in the formation of two enantiomers **6a** and **6b**. When an aldol addition results in an access of one of the diastereomeric pair (either **7** or **8**), the reaction is said to exhibit *simple diastereoselectivity* (*syn*/*anti*). In the case of *syn* diastereomers, both substituents at the chiral centers are directed either toward or away from the viewer, while in the case of *anti* diastereomers one of the substituents is directed toward the viewer and another away from the viewer. Interestingly, it was established that (*Z*)–configured enolates furnish mainly *syn*-aldols whereas (*E*)-enolates predominantly yield *anti*-aldol compounds [209-211]. Therefore, several of procedures for selective preparation of (Z) or (E) enolates have been published [212]. However, when either or both carbonyl compounds (electrophilic or nucleophilic), participating in an aldol addition, are chiral or if both carbonyl components are achiral and the reaction is mediated by a chiral catalyst (including enzymes or antibodies), chiral ligands at the metal, or chiral solvents, the reaction exhibits *induced stereoselectivity*. In this case, one stereoisomer may be preferred over the others and a selective formation of only one diastereomer may be achieved.



Scheme 1.13: Depiction of a general stereochemical pattern in aldol reaction [193].

As already mentioned, the aldol addition may be followed by water elimination and the reaction is called *aldol condensation*. Since the OH group must be in the *anti* position relative to the H atom for E_2 elimination to occur, the *syn* aldol addition products in this case give (*E*) condensation product, while the *anti* aldol addition stereoisomers yield the (*Z*) product. The numbers of different methods for aldol reaction is vast and some excellent reviews have been published on this topic [213-216].

Industrially, aldol condensation is mostly catalysed by stoichiometric amounts of aqueous alkaline solution, consequently leaving behind large amounts of waste salts, which need an appropriate disposal treatment [194]. In addition, strong acids and bases such as metal hydroxides or mineral acids, commonly used as catalysts, are aggressive and corrosive reagents, which include the risk at handling and are difficult to recycle. Besides, the aggressive basic reagents often result in poor reaction selectivity. Therefore, the development of new catalytic approaches towards regioselective aldol condensation is still regarded as an attractive topic in organic synthesis.

Chapter 2

Aim of the Thesis

The discovery and development of chemical transformations and catalysis that are not harmful to the environment has been playing an increasingly important role in sustainable development of organic chemistry. Although metal catalysts are usually very effective and efficient, they often present a challenge in terms of production and purification processes in the chemical and pharmaceutical industry. Therefore, metal-free catalysis has lately gained interest, searching for greener alternatives in organic synthesis. Accordingly, the goal of the doctoral thesis is to explore and exploit the capabilities of certain halogen compounds as metal-free mediators in transformations of some oxygen functional groups in organic molecules. In this context, the purpose of the dissertation is the development of new green chemical catalytic methods for important and established organic reactions, such as dehydrative C—C coupling, esterification and aldol condensation. The methodologies were designed to include the use of environmentally friendlier, metal-free, easy-to-handle bench-top reagents, such as iodine, *N*-halosuccinimides and dibromantin. For each method, the objectives were to find the optimal reaction conditions at lower temperatures (up to 100 °C), preferably without the need for organic solvent or at least in solutions in non-halogenated or other environmentally acceptable solvents. The purpose of the optimization was to achieve the optimal conversion and selectivity of the reaction systems, to perform the reaction scope studies for each method and to apply the developed reaction systems on various substrates with different functional groups. The goal was also to explore the possibilities of applying the methodologies on scale-up experiments. The thesis includes three original research objects. In the first section (Chapter 4), the molecular iodine is promoted as a mild catalyst for cross-coupling of alkenes and alcohols. In the second section (Chapter 5), the method for direct esterification between carboxylic acids and alcohols under mild reaction conditions is presented, where *N*-bromosuccinimide acted as a convenient metal-free and low-cost mediator. Last but not least, the third section (Chapter 6) describes the pre-catalytic activity of 1,3-dibromo-5,5-dimethylhydantoin in esterification of carboxylic acids and alcohols and in aldol condensation of aldehydes.

Chapter 3

Materials and Methods

Reagents and Solvents

Compounds, reagents and solvents were obtained from commercial sources and were of reagent grade purity or better (Merck, Darmstadt, Germany; Sigma Aldrich, St. Louis, MO, USA; Carlo Erba, Milano, Italy; Fluka, Seelze, Germany, Fisher Scientific, Waltham, MA, USA; Apollo Scientific, Bredbury, United Kingdom; etc.).

TLC Chromatography

Reactions were monitored by thin layer chromatography (TLC) with silica-gel-coated plates (Silica gel/TLC cards; DC-Alufolien-Kieselgel; with 60 Å medium pore diameter; Sigma Aldrich), and detection was conducted by UV absorption (254 nm, Camag, Muttenz, Switzerland) or $KMnO_4$ solution (TLC stain) and heating. The solution of potassium permanganate was prepared by dissolving 1.5 g of $KMnO_4$, 10 g of K_2CO_3 and 1.25 mL 10% NaOH in 200 mL of deionized water. Purification of certain products was conducted on preparative silica gel glass plates (PLC Kieselgel 60 F254 with 2 mm layer thickness).

Column Chromatography

Silica gel Fluka Kiselgel 60 with particle size of 0.063-0.2 mm was used as the stationary phase.

Nuclear Magnetic Resonance (NMR)

NMR spectra were measured at the National Institute of Chemistry (Ljubljana, Slovenia) and were recorded on a Varian Inova 300 spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C, 285 MHz ^{19}F) at 25 °C. ^{1}H-NMR spectra were obtained as solutions in CDCl3 with TMS as an internal standard. ^{19}F-NMR spectra were obtained as solutions in $CDCl_3$ with $CFCl_3$ as an internal standard.

Mass Spectroscopy

Mass spectra (ESI) and HR-MS were measured at the Centre for mass spectroscopy at the Jožef Stefan Institute on Water-Micromass Q-TOF Premier.

Density Functional Theory Calculations (DFT)

Density functional theory (DFT) calculations were performed with the PWscf (Plain-Wave Self-Consistent Field) code from the Quantum ESPRESSO distribution [217, 218], using the generalized gradient approximation (GGA) of Perdew–Burke–Ernzerhof (PBE) [219]. Bader charge analysis was performed by generating charge densities with single point self-consistent-field calculations of Ultra-Soft Pseudopotential (US-PP) optimized [220] structures using the PAW (projector-augmented-wave) potentials [221] and 1000 Ry kinetic energy cutoff for charge density, and then computing the Bader charges using the Bader program [222, 223].

Chapter 4

Molecular Iodine as a Mild Catalyst for Cross-Coupling of Alkenes and Alcohols

Carbon–carbon (C–C) bond formation is well known as one of the most intrinsic approaches toward molecular diversity in organic synthesis. Alcohols and aromatic hydrocarbons are among the most accessible and frequently used feedstocks in industry and their exploitation in C–C coupling reactions has become one of the perspective approaches in direct functionalization of C–H bonds, avoiding the need for halogen-containing intermediates and reducing the number of synthetic steps. In compliance with the second green chemistry principle, the efficiency as well as atom economy of the reaction is thereby increased. Besides, the only side product resulting from associated coupling reaction would be water. In pursuit of environmentally friendlier chemical approaches to organic synthesis, a new metal-free method for direct dehydrative cross-coupling of alcohols and alkenes using molecular iodine as a Lewis acid catalyst under solvent-free reaction conditions is presented. The reaction is tolerant to air and allows a simple synthetic procedure, furnishing Csp^3–Csp^2 coupling products in high yields up to 97 %. The method has proved effective in coupling of secondary benzyl alcohols with phenyl-substituted alkenes.

Author's Contribution

Klara Čebular performed the literature overview, participated in conceptualization of the research and co-formulated the basic idea for the object of investigation as well as co-planned, co-designed and performed experiments. The author participated in the formal analysis of the obtained results and their interpretation, in writing of the original draft of the manuscript and in its revision and edit.

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Conference paper

Klara Čebular* and Stojan Stavber

Molecular iodine as a mild catalyst for cross-coupling of alkenes and alcohols

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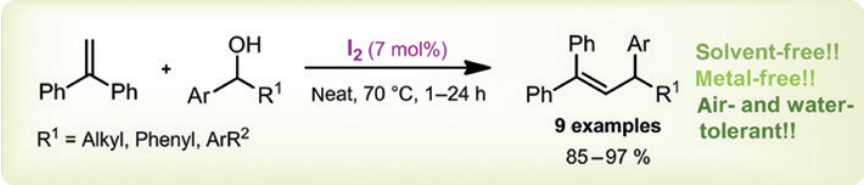
Abstract: C–C bond formation is one of the most fundamental approaches toward molecular diversity in organic synthesis. In pursuit of environmentally friendlier chemical approaches to organic chemistry, we present a new metal-free method for direct dehydrative cross-coupling of alcohols and alkenes using molecular iodine as a Lewis acid catalyst under solvent-free reaction conditions. The reaction is atom-economical, tolerant to air and allows simple synthetic procedure, furnishing C_{sp^3}–C_{sp^2} coupling products with yields up to 97 %. The method has proved efficient for coupling of secondary benzyl alcohols with phenyl-substituted alkenes.



Keywords: alcohols; alkenes; cross-coupling reactions; ICGC-6; iodine; solvent-free reactions.

Introduction

Carbon–carbon (C–C) bond construction is one of the most vital approaches for the synthesis of complex natural backbones and bioactive compounds such as pharmaceuticals and agrochemicals. These reactions have encouraged scientific exploration from the very beginning and have revolutionised the field of organic chemistry, as has been proven in 2010, when R. F. Heck, E. Negishi and A. Suzuki won the Nobel Prize in chemistry for Pd catalysed C–C coupling [1].

The expanding recognition of green chemistry and its 12 principles in academic and industrial community in the course of the recent decades has resulted in a movement toward a more sustainable world [2]. As alcohols and aromatic hydrocarbons are among the most abundant and commonly used feedstocks in industrial processes, their exploitation in C–C coupling reactions has become one of the significant approaches in direct functionalization of C–H bonds, avoiding the need for halogen-containing

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intermediates and thereby eliminating synthetic steps, which results in enhanced atom economy [3]. Alcohols are a highly attractive class of alkylating agents since they are inexpensive, they are usually easily derived from natural sources and the only side product resulting from associated coupling reaction is water [4]. On the other hand, the flexibility of the alkene functional group offers leverage for subsequent transformation into various other moieties [5]. Therefore, their dehydrative coupling is an attractive waste-free approach, resulting in generation of substituted alkenes as coupling products, which provides an excellent platform for further modification. In addition, some of these products, such as 4*H*-chromenes, also exhibit biological activities [6].

Previously described methods for dehydrative coupling of alcohols and alkenes can be divided into two basic approaches: metal catalysis and metal-free catalysis. The majority of known methods include the use of very effective transition metal catalysts, such as complexes of Pd, Cu, Ni, Fe, Ru and Lewis acids based on weak metals (e.g. Bi, In and Ga) [7–17]. However, toxicity of organometallic reagents and their removal to meet the strict specifications of pharmaceutical grade purity is a challenging and demanding process. Therefore, metal-free catalysis has lately gained interest, searching for greener alternatives in organic synthesis. Among the metal-free synthetic approaches, classic Brønsted [18–20] and Lewis acids [21, 22] are most commonly used, however, reactions catalysed by acid-functionalised ionic liquids [23, 24] and solid supported catalysts [25, 26] have also been reported. The aggressiveness of strong Brønsted acid/base catalysis can lead to poor reaction selectivity and the use of toxic halogenated solvents in numerous examples is not among the favourable practises due to the risks of carcinogenicity and ozone layer depletion. On the other hand, ionic liquids are considered a greener alternative to many commonly used solvents, yet they suffer from drawbacks such as toxicity, difficult preparation and high cost [27]. In fact, from the green-chemical standpoint, the best solvent for the reaction media is considered 'no solvent', hence solvent-free reaction conditions are preferable, if possible [28–30].

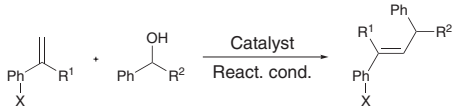
Iodine, as an easily manipulable solid, soluble in many organic solvents, has recently been recognised as a perspective catalyst in organic synthesis. Thirty thousand tons of iodine is produced annually and 16 % of it is utilised in industrial catalysis [31]. Its catalytic activity is attributed to an attractive halogen bond between the iodine atoms and the substrate molecule [32], which is the consequence of a positive polarization of the iodine atoms (the σ hole) due to an anisotropic electron distribution [33, 34]. Unlike the heavy metals, iodine is an environmentally friendly and a relatively inexpensive element, which exhibits high catalytic activity even under solvent-free reaction conditions (SFRC) [35–39]. Aside from being a metal-free substance, it has several assets, such as broad catalytic potential, water-tolerance, lower price and environmental friendliness. It is also a weak oxidant and a weak electrophile. Therefore, it is not surprising that it is employed both as a stoichiometric reagent and as a catalyst [40, 41] in numerous organic transformations.

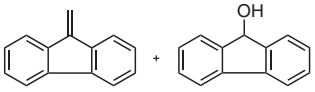
Iodine mediated coupling of activated aromatics, such as indole derivatives, with *E*-1,3-diphenyl-2-propen-1-ol has previously been reported [42]. However, to the best of our knowledge, iodine catalysed direct cross-coupling of alcohols and olefins has not been published so far. In our continuous pursuit of environmentally friendlier chemical approaches to organic synthesis [43–47], we present a metal-free method for direct dehydrative cross-coupling of alcohols and alkenes using molecular iodine as a mild Lewis acid catalyst under solvent-free reaction conditions. The efficiencies of previously used catalysts relative to iodine for cross-coupling of some chosen phenyl ethenes with benzyl alcohols are listed in Table 1. From the collected data it is evident that reaction yield in case of iodine use is comparable with the best yields of cross-coupling with other catalysts.

Results and discussion

Substitution of hydroxyl group in alcohols is a common strategy for the synthesis of bioactive substances in pharmaceutical industry, which is achieved by activation of alcohol molecule. As already mentioned, this approach is attractive from the green chemical perspective, as it should furnish water as the only by-product [48]. However, the substitution of hydroxyl group is a challenging transformation, as hydroxide is a poor

Table 1: Comparison of catalyst efficiency for cross-coupling of phenyl ethenes and benzyl alcohols.



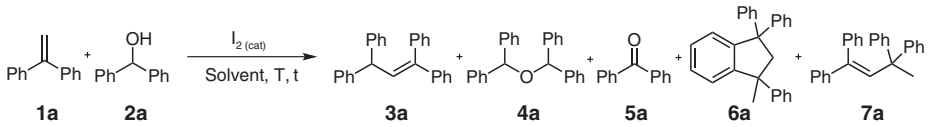
Entry	X	R^1	R^2	Catalyst	Reaction conditions[a]	Yield (%)	Ref.
1	H	Ph	C≡CPh	$Cu(OTf)_2$	DCE, reflux, 10 min	94	[5]
2	H	Ph	Ph	$FeCl_3 \cdot 6H_2O$/TsOH	DCM, 45 °C, 2.5 h	92	[15]
3	H	Ph	C≡CPh	$FeCl_3 \cdot 6H_2O$	MeCN, 80 °C, 0.5 h	81	[16]
4	*p*-Me	H	Ph	$(CF_3CO)_2O/Pd(OAc)_2/PPh_3$	DMF, 100 °C, 39 h	56	[17]
5				HCl	MeCOOH (anhydrous), reflux, 1.25 h	30	[18]
6	H	Ph	Ph	TfOH	DBE, 60 °C, 4–24 h	98	[19]
7	H	Ph	Ph	[BsOdP][OTf][b]	DCM, 80 °C, 3 h	91	[23]
8	H	H	Ph	$[NMP]^+HSO_4^-$[c]	80 °C, 3 h	90	[24]
9	H	H	Ph	SiO_2/policresulen	DBE, 80 °C, 5 h	92	[25]
10	H	Ph	Ph	$NaHSO_4/SiO_2$	DCE, 60 °C, 4 h	90	[26]
11	H	Ph	Ph	I_2	Neat, 70 °C, 1 h	95	This work

[a]DCE, 1,2-dichloroethane; DCM, dichloromethane; DMF, dimethylformamide; DBE, 1,2-dibromoethane. [b][BsOdP][OTf], 1-octadecyl-1-(4-sulfobutyl)pyrrolidin-1-ium trifluoromethanesulfonate. [c]$[NMP]^+HSO_4^-$, *N*-methyl-2-pyrrolidone hydrogen sulfate.

leaving group, thereby demanding an additional activation. Such direct activation can be achieved through S_N1 reactions on benzylic, allylic and propargylic alcohols by the use of Brønsted or Lewis acids [49].

With this in mind, the coupling of benzhydrol **1a** and 1,1-diphenylethylene **2a** has been chosen as a model reaction to employ iodine as a catalyst in direct cross-coupling of alkenes and alcohols and to study the effects of different reaction conditions. Initially, the effect of different solvents on conversion of 1,1-diphenylethylene was examined. Beside the solvents listed (Table 2, entries 1–6), also MeOH, EtOH, *i*-PrOH, Me_2CO,

Table 2: The effect of solvent and catalyst loading on the cross-coupling of **1a** with **2a**.[a]



Entry	Solvent	I_2 (mol%)	Conversion (%)[b]	Selectivity[b] 3a/4a/5a/6a/7a
1	Water	7	23	41:41:18:0:0
2	2-MeTHF	7	40	54:35:11:0:0
3	TFE	7	99	86:3:2:9:0
4	Solkane®	7	100	79:5:3:13:0
5	*n*-hexane	7	100	81:6:4:9:0
6	Neat	7	100	81:6:0:13:0
7	Neat	0	0	/
8	Neat	3	57	66:28:6:0:0
9	Neat	5	98	80:8:0:12:0
10	Neat	9	100	80:8:0:12:0

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (0–9 mol%), solvent (1 mL), 70 °C, 24 h. [b]Determined by ^1H NMR spectroscopy with respect to the 1,1-diphenylethylene **1a**.

EtOAc and MeCN have been tested as reaction mediums; however, they all reacted with **2a** and were therefore inappropriate for further studies. Quantitative conversion was achieved, when Solkane® (1,1,1,3,3-pentafluorobutane), *n*-hexane or no solvent were used (Table 2, entries 4–6). As the selectivity of the reaction was approximately the same in all three cases, further examinations were carried out under neat reaction conditions. The catalyst amount was varied and a considerable increase in conversion was observed, when the amount of iodine was changed from 3 mol% to 5 mol%. The complete conversion was achieved at 7 mol% of the catalyst and no significant improvement in selectivity was detected with additional raise of the catalyst loading (Table 2, entries 6–10).

Furthermore, the effect of temperature on the reaction system was investigated. Although quantitative conversion has been obtained already at 40 °C, the selectivity of the reaction improved, when the temperature was raised to 70 °C, increasing the percentage of the desired coupling product prop-1-ene-1,1,3,3-tetrayltetrabenzene **3a** in the reaction mixture from 67 % to 81 % (Table 3). In order to reduce the time needed for efficient conversion of the starting material, reaction time screening was subsequently performed and the results showed quantitative conversion already after 1 h without the loss of selectivity. The side products **6a** and **7a** are the consequence of 1,1-diphenylethylene cyclodimerisation and dimerisation, respectively, since phenyl-substituted alkenes are usually very sensitive to reaction conditions and often undergo polymerisation. As previously demonstrated by our group, when 2-phenyl propene **8** is heated in the presence of 5 mol% of iodine for 15 min at 70 °C, complete conversion to indane derivative **9** is achieved (Fig. 1). The authors concluded that firstly dimeric alkene **10** is formed, which is furtherly cyclised to indane derivative [50].

Inspired by these facts, we increased the amount of alcohol **2a** from 1.0 to 1.1 equiv. with respect to alkene with the aim to move the equilibrium toward the desired coupling product **3a**. The result was rewarding, as 1,1-diphenylethylene **1a** was quantitatively converted into polysubstituted olefin **3a**, while the remaining excessive amount of alcohol was transformed into dimeric ether **4a**.

Encouraged by these promising results, we examined the scope of the reaction system by applying the obtained optimal reaction conditions on cross-coupling reaction of 1,1-diphenylethylene with different alcohols. The method proved efficient on secondary benzyl alcohols, as depicted in Table 4. The coupling reaction with benzyl alcohols bearing electron-donating groups was finished in 1 h (Table 4, entries 2 and 3),

Table 3: Temperature optimization for cross-coupling of benzhydrol and 1,1-diphenylethylene.[a]

Entry	Temperature (°C)	Conversion (%)[b]	Selectivity[b] 3a/4a/5a/6a/7a
1	23	98	69:16:0:0:14
2	40	100	67:13:0:13:8
3	50	98	68:10:0:15:5
4	60	99	72:8:0:14:5
5	70	100	81:6:0:13:0

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (7 mol%), no solvent, 24 h. [b]Determined by ^{1}H NMR spectroscopy with respect to the 1,1-diphenylethylene **1a**.

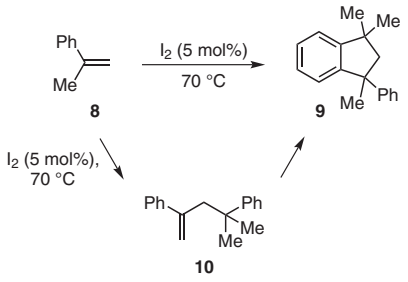
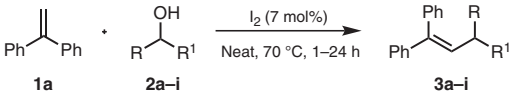
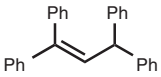
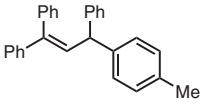
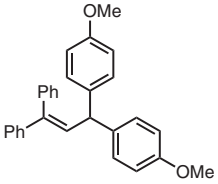
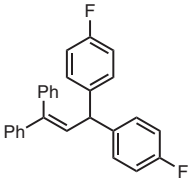
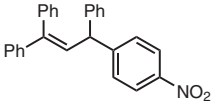
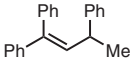
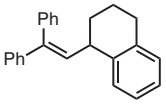
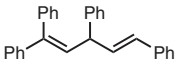
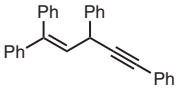


Fig. 1: Dimerisation and subsequent cyclisation of alkene **8** to indane derivative **9**.

Table 4: Synthesis of polysubstituted olefins **3a–i** catalysed by molecular iodine.[a]



1a **2a–i** **3a–i**

Entry	Product	Structure	Time (h)	Yield (%)[b]
1	**3a**		1	95
2	**3b**		1	97
3	**3c**		1	85
4	**3d**		6	92
5	**3e**		6	90
6	**3f**		21	95
7	**3g**		24	87
8	**3h**		3	96
9	**3i**		2	97

[a]Reaction conditions: all reactions were carried out under neat reaction conditions at 70 °C using 1,1-diphenylethylene **1a** (1.0 mmol), alcohol (1.1 mmol) and I_2 (0.07 mol). [b]In all cases the conversion of the starting material was >95 % and the yields of the pure products were calculated based on **1a**.

while the electron-withdrawing groups (*p*-F and *p*-NO_2) bonded to the phenyl ring of the alcohols resulted in longer reaction time of 6 h (Table 4, entries 4 and 5). In cases where benzyl position of the alcohol was substituted with alkyl group (Table 4, entries 6 and 7), the reaction was considerably slower relative to the cases where it was substituted with allyl or propargyl group (Table 4, entries 8 and 9).

These results are consistent with our expectations related to the impact of electron donating/accepting moieties and conjugation on stabilisation of the carbocation, formed from alcohol molecule by dehydroxylation. To confirm the synthetic value of the presented methodology, the coupling reaction of **1a** and **2a** was

performed also on 20 mmol scale (3.6 g of alkene **1a** and 4.0 g of **2a**) and 95 % of the pure coupling product was isolated after 3 h.

In order to get clearer insight into the course of the reaction pathway, some control experiments were performed. Under the typical reaction conditions (Table 4) after 1 h benzhydrol **2a** was quantitatively converted into dimeric ether **4a** and when the latter was subsequently used as a starting material instead of **2a** in the coupling reaction with 1,1-diphenylethylene **1a**, the complete conversion to the polysubstituted olefin **3a** was detected after 3 h (Fig. 2). These results strongly suggest the involvement of the dimeric ether **4a** as the intermediate in the reaction pathway. The formation of **4a** could be explained by the reaction between a molecule of alcohol and a stable benzylic carbocation, derived from another alcohol molecule. However, the direct reaction between carbocation and alkene molecule cannot be completely excluded. The proposed reaction pathway is illustrated in Fig. 3. To confirm the involvement of the intermediate **11**, the reaction between asymmetric alkene 1-methoxy-4-(1-phenylvinyl)benzene **1b** and benzhydrol **2a** was conducted, leading to 100 % conversion of the **1b** to the *E*- (**3j**) and *Z*- (**3j′**) isomers of the corresponding coupling product in ratio 1:1 (Fig. 4). The planar molecular geometry of the carbocation intermediate **11a** as the consequence of sp^2 hybridization on the carbon atom bearing the positive charge allows deprotonation from either of the planar sides of the molecule with the same probability, therefore yielding *E*- and *Z*- isomer in equal ratios.

In addition, the dehydrative cross-coupling reaction of benzhydrol with styrene as one of the most interesting and widely available phenyl-substituted alkene was examined. Unfortunately, beside the selective formation of (*E*)-prop-2-ene-1,1,3-triyltribenzene, a considerable amount of polymeric material was formed. Similarly, α-alkyl substituted styrene derivatives were also found inappropriate alkene starting materials due

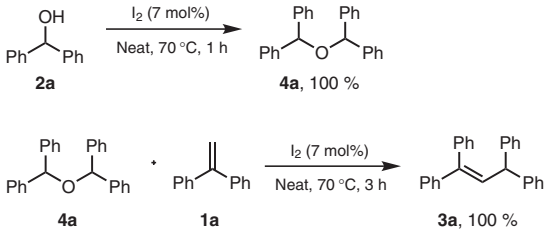


Fig. 2: Control experiments.

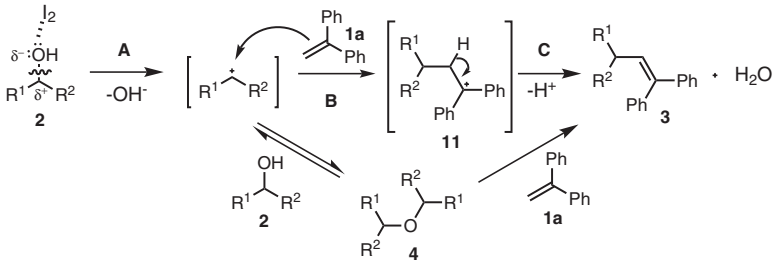


Fig. 3: Plausible reaction pathway for the direct dehydrative coupling.

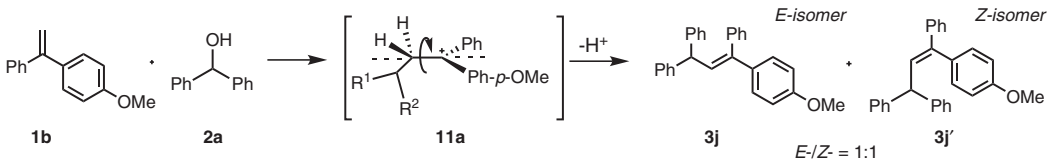


Fig. 4: The reaction of 1-methoxy-4-(1-phenylvinyl)benzene **1b** with benzhydrol **2a**.

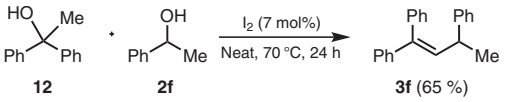


Fig. 5: The reaction between tertiary and secondary benzyl alcohol **12** and **2f**.

to the diversity of possible deprotonation positions in the carbocation intermediate **11** during the C-step of the reaction pathway.

Due to the low cost and ready availability of some alcohols as starting materials relative to alkenes and in behalf of the well-known proneness to elimination reaction of tertiary alcohols in the presence of Brønsted/Lewis acids, the possibility of the use of tertiary benzyl alcohols as potential substitutes for the alkenes as starting compounds was investigated. The equimolar mixture of 1,1-diphenylethanol **12** and 1-phenylethanol **2f** in the presence of I_2 (7 mol%) was heated for 24 h, resulting in formation of polysubstituted olefin **3f** in 65 % yield (Fig. 5).

Conclusion

In summary, a convenient method for direct dehydrative coupling of various benzylic alcohols with phenyl-substituted alkenes was developed, using iodine as an environmentally friendly metal-free Lewis acid catalyst under solvent-free reaction conditions. The reaction is assumed to proceed *via* carbocation intermediate, furnishing polysubstituted olefins in high yields. The scale-up procedure was conducted, verifying the synthetic applicability of the presented method. Finally, the possibility of direct coupling between tertiary and secondary benzyl alcohols was examined.

Experimental section

General procedure for the direct coupling of alkenes with alcohols

A mixture of alcohol (1.1 mmol), alkene (1.0 mmol), and iodine (0.07 mmol, 17.8 mg) was stirred at 70 °C in a sealed 10 mL tube for 1–24 h. The progress of the reaction was monitored by TLC chromatography or ^{1}H NMR spectroscopy. After the completion of the reaction, the mixture was cooled to room temperature, dissolved in ethyl acetate (5 mL) and washed with 10 mL of 10 % $Na_2S_2O_{3\,(aq)}$. The water phase was extracted with ethyl acetate (2×10 mL). The organic layers were combined and dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with silica-gel column chromatography (CH_2Cl_2/*n*-hexane).

Experimental procedure for large-scale synthesis of prop-1-ene-1,1,3,3-tetrayltetrabenzene (3a)

Benzhydrol **2a** (22.0 mmol, 4.094 g) and 7 mol% iodine (0.356 g) were triturated in a mortar for 1 min and transfered to a sealed 25 mL reactor tube. 1,1-Diphenylethylene **1a** (20.0 mmol, 3.530 mL) was added and the mixture was stirred at 70 °C for 3 h. After the completion of the reaction, the mixture was cooled to room temperature, dissolved in ethyl acetate (30 mL) and washed with 50 mL of 10 % $Na_2S_2O_{3\,(aq)}$. The water phase was extracted with ethyl acetate (2×30 mL). The organic layers were combined and dried with anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified with silica-gel column chromatography (CH_2Cl_2/*n*-hexane, 1:3). Yield: 6.590 g, 95 %; white solid.

Prop-1-ene-1,1,3,3-tetrayltetrabenzene (3a) [15]

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:3); yield: 329 mg, 95 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–6.98 (m, 20H), 6.54 (d, *J* = 10.6 Hz, 1H), 4.94–4.72 (m, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 144.6, 142.3, 141.7, 139.8, 131.1, 129.9, 128.6, 128.5, 128.4, 128.3, 127.6, 127.4, 127.4, 126.4, 50.7.

(3-(*p*-Tolyl)prop-1-ene-1,1,3-triyl)tribenzene (3b) [17]

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:3); yield: 350 mg, 97 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–6.99 (m, 20H), 6.53 (d, *J* = 10.6 Hz, 1H), 4.77 (d, *J* = 10.6 Hz, 1H), 2.32 (s, 3H).^{13}C NMR (76 MHz, $CDCl_3$) δ 144.9, 142.4, 141.6, 141.5, 139.8, 135.8, 131.3, 129.9, 129.3, 128.6, 128.4, 128.4, 128.3, 128.2, 127.6, 127.4, 127.3, 126.3, 50.3, 21.2.

4,4′-(3,3-Diphenylprop-2-ene-1,1-diyl)bis(methoxybenzene) (3c) [51]

Column chromatography (SiO_2, gradient elution CH_2Cl_2/*n*-hexane, 1:1–3:1); yield: 346 mg, 85 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.12 (m, 10H), 7.06 (d, *J* = 8.6 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 4H), 6.48 (d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 6H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 158.1, 142.4, 141.1, 139.9, 137.1, 131.7, 129.9, 129.3, 128.4, 128.2, 127.6, 127.4, 127.3, 114.0, 55.4, 49.0.

4,4′-(3,3-Diphenylprop-2-ene-1,1-diyl)bis(fluorobenzene) (3d)

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:3); yield: 352 mg, 92 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–6.88 (m, 18H), 6.44 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 10.5 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 161.60 (d, *J* = 244.9 Hz), 142.07 (d, *J* = 6.7 Hz), 140.18 (d, *J* = 3.0 Hz), 139.6, 130.6, 129.9, 129.8, 128.5, 128.3, 127.6, 115.51 (d, *J* = 21.2 Hz), 49.2; ^{19}F NMR (285 MHz, $CDCl_3$) δ –117.08 (ttd, *J* = 8.6, 5.4, 0.7 Hz).

(3-(4-Nitrophenyl)prop-1-ene-1,1,3-triyl)tribenzene (3e)

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:1); yield: 352 mg, 90 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.6 Hz, 2H), 7.41–7.08 (m, 17H), 6.50 (d, *J* = 10.4 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 152.0, 146.3, 143.0, 142.9, 141.4, 139.1, 129.4, 128.9, 128.9, 128.7, 128.3, 128.1, 128.0, 127.5, 127.3, 126.7, 123.6, 50.4.

But-1-ene-1,1,3-triyltribenzene (3f) [19]

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:6); yield: 270 mg, 95 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.09 (m, 15H), 6.19 (s, 1H), 3.60 (dq, *J* = 10.3, 6.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 146.3, 142.5, 140.3, 140.2, 134.3, 129.9, 128.6, 128.4, 128.2, 127.4, 127.2, 127.1, 127.1, 126.1, 39.4, 22.5.

1-(2,2-Diphenylvinyl)-1,2,3,4-tetrahydronaphthalene (3g)

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:6); yield: 270 mg, 87 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–6.91 (m, 14H), 6.13 (d, *J* = 10.3 Hz, 1H), 3.60 (dt, *J* = 14.7, 7.3 Hz, 1H), 2.91–2.60 (m, 2H), 2.07–1.81 (m,

2H), 1.78–1.52 (m, 2H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 142.5, 141.4, 140.2, 139.3, 136.9, 133.7, 129.9, 129.3, 128.5, 128.3, 127.4, 127.2, 127.1, 126.1, 125.8, 39.5, 30.7, 29.8, 21.9.

(*E*)-Penta-1,4-diene-1,1,3,5-tetrayltetrabenzene (3h)

Column chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:4); yield: 357 mg, 96 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.15 (m, 20H), 6.45–6.40 (m, 2H), 6.31 (d, *J* = 10.2 Hz, 1H), 4.36 (dd, *J* = 10.2, 3.8 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 143.7, 142.3, 142.0, 139.9, 137.5, 132.5, 130.4, 130.0, 129.9, 128.8, 128.7, 128.5, 128.3, 127.9, 127.6, 127.4, 127.4, 126.6, 126.4, 77.2, 48.4.

Pent-1-en-4-yne-1,1,3,5-tetrayltetrabenzene (3i) [16]

Column chromatography (SiO_2, gradient elution CH_2Cl_2/*n*-hexane, 1:4–1:3); yield: 359 mg, 97 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.18 (m, 20H), 6.23 (d, *J* = 10.1 Hz, 1H), 4.73 (d, *J* = 10.1 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 141.9, 141.8, 140.8, 139.3, 131.8, 130.0, 128.7, 128.6, 128.6, 128.3, 128.3, 128.0, 127.7, 127.7, 127.6, 127.5, 127.0, 123.7, 89.9, 84.1, 38.0.

(*E*/*Z*)-(3-(4-methoxyphenyl)prop-2-ene-1,1,3-triyl)tribenzene (3j/3j′) [52]

The isomers could not be completely separated; partial separation in ratio E/Z = 5:6 was achieved with preparative TLC chromatography (SiO_2, CH_2Cl_2/*n*-hexane, 1:3); yield: 324 mg, 86 %; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–6.97 (m, 40H), 6.89 (m, 2H, **3j′**), 6.82–6.76 (m, 2H, **3j**), 6.49 (d, *J* = 10.5 Hz, 1H, **3j′**), 6.45 (d, *J* = 10.5 Hz, 1H, **3j**), 4.86 (d, *J* = 10.5 Hz, 1H, **3j′**), 4.78 (d, *J* = 10.5 Hz, 1H, **3j**), 3.83 (s, 3H, **3j′**), 3.77 (s, 3H, **3j**). ^{13}C NMR (76 MHz, $CDCl_3$) δ 159.1, 158.9, 144.8, 144.8, 142.8, 141.4, 141.2, 140.1, 135.0, 132.1, 131.1, 130.9, 129.9, 129.5, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 127.7, 127.3, 127.3, 126.3, 126.3, 113.8, 113.6, 55.4, 55.3, 50.7, 50.6.

Supporting information

The copies of ^{1}H, ^{13}C and ^{19}F NMR of the purified products and other experimental procedures are available online.

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Chapter 5

Esterification of Aryl/Alkyl Acids Catalysed by *N*-bromosuccinimide under Mild Reaction Conditions

From the industrial and sustainability standpoint, the exemplary esterification methodology would include the use of an easily manipulable, metal-free, recyclable and low-priced benchtop catalyst under mild solvent-free reaction conditions without the need for simultaneous water-removal. *N*-halosuccinimides (NXSs) are among convenient, easily manipulable and low-priced halogenation reagents in organic synthesis. In the present chapter, *N*-bromosuccinimide (NBS) has been promoted as the most efficient and selective catalyst among the NXSs in the reaction of direct esterification of aryl and alkyl carboxylic acids. Comprehensive esterification of substituted benzoic acids, mono-, di- and tri-carboxy alkyl derivatives has been conducted under neat reaction conditions. The methodology is metal-free, air- and moisture-tolerant, allowing for a simple synthetic and isolation procedure as well as the large-scale synthesis of aromatic and alkyl esters with yields up to 100%. In addition, a protocol for the recycling of the catalyst has been proposed.

Author's contribution

Klara Čebular performed the literature overview and co-planned, co-designed and performed the experiments. The author participated in the formal analysis of the obtained results and their interpretation, in writing of the original draft of the manuscript and in its revision and edit.

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Esterification of Aryl/Alkyl Acids Catalysed by *N*-bromosuccinimide under Mild Reaction Conditions

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Abstract: *N*-halosuccinimides (NXSs) are well-known to be convenient, easily manipulable and low-priced halogenation reagents in organic synthesis. In the present work, *N*-bromosuccinimide (NBS) has been promoted as the most efficient and selective catalyst among the NXSs in the reaction of direct esterification of aryl and alkyl carboxylic acids. Comprehensive esterification of substituted benzoic acids, mono-, di- and tri-carboxy alkyl derivatives has been performed under neat reaction conditions. The method is metal-free, air- and moisture-tolerant, allowing for a simple synthetic and isolation procedure as well as the large-scale synthesis of aromatic and alkyl esters with yields up to 100%. Protocol for the recycling of the catalyst has been proposed.

Keywords: esterification; *N*-halosuccinimide; metal-free catalyst; aryl acids; alkyl acids

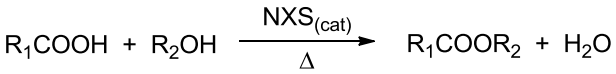
1. Introduction

Esterification reaction is one of the most important synthetic routes in organic synthesis due to the significance of its products. It is an irreplaceable reaction step during the synthesis of pharmaceuticals, cosmetics, plasticizers, perfumes, flavour chemicals, fine chemicals, electronic materials, solvents and chiral auxiliaries [1] and together with transesterification, it is a transformation of major significance in the biodiesel production [2–5]. Aside from being among the most prevalent final products and/or intermediates in the fields of science and industry, esters also play a significant role in biology, as the ester bonds are key linking groups in many primary lipid metabolites as well as secondary cyclodepsipeptide and polyketide metabolites [6]. As a result, a plethora of approaches have been reported for ester preparation, one of the most common being the reaction of direct esterification between carboxylic acids and alcohols (Fischer esterification) [7]. Conventionally, it is performed with excessive amounts of reagents/dehydrating agents or with activated carboxylic acid derivatives in the presence of a stoichiometric base, which results in significant amounts of by products and waste at the end of the process as well as in energy-, time- and solvent-consuming purification [8]. Therefore, methods of catalytic direct condensation between carboxylic acids and alcohols, which lack these disadvantages, have recently become an attractive research subject, employing a broad spectra of different catalysts, such as Brønsted acids [9], metal catalysts [10,11], Lewis acids [12,13], solid-supported catalysts [14,15] and solid acids [16,17], ionic liquids [18,19], PPh_3-based catalysts [20], enzymes [21,22], zeolites [23,24], etc. From the industrial and sustainability perspective, the ideal esterification method would include the use of easily manipulable, metal-free, low-cost, water-

and air-tolerant recyclable catalyst and mild solvent-free reaction conditions without the need for stoichiometric amounts of activators, large excesses of reagents and simultaneous removal of water. It should also be applicable to a broad substrate scope with high selectivity; it should be suitable for large-scale synthesis and allow a simple purification procedure, providing high product yields. The majority of known methods do not comply with at least one of the mentioned criteria; therefore, the field of sustainable design of esterification methods remains an attractive research challenge.

N-halosuccinimides (NXSs) belong to the class of *N*-halo reagents which are widely used in organic synthesis as halogenating, hydroxyhalogenating, oxidizing and condensing agents [25]. Their reactivity originates from the great lability of the N–X bond and various modes of its splitting [26]. Depending on the reaction conditions, different highly reactive species can be formed: *N*-radicals, *N*-cations, *N*-anions as well as their corresponding halogen counter particles, etc. [27]. Due to these convenient chemical properties, together with their metal-free character, low-cost, accessibility and higher stability relative to other *N*-halo reagents, NXSs have recently been attracting attention as mediators in substoichiometric amounts for different types of organic transformations [28–31]. The catalytic potential of *N*-bromosuccinimide (NBS) has recently been reviewed [32]; however, to the best of our knowledge, the use of *N*-bromosuccinimide as the only catalytic component in substoichiometric amounts for direct dehydrative esterification between alcohols and carboxylic acids has not been explored so far.

In our continuous pursuit of sustainable synthetic protocols [33–37], including those where NXSs are used as reagents [38–45], we now report and introduce the use of substoichiometric amounts of these compounds as mediators for efficient and selective comprehensive metal-free direct esterification of carboxyl functionality in organic molecules under neat reaction conditions (Scheme 1).



Scheme 1. Direct dehydrative esterification of carboxylic acids catalysed by substoichiometric amounts of NXSs.

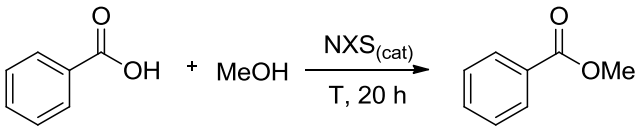
2. Results and Discussion

Previously, some advantages of *N*-bromosuccinimide (NBS) as a catalyst in reactions of transesterification have been observed, but the reaction was limited to transesterification of α-keto esters [46] or acetylation of alcohols using acetic anhydride [47]. In addition, esterification of carboxylic acids with alcohols in the presence of triphenylphosphine (PPh_3) and *N*-bromo/iodosuccinimides has been reported as a method for ester preparation [48]. however, its significant drawback is posed by the by-product, phosphine oxide, formed in equimolar amounts, as it is difficult to remove during the purification step. Besides, the esterification was performed in halogenated solvent (dichloromethane) in the presence of equimolar amounts of base (pyridine) and NBS/NIS. Furthermore, molecular iodine has been presented as a convenient Lewis acid catalyst for direct dehydrative esterification, but attempts to prepare esters from corresponding aromatic acids have been found unsuccessful [49] or unselective [50,51]. Furthermore, bromine (Br_2)-mediated esterification of carbocyclic acids with methanol has been reported [52], though this methodology carries handling safety risks due to the potentially hazardous effects of Br_2/MeOH solution [53]. All the aforementioned provided us with an impetus to improve the reaction of direct esterification of aryl/alkyl acids. Since *N*-halosuccinimides have been widely used as more convenient and safer X_2 substitutes in halogenation reactions, the catalytic activity of corresponding *N*-halosuccinimide derivatives in the reaction of direct condensation between various structurally different carboxylic acid and alcohols has been investigated and presented herein.

Initially, benzoic acid (**1**) has been chosen as an aromatic acid model molecule to verify expectations and optimize reaction protocols. In the typical experimental procedure, **1** has

been refluxed with methanol (MeOH) in the presence of substoichiometric amounts of NXS: *N*-chlorosuccinimide (NCS), NBS, or *N*-iodosuccinimide (NIS). The results presented in Table 1 reveal that NBS seems to be the most promising catalyst in reactions of esterification, while without the presence of any of the NXSs, no conversion of starting material has been observed. In search of optimal reaction conditions, the effect of catalyst NBS loading has been examined by changing the amount of catalyst from 3 mol% to 15 mol% (Table 1). The amount below 7 mol% NBS furnished significantly lower conversion, while increasing the amount above 7 mol% did not significantly improve the yield of the corresponding ester. Therefore, further studies were carried out with 7 mol% of NBS. Moreover, the influence of temperature on the conversion of **1** to methyl benzoate (**1a**, Table 1) has been studied. The variation of temperature from 30 °C to 100 °C has been found to have a significant impact on the conversion of the acid to ester with the optimal temperature being 70 °C. Moreover, under dry reaction conditions (in the presence of Na_2SO_4) the efficiency of the esterification dropped considerably (entry 8). The promoting activities of NXSs, halogen mineral acids and molecular bromine were compared in the present esterification reaction. In the case of both aqueous hCl (entry 12) and molecular Br_2 (entry 15), the conversions were comparable and their activity was similar to that of NBS (entry 6). On the other hand, the esterification efficiency in the case of both hBr and hI was considerably lower (entry 13 and 14) and resulted in the conversion yields of 84% and 68%, respectively. From the green-chemical point of view, NBS exhibited the highest catalytic activity among the examined catalysts.

Table 1. Catalyst loading and temperature optimization studies [1].



1 **1a**

Entry	NXS	Loading [mol%]	Temperature [°C]	Conversion of Benzoic Acid to Methyl Benzoate [%] [2]
1	/	/	70	0
2	NCS	15	70	17
3	NBS	15	70	94
4	NIS	15	70	30
5	NBS	10	70	94
6	NBS	7	70	94
7	NBS	3	70	76
8 [3]	NBS	7	70	<10
9	NBS	7	30	0
10	NBS	7	50	75
11	NBS	7	100	94
12	hCl	7	70	93
13	hBr	7	70	84
14	hI	7	70	68
15	Br_2	7	70	94

[1] Reaction conditions: **1** (1.0 mmol), MeOH (0.5 mL), NXS, hCl (37%), hBr (48%), hI (57%), Br_2, T, 20 h. [2] Conversions were determined by ^{1}H-NMR analysis of the crude reaction mixtures. [3] Freshly dried MeOH was used and the reaction performed over anhydrous Na_2SO_4.

The optimal reaction conditions presented above (entry 6, Table 1) have been applied to 1-octanoic acid (**2**) as an alkyl acid model compound. As expected, 1-octanoic acid has been quantitatively converted to the corresponding methyl octanoate (**2a**, Figure 1), while in the absence of NBS, no conversion of the starting material was observed.

To compare the reactivity of the aromatic and alkyl acids, the optimization of reaction time has been performed (Figure 1). Relative to benzoic acid, significantly higher activity of alkyl acid (**2**) has been observed, which was in accordance with our expectations. Due to resonance stabilization of

carboxyl group in aromatic acids, its lower activation resulted in longer reaction time and slightly lower conversion.

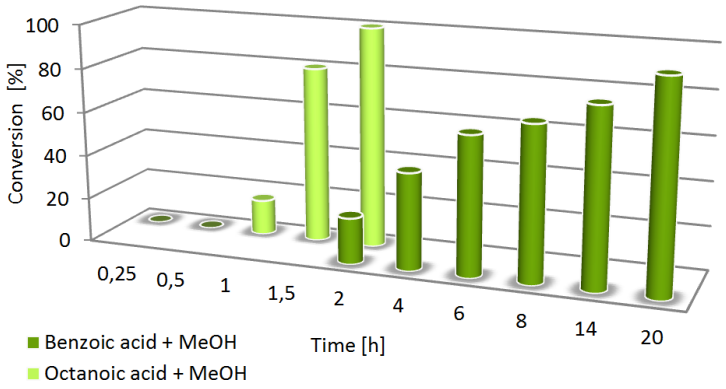
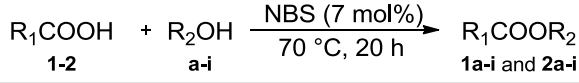


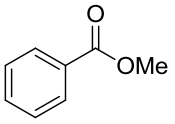
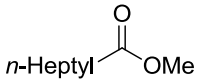
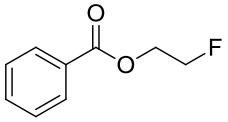
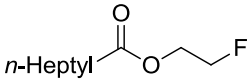
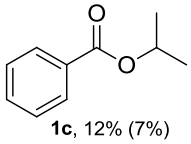
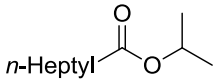
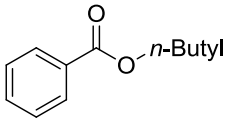
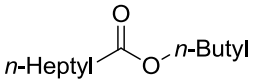
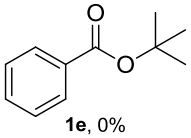
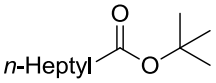
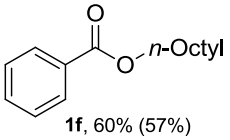
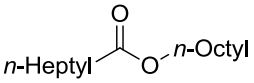
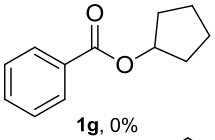
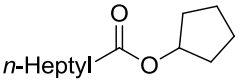
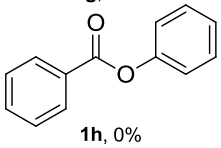
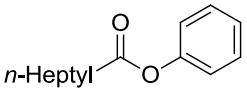
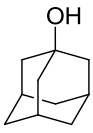
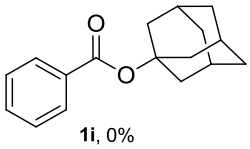
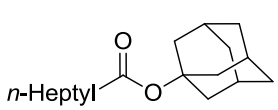
Figure 1. The effect of reaction time on the efficiency of esterification of benzoic (**1**) and octanoic acid (**2**) with methanol in the presence of 7 mol% of NBS at 70 °C.

Encouraged by these promising results, the scope of the alcohols, suitable for esterification with acids **1** and **2**, has been studied (Table 2). It can be observed that almost in all cases, alkyl acid (**2**) is significantly more active than aromatic acid (**1**) and the conversions to the corresponding esters (**2a–i**) are higher. Since nucleophilic characters, as well as steric properties, have been envisioned to have a considerable impact on reaction kinetics, different alcohols have been tested (**a–i**, Table 2). 2-Fluoro-1-ethanol (FCH_2CH_2OH, **b**) is a significantly weaker nucleophile than MeOH, therefore the reaction time for esterification of **1** as well as of **2** had to be prolonged. The elongation of the alcohol alkyl chain (**a**, **d**, **f**) had a stronger impact on esterification efficiency of benzoic acid than on esterification efficiency of octanoic acid, resulting in higher yields of octanoate esters (**2a**, **2d**, **2f**) relative to benzoate esters (**1a**, **1d**, **1f**). Moreover, the effect of increased steric hindrance of the nucleophilic alcohol component was followed by varying the bulkiness of alcohol from primary to tertiary structure (**a**, **c** and **g**, **e** and **i**). Interestingly, the esterification of octanoic acid was considerably less affected by the structural change from primary (MeOH, **2a**) to secondary alcohol (*i*-PrOH and cyclopentanol, **2c** and **2g**) than the transformation of benzoic acid, where low (*i*-PrOH, **1a**) or no conversion (cyclopentanol, **1g**) was detected. Unfortunately, the limitation of the method was observed in reactions with bulky tertiary alcohols *t*-BuOH (**e**) and adamantanol (**i**), where no product was detected. Similarly, when phenol (**h**) has been used as the nucleophile, no reaction products were noticed, which can be assigned to the low nucleophilicity originating from the relatively high acidity of phenol molecule.

Due to the commercial importance of certain methyl esters in biodiesel production (fatty acid methyl esters, FAME) and perfumery (methyl benzoate), esterification of different types of carbocyclic acids with MeOH under optimal reaction conditions has been furtherly investigated (Table 3). As can be noticed, electronic effects of substituents, as well as their position on the phenyl ring of the investigated aromatic acids have exhibited a significant influence on the conversion of acids (**3–12**) to their corresponding methyl esters.

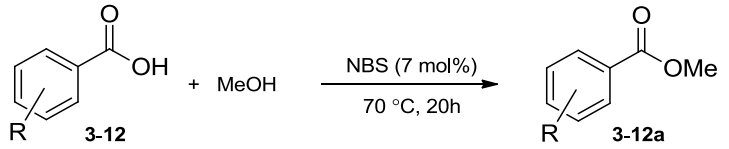
Table 2. The effect of alcohol structure on esterification of benzoic (**1**) and octanoic acid (**2**) [1,2,3].



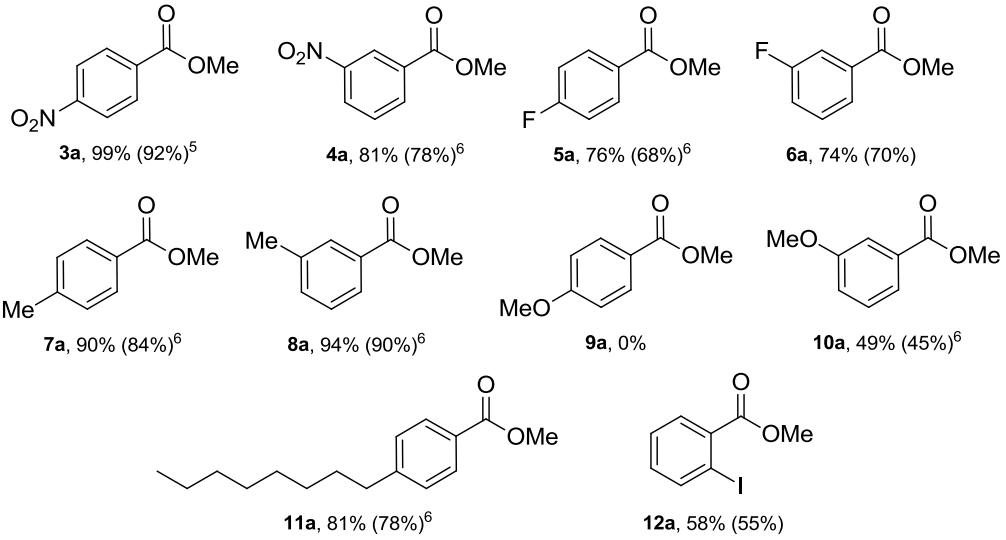
R_2OH	R_1 = Ph	R_1 = Heptyl
MeOH (**a**)	 **1a**, 94% (90%)	 **2a**, 100% (97%) [5]
FCH_2CH_2OH (**b**)	 **1b**, 99% (95%) [4]	 **2b**, 96% (92%) [4]
i-PrOH (**c**)	 **1c**, 12% (7%)	 **2c**, 85% (80%)
n-BuOH (**d**)	 **1d**, 80% (75%)	 **2d**, 100% (95%) [6]
t-BuOH (**e**)	 **1e**, 0%	 **2e**, 0%
n-Octanol (**f**)	 **1f**, 60% (57%)	 **2f**, 91% (87%)
Cyclopentanol (**g**)	 **1g**, 0%	 **2g**, 99% (94%) [6]
Phenol (**h**)	 **1h**, 0%	 **2h**, 0%
 (**i**)	 **1i**, 0%	 **2i**, 0%

[1] Reaction conditions: carboxylic acid (1 mmol), alcohol (1 mmol, 2 mmol or 0.5 mL), NBS (0.07 mmol), 70 °C, 20 h. [2] Conversions were determined by ^{1}H NMR spectroscopy. [3] The values in brackets stand for yields of isolated products. [4] Conversion (yield of isolated product) after 40 h. [5] Conversion (yield of isolated product) after 2 h. [6] Conversion (yield of isolated product) after 15 h.

Table 3. Esterification of substituted benzoic and different alkyl carboxylic acids with MeOH in the presence of NBS [1,2,3].



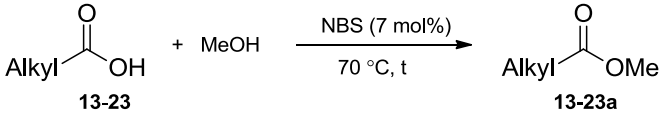
Methyl Benzoates



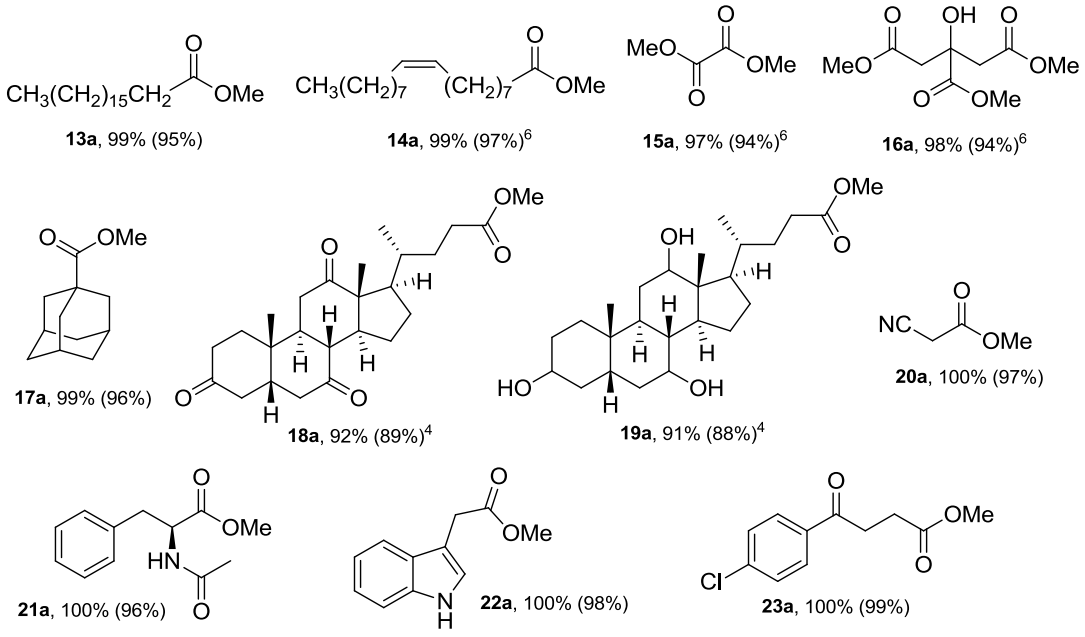
3a, 99% (92%)[5] **4a**, 81% (78%)[6] **5a**, 76% (68%)[6] **6a**, 74% (70%)

7a, 90% (84%)[6] **8a**, 94% (90%)[6] **9a**, 0% **10a**, 49% (45%)[6]

11a, 81% (78%)[6] **12a**, 58% (55%)



Methyl Alkyl Esters and Methyl Esters of Cholic Acid Derivatives



13a, 99% (95%) **14a**, 99% (97%)[6] **15a**, 97% (94%)[6] **16a**, 98% (94%)[6]

17a, 99% (96%) **18a**, 92% (89%)[4] **19a**, 91% (88%)[4] **20a**, 100% (97%)

21a, 100% (96%) **22a**, 100% (98%) **23a**, 100% (99%)

[1] Reaction conditions: carboxylic acid (1 mmol), MeOH (0.5 mL), NBS (0.07 mmol), 70 °C, 1–20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets stand for yields of isolated products. [4] Reaction conditions: carboxylic acid (0.25 mmol), MeOH (2 mL), NBS (0.018 mmol), 70 °C, 1 h; conversion (yield of isolated product) after 1 h. [5] 1.5 mL of MeOH was used. [6] 2 mL of MeOH was used.

Strong electron-withdrawing (4-NO_2, 3-NO_2), as well as weak electron-donating groups (4-Me, 3-Me) with only positive inductive +I and no mesomeric effect (M) have expressed moderate impact on the yield, while substituents with positive mesomeric (+M) and negative inductive (–I) effects (4-F, 3-F) have resulted in a decrease in the conversion. The strong electron-donating group at para position (–OMe, compound **9**) has completely inhibited the reaction due to the strong resonance interaction between the lone electron pair of the substituent and carboxyl functional group, while *m*–positioned methoxy group which could not resonate with carboxyl moiety, resulted in fair yield of target benzoate **10a**. On the other hand, in the case of aliphatic carboxylic acids, no scope limits have been observed and methyl stearate (**13a**), as well as methyl oleate (**14a**), methyl 2-cyanoacetate (**20a**), (*S*)-methyl 2-acetamido-3-phenylpropanoate (**21a**), methyl 2-(1*H*-indol-3-yl)acetate (**22a**) and methyl 4-(4-chlorophenyl)-4-oxobutanoate (**23a**) have been obtained almost quantitatively, while dimethyl oxalate (**15a**), trimethyl citrate (**16a**), and adamantane-1-carboxylic acid methyl ester (**17a**) have been gained in excellent yields.

Furthermore, the applicability of the method on more complex structural backbones has been demonstrated by performing the esterification of two significant steroidal carboxylic acids: cholic acid as one of the most common bile acids, formed as an end product of cholesterol metabolism in the liver [54], and its derivative dehydrocholic acid, which is the main component in many drugs against cholestatic liver disease and for dissolution of cholesterol gallstones [55]. In both cases, an excellent conversion of the starting material was achieved already after 1 h. Although in the crude reaction mixture obtained after esterification of dehydrocholic acid, partial conversion to ketal was observed, it was quantitatively converted into the corresponding ester during the isolation step by washing the mixture with 10% $hCl_{(aq)}$.

Moreover, to confirm the synthetic value of the presented methodology, synthesis of methyl benzoate (**1a**), methyl stearate (**13a**) and methyl citrate (**16a**) has been performed on 10–40 mmol scale with high to excellent yields (85–100%).

3. Materials and Methods

3.1. General Information

All reactions were performed in Mettler-Toledo Easymax 102 Advanced Synthesis Workstation using 25 mL reactor tubes. NMR spectra were recorded on Varian Inova 300 spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C, 285 MHz ^{19}F) at 25 °C. ^{1}H-NMR spectra were obtained as solutions in $CDCl_3$ with TMS as the internal standard. ^{19}F-NMR spectra were obtained as solutions in $CDCl_3$ with $CFCl_3$ as the internal standard. *N*-bromosuccinimide was freshly recrystallized before use. All other chemicals used for synthetic procedures were obtained from commercial sources and were of reagent grade purity or better (Merck, Sigma Aldrich, Carlo Erba, Fluka, Fisher Scientific, Apollo Scientific, etc.). Reactions were monitored by TLC with silica gel coated plates Silica gel/TLC cards, DC-Alufolien-Kieselgel with 60 Å medium pore diameter (Sigma Aldrich) and detection was conducted by UV absorption (254 nm). Purification of certain products was conducted on preparative silica gel glass plates PLC Kieselgel 60 F254 with 2 mm layer thickness. Succinimide, isolated at the end of the reaction, can easily be recycled back to *N*-bromosuccinimide according to the standard procedure by NaOH, as elaborated in other reports [56]. Copies of ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra of isolated final products are available in Supplementary material file online.

3.2. Experimental Procedures

3.2.1. General Procedure for the Esterification between Carboxylic Acids and Alcohols

The mixture of carboxylic acid, alcohol and *N*-bromosuccinimide was stirred in a 25 mL reactor tube at 70 °C for 2–40 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The isolation procedure was as

follows, except where noted differently in Section 3.2.6. The residue was dissolved in ethyl acetate and consecutively washed with 10 mL of 10% $Na_2S_2O_{3\,(aq)}$, 5 mL of saturated $NaHCO_{3\,(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure.

3.2.2. Scale-Up Procedure for Preparation of Methyl Benzoate (**1a**) and Isolation of Succinimide

The mixture of benzoic acid (40 mmol, 4.88 g), MeOH (20 mL) and *N*-bromosuccinimide (2.80 mmol, 0.50 g) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was washed with distilled water (20 mL) and the water phase was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined and washed with the mixture of 10 mL of saturated $NaHCO_{3\,(aq)}$, 10 mL of 10% $Na_2S_2O_{3\,(aq)}$ and 15 mL of distilled water. The water layer was again extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl benzoate as colourless oil. The water layer from the first washing of the crude reaction mixture was evaporated under the reduced pressure to give succinimide as a white solid.

Yield (methyl benzoate): 4.60 g, 85%.
Yield (succinimide [57]): 272 mg, 98%.
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 2.72 (s, 4H).
^{13}C NMR (76 MHz, $CDCl_3$) δ 178.8, 29.4.

3.2.3. Scale-Up Procedure for Preparation of Trimethyl Citrate (**16a**)

The mixture of citric acid (11 mmol, 2.11 g), MeOH (20 mL) and *N*-bromosuccinimide (0.77 mmol, 0.138 g) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate, washed with the mixture of 10 mL of saturated $NaHCO_{3\,(aq)}$, 10 mL of 10% $Na_2S_2O_{3\,(aq)}$ and 25 mL of distilled water and the water phase was extracted with ethyl acetate (2 × 25 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl citrate as a white solid.

Yield: 2.55 g, 99%.

3.2.4. Scale-Up Procedure for Preparation of Methyl Stearate (**13a**)

The mixture of stearic acid (10 mmol, 2.85 g), MeOH (20 mL) and *N*-bromosuccinimide (0.70 mmol, 0.125 g) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate, washed with the mixture of 10 mL of saturated $NaHCO_{3\,(aq)}$, 10 mL of 10% $Na_2S_2O_{3\,(aq)}$ and 15 mL of distilled water and the water phase was extracted with ethyl acetate (2 × 25 mL). The organic layers were combined, washed with distilled water (2 × 20 mL), dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl stearate as a white solid.

Yield: 2.99 g, 100%.

3.2.5. Procedure for Recycling of *N*-bromosuccinimide (NBS) from Waste Succinimide

Succinimide (0.272 g, 2.75 mmol) was dissolved in a mixture of 1.36 g (3.29 mmol) NaOH, 0.5 g crushed ice and 1.5 mL of cold water. To this mixture, 0.156 mL (3.02 mmol, 0.483 g) of Br_2 was added while stirring. It was stirred for five minutes and then the product was filtered, washed with cold water and dried in a desiccator to isolate 0.348 g (71%) of NBS.

3.2.6. Detailed Procedures for the Preparation of Synthesized Compounds

Methyl benzoate (**1a**) [17]. Synthesized according to the general procedure. Reaction conditions: benzoic acid (1 mmol, 122.1 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 122 mg of colourless oil (90%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2H), 7.59–7.51 (m, 1H), 7.43 (ddt, *J* = 8.2, 6.8, 1.1 Hz, 2H), 3.91 (s, 3H); ^{13}C-NMR (76 MHz, CDCl3) δ 167.2, 133.0, 130.3, 129.7, 128.4, 52.2; hRMS (ESI) for $C_8H_8O_2$: calculated m/z = 137.0603 (MH^+); found m/z = 137.0606 (MH^+).

Methyl octanoate (**2a**) [58]. Synthesized according to the general procedure. Reaction conditions: octanoic acid (1 mmol, 158.5 µL), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 2 h. Purification: Not necessary. Yield: 153 mg of colourless oil (97%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.69–1.56 (m, 2H), 1.35–1.25 (m, 8H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 174.5, 51.5, 34.2, 31.8, 29.2, 29.0, 25.1, 22.7, 14.2; hRMS (ESI) for $C_9H_{18}O_2$: calculated m/z = 159.1385 (MH^+); found m/z = 159.1389 (MH^+).

Methyl 4-nitrobenzoate (**3a**) [17]. Synthesized according to the general procedure. Reaction conditions: 4-nitrobenzoic acid (1 mmol, 167.1 mg), MeOH (1.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 167 mg of white solid (92%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.34–8.19 (m, 4H), 3.99 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 165.2, 150.6, 135.6, 130.8, 123.6, 77.2, 52.9.

Methyl 3-nitrobenzoate (**4a**) [59]. Synthesized according to the general procedure. Reaction conditions: 3-nitrobenzoic acid (1 mmol, 167.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 141 mg of yellow solid (78%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.94–8.75 (m, 1H), 8.50–8.30 (m, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 4.00 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 165.0, 148.3, 135.3, 131.9, 129.7, 127.4, 124.6, 52.8; hRMS (ESI) for $C_8H_7NO_4$: calculated m/z = 182.0453 (MH^+); found m/z = 182.0457 (MH^+).

Methyl 4-fluorobenzoate (**5a**) [60]. Synthesized according to the general procedure. Reaction conditions: 4-fluorobenzoic acid (1 mmol, 140.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 105 mg of colourless oil (68%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 10.1, 5.2, 2.5 Hz, 2H), 7.13–7.03 (m, 2H), 3.89 (s, 3H); ^{13}C-NMR (76 MHz, CDCl3) δ 166.2, 165.8 (d, *J* = 253.5 Hz) 132.2 (d, *J* = 9.4 Hz), 126.5 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 22.0 Hz), 52.2; ^{19}F-NMR (285 MHz, CDCl3) δ -106.34 (tt, *J* = 8.5, 5.4 Hz); hRMS (ESI) for $C_8H_7FO_2$: calculated m/z = 155.0508 (MH^+); found m/z = 155.0505 (MH^+).

Methyl 3-fluorobenzoate (**6a**) [61]. Synthesized according to the general procedure. Reaction conditions: 3-fluorobenzoic acid (1 mmol, 140.1 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 108 mg of colourless oil (70%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.71 (ddd, *J* = 9.4, 2.6, 1.5 Hz, 1H), 7.41 (td, *J* = 8.0, 5.6 Hz, 1H), 7.25 (tdd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 3.92 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 166.0, 162.6 (d, *J* = 246.6 Hz), 132.4 (d, *J* = 7.6 Hz), 130.1 (d, *J* = 7.6 Hz), 125.4 (d, *J* = 2.9 Hz), 120.1 (d, *J* = 21.4 Hz), 116.6 (d, *J* = 23.0 Hz), 52.4; ^{19}F-NMR (285 MHz, $CDCl_3$) δ -112.92 (ddd, *J* = 9.4, 8.4, 5.6 Hz); hRMS (ESI) for $C_8H_7FO_2$: calculated m/z = 155.0508 (MH^+); found m/z = 155.0511 (MH^+).

Methyl 4-methylbenzoate (**7a**) [60]. Synthesized according to the general procedure. Reaction conditions: 4-methylbenzoic acid (1 mmol, 136.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 126 mg of colourless oil (84%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97–7.86 (m, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.88 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 167.2, 143.6, 129.6, 129.1, 127.5, 52.0, 21.7; hRMS (ESI) for $C_9H_{10}O_2$: calculated m/z = 151.0759 (MH^+); found m/z = 151.0755 (MH^+).

Methyl 3-methylbenzoate (**8a**) [60]. Synthesized according to the general procedure. Reaction conditions: 3-methylbenzoic acid (1 mmol, 136.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 136 mg of colourless oil (90%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ

7.88–7.81 (m, 1H), 7.39–7.28 (m, 1H), 3.91 (s, 2H), 2.40 (s, 1H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 167.3, 138.2, 133.7, 130.2, 130.2, 128.3, 126.8, 52.1, 21.3; hRMS (ESI) for $C_9H_{10}O_2$: calculated m/z = 151.0759 (MH^+); found m/z = 151.0762 (MH^+).

Methyl 3-methoxybenzoate (**10a**) [62]. Synthesized according to the general procedure. Reaction conditions: 3-methoxybenzoic acid (1 mmol, 152.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 75 mg of yellow oil (45%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66–7.53 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.09 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 167.0, 159.6, 131.5, 129.4, 122.0, 119.5, 114.0, 55.4, 52.2; hRMS (ESI) for $C_9H_{10}O_3$: calculated m/z = 167.0708 (MH^+); found m/z = 167.0717 (MH^+).

Methyl 4-octylbenzoate (**11a**) [63]. Synthesized according to the general procedure. Reaction conditions: 4-octylbenzoic acid (1 mmol, 234.3 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 194 mg of yellow oil, (78%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02–7.87 (m, 2H), 7.31–7.16 (m, 2H), 3.89 (s, 3H), 2.73–2.57 (m, 2H), 1.69–1.54 (m, 2H), 1.43–1.19 (m, 10H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 167.3, 148.6, 129.7, 128.5, 127.7, 52.0, 36.1, 32.0, 31.2, 29.5, 29.4, 29.3, 22.8, 14.2; hRMS (ESI) for $C_{16}H_{24}O_2$: calculated m/z = 249.1855 (MH^+); found m/z = 249.1853 (MH^+).

Methyl 2-iodobenzoate (**12a**) [64]. Synthesized according to the general procedure. Reaction conditions: 2-iodobenzoic acid (1 mmol, 248.0 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 144 mg of colourless oil (55%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.9, 1.1 Hz, 1H), 7.76 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (td, J = 7.6, 1.1 Hz, 1H), 7.11 (td, J = 7.7, 1.7 Hz, 1H), 3.90 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 166.9, 141.3, 135.1, 132.7, 130.9, 127.9, 94.1, 52.5; hRMS (ESI) for $C_8H_7IO_2$: calculated m/z = 262.9569 (MH^+); found m/z = 262.9563 (MH^+).

Methyl stearate (**13a**) [14]. Synthesized according to the general procedure. Reaction conditions: stearic acid (1 mmol, 284.5 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 285 mg of white solid (95%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.69–1.55 (m, 2H), 1.37–1.20 (m, 28H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 174.5, 51.6, 34.3, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.3; hRMS (ESI) for $C_{19}H_{38}O_2$: calculated m/z = 299.2950 (MH^+); found m/z = 299.2957 (MH^+).

Methyl oleate (**14a**) [14]. Synthesized according to the general procedure. Reaction conditions: oleic acid (1 mmol, 315.6 μL), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 15 h. Purification: Not necessary. Yield: 289 mg of colorless oil, (97%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.34 (ddd, J = 5.6, 3.5, 2.1 Hz, 2H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.10–1.91 (m, 4H), 1.71–1.54 (m, 2H), 1.42–1.17 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 174.4, 130.1, 129.9, 51.5, 34.2, 32.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.3, 29.2, 27.3, 27.3, 25.1, 22.8, 14.2; hRMS (ESI) for $C_{19}H_{36}O_2$: calculated m/z = 297.2794 (MH^+); found m/z = 297.2798 (MH^+).

Dimethyl oxalate (**15a**) [65]. Synthesized according to the general procedure. Reaction conditions: oxalic acid (1 mmol, 90.0 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 15 h. Purification: Not necessary. Yield: 110 mg of white solid (93%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 6H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 157.8, 53.5; hRMS (ESI) for $C_4H_6O_4$: calculated m/z = 119.0344 (MH^+); found m/z = 119.0342 (MH^+).

Trimethyl citrate (**16a**) [66]. Synthesized according to the general procedure. Reaction conditions: citric acid (1 mmol, 210.1 mg), MeOH (2 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 220 mg of white solid (94%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 1H), 3.81 (s, 3H), 3.67 (s, 6H), 2.89 (d, J = 15.6 Hz, 2H), 2.79 (d, J = 15.6 Hz, 2H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.8, 170.2, 73.3, 53.2, 52.0, 43.1; hRMS (ESI) for $C_9H_{14}O_7$: calculated m/z = 235.0818 (MH^+); found m/z = 235.0815 (MH^+).

Adamantane-1-carboxylic acid methyl ester (**17a**) [61]. Synthesized according to the general procedure. Reaction conditions: 1-adamantanecarboxylic acid (1 mmol, 180.2 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 186 mg of white solid (96%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.01–1.92 (m, 3H), 1.88–1.80 (m, 6H), 1.74–1.59 (m, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 178.08, 51.44, 40.64, 38.81, 36.46, 27.91; hRMS (ESI) for $C_{12}H_{18}O_2$: calculated m/z = 195.1385 (MH^+); found m/z = 195.1382 (MH^+).

Methyl 3,7,12-trioxo-5β-cholan-24-oate (**18a**) [67]. The mixture of dehydrocholic acid (0.25 mmol, 101.6 mg), MeOH (2 mL) and *N*-bromosuccinimide (0.018 mmol, 3.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 1 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and first washed with the mixture of 10 mL of 10% $Na_2S_2O_{3\,(aq)}$, 5 mL of saturated $NaHCO_{3\,(aq)}$ and 10 mL of distilled water and then with 10 mL of 10% $hCl_{\,(aq)}$. The water phase was extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure. Purification: Not necessary. Yield: 93 mg of white solid (89%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.01–2.75 (m, 3H), 2.51–1.16 (m, 21H), 1.41 (s, 3H), 1.08 (s, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 212.0, 209.1, 208.8, 174.5, 56.9, 51.8, 51.5, 49.0, 46.9, 45.7, 45.6, 45.0, 42.8, 38.7, 36.5, 36.1, 35.6, 35.3, 31.3, 30.5, 27.7, 25.2, 22.0, 18.7, 11.9; hRMS (ESI) for $C_{25}H_{36}O_5$: calculated m/z = 417.2641 (MH^+); requires m/z = 417.2644 (MH^+).

Methyl 3α,7α,12α-trihydroxy-5β-cholan-24-oate (**19a**) [68]. The mixture of cholic acid (0.25 mmol, 102.1 mg), MeOH (2 mL) and *N*-bromosuccinimide (0.018 mmol, 3.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 1 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 10 mL of 10% $Na_2S_2O_{3\,(aq)}$, 5 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure. Purification: Not necessary. Yield: 93 mg of white solid (88%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 1H), 3.83 (s, 1H), 3.66 (s, 3H), 3.55 (s, 3H), 3.49–3.32 (m, 1H), 2.48–1.07 (m, 24H), 0.98 (d, J = 5.8 Hz, 3H), 0.88 (s, 3H), 0.67 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 174.7, 72.9, 71.7, 68.3, 51.3, 46.8, 46.2, 41.4, 41.4, 39.3, 39.3, 35.2, 35.2 34.6, 34.6, 31.0, 30.8, 30.2, 28.0, 27.4, 26.1, 23.1, 22.3, 17.2, 12.3; hRMS (ESI) for $C_{25}H_{42}O_5$: calculated m/z = 423.3110 (MH^+); found m/z = 423.3128 (MH^+).

Methyl 2-cyanoacetate (**20a**) [69]. Synthesized according to the general procedure. Reaction conditions: Cyanoacetic acid (1 mmol, 85.1 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 96 mg of colourless oil (97%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.46 (s, 2H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 163.6, 113.2, 53.5, 24.4; hRMS (ESI) for $C_4H_5NO_2$: calculated m/z = 100.0399 (MH^+); found m/z = 100.0398 (MH^+).

(S)-Methyl 2-acetamido-3-phenylpropanoate (**21a**) [70]. Synthesized according to the general procedure. Reaction conditions: *N*-Acetyl-L-phenylalanine (1 mmol, 207.2 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 208 mg of white solid (91%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33–7.18 (m, 3H), 7.18–7.05 (m, 2H), 6.38 (d, J = 7.5 Hz, 1H), 4.95–4.77 (m, 1H), 3.69 (s, 3H), 3.21–2.93 (m, 2H), 1.95 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 172.2, 169.8, 136.0, 129.2, 128.5, 127.0, 53.2, 52.2, 37.8, 22.9; hRMS (ESI) for $C_{12}H_{15}NO_3$: calculated m/z = 222.1130 (MH^+); found m/z = 222.1135 (MH^+).

Methyl 2-(1H-indol-3-yl)acetate (**22a**) [71]. Synthesized according to the general procedure. Reaction conditions: heteroauxin (1 mmol, 175.2 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 185 mg of brown oil (98%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.56 (dd, J = 6.7, 1.6 Hz, 2H), 7.24–6.98 (m, 3H), 6.84 (d, J = 2.4 Hz, 1H), 3.72 (s, 2H), 3.63 (s, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.0, 136.1, 127.1, 123.4, 122.0, 119.5, 118.6, 111.4, 107.8, 52.0, 31.1; hRMS (ESI) for $C_{11}H_{11}NO_2$: calculated m/z = 190.0868 (MH^+); found m/z = 190.0865 (MH^+).

Methyl 4-(4-chlorophenyl)-4-oxobutanoate (**23a**) [72]. Synthesized according to the general procedure. Reaction conditions: 3-(4-Chlorobenzoyl)propionic acid (1 mmol, 212.6 mg), MeOH (0.5 mL), NBS (0.070 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 224 mg of white solid (99%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90–7.81 (m, 2H), 7.41–7.33 (m, 2H), 3.64 (s, 3H), 3.22 (t, *J* = 6.6 Hz, 2H), 2.70 (t, *J* = 6.6 Hz, 2H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 196.8, 173.2, 139.6, 134.8, 129.4, 128.9, 51.8, 33.3, 27.9; hRMS (ESI) for $C_{12}H_{18}O_2$: calculated *m*/*z* = 249.0294 (MNa^+); found *m*/*z* = 249.0297 (MNa^+).

2-Fluoroethyl benzoate (**1b**) [73]. Synthesized according to the general procedure. Reaction conditions: benzoic acid (1 mmol, 122.1 mg), 2-fluoroethanol (0.5 mL), NBS (0.07 mmol, 12.5 mg), 70 °C, 40 h. Purification: Preparative TLC (CH_2Cl_2/MeOH = 200:1). Yield: 160 mg of colourless oil (95%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20–7.86 (m, 2H), 7.60–7.52 (m, 1H), 7.49–7.37 (m, 2H), 4.85–4.44 (m, 4H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 166.4, 133.3, 129.8, 128.5, 81.5 (d, *J* = 170.6 Hz), 63.9 (d, *J* = 20.2 Hz); ^{19}F NMR (285 MHz, CDCl3) δ 5.03 (tt, *J* = 47.4, 28.6 Hz); hRMS (ESI) for $C_9H_9FO_2$: calculated *m*/*z* = 169.0665 (MH^+); found *m*/*z* = 169.0668 (MH^+).

*Isopropyl benzoate (**1c**)* [74]. Synthesized according to the general procedure. Reaction conditions: benzoic acid (1 mmol, 122.1 mg), isopropanol (0.5 mL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 12 mg of colourless oil (7%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09–7.99 (m, 2H), 7.59–7.50 (m, 1H), 7.47–7.38 (m, 2H), 5.26 (hept, *J* = 6.3 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 6H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 166.3, 132.8, 131.1, 129.6, 128.4, 68.5, 22.1.

2-Fluoroethyl octanoate (**2b**) [75]. Synthesized according to the general procedure. Reaction conditions: octanoic acid (1 mmol, 158.5 µL), 2-fluoroethanol (0.5 mL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 175 mg of yellow oil (92%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.73–4.20 (m, 4H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.71–1.57 (m, 2H), 1.42–1.19 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.7, 81.5 (d, *J* = 170.3 Hz), 63.2 (d, *J* = 20.1 Hz), 34.2, 31.7, 29.1, 29.0, 25.0, 22.7, 14.1; ^{19}F-NMR (285 MHz, CDCl3) δ 4.86 (tt, *J* = 47.4, 28.7 Hz); hRMS (ESI) for $C_{10}H_{19}FO_2$: calculated *m*/*z* = 191.1447 (MH^+); found *m*/*z* = 191.1446 (MH^+).

Isopropyl octanoate (**2c**) [76]. Synthesized according to the general procedure. Reaction conditions octanoic acid (1 mmol, 158.5 µL), isopropanol (0.5 mL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Not necessary. Yield: 149 mg of colourless oil (80%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.00 (hept, *J* = 6.3 Hz, 1H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.67–1.55 (m, 2H), 1.35–1.25 (m, 8H), 1.23 (d, *J* = 6.3 Hz, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.4, 67.3, 34.8, 31.7, 29.2, 29.0, 25.1, 22.7, 21.9, 14.1; hRMS (ESI) for $C_{11}H_{22}O_2$: calculated *m*/*z* = 187.1698 (MH^+); found *m*/*z* = 187.1703 (MH^+).

n-Butyl benzoate (**1d**) [77]. Synthesized according to the general procedure. Reaction conditions: benzoic acid (1 mmol, 122.1 mg), *n*-butanol (0.5 mL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Preparative TLC (CH_2Cl_2/MeOH = 200:1). Yield: 134 mg of colourless oil (75%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10–7.99 (m, 2H), 7.58–7.49 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 4.32 (t, *J* = 6.6 Hz, 2H), 1.84–1.66 (m, 2H), 1.56–1.39 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (76 MHz, CDCl3) δ 166.7, 132.8, 130.6, 129.6, 128.4, 64.9, 30.9, 19.4, 13.8; hRMS (ESI) for $C_{11}H_{14}O_2$: calculated *m*/*z* = 179.1072 (MH^+); found *m*/*z* = 179.1070 (MH^+).

n-Butyl octanoate (**2d**) [4]. Synthesized according to the general procedure. Reaction conditions octanoic acid (1 mmol, 158.5 µL), *n*-butanol (1 mmol, 92 µL), NBS (0.07 mmol, 12.5 mg), 70 °C, 15 h. Purification: Not necessary. Yield: 190 mg of colourless oil (95%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.07 (t, *J* = 6.6 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.70–1.52 (m, 4H), 1.47–1.21 (m, 10H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 174.0, 64.1, 34.4, 31.8, 30.8, 29.2, 29.0, 25.1, 22.7, 19.2, 14.1, 13.7; hRMS (ESI) for $C_{12}H_{24}O_2$: calculated *m*/*z* = 201.1855 (MH^+); found *m*/*z* = 201.1857 (MH^+).

*n-Octyl benzoate (**1f**)* [58]. Synthesized according to the general procedure. Reaction conditions: benzoic acid (1 mmol, 122.1 mg), *n*-octanol (1 mmol, 158 µL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Preparative TLC (CH_2Cl_2/Hexane = 1:1). Yield: 134 mg of white solid (57%); ^{1}H-NMR (300 MHz,

CDCl3) δ 8.10–8.00 (m, 2H), 7.59–7.51 (m, 1H), 7.47–7.39 (m, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 1.83–1.70 (m, 2H), 1.51–1.21 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 166.8, 132.9, 130.7, 129.7, 128.4, 65.3, 31.9, 29.4, 29.3, 28.9, 26.2, 22.8, 14.2; hRMS (ESI) for $C_{15}H_{22}O_2$: calculated m/z = 235.1698 (MH^+); found m/z = 235.1697 (MH^+).

n-Octyl octanoate (**2f**) [78]. Synthesized according to the general procedure. Reaction conditions: octanoic acid (1 mmol, 158.5 μL), *n*-octanol (1 mmol, 158 μL), NBS (0.07 mmol, 12.5 mg), 70 °C, 20 h. Purification: Preparative TLC (CH_2Cl_2/MeOH = 200:1). Yield: 223 mg of colourless oil (87%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.06 (t, *J* = 6.7 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.68–1.54 (m, 4H), 1.39–1.19 (m, 18H), 0.88 (t, *J* = 6.3 Hz, 6H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.9, 64.4, 34.4, 31.9, 31.8, 29.3, 29.3, 29.2, 29.0, 28.8, 26.0, 25.1, 22.7, 22.7, 14.1, 14.1; hRMS (ESI) for $C_{16}H_{32}O_2$: calculated m/z = 257.2481 (MH^+); found m/z = 257.2486 (MH^+).

Cyclopentyl octanoate (**2g**) [79]. Synthesized according to the general procedure. Reaction conditions: octanoic acid (1 mmol, 158.5 μL), cyclopentanol (1 mmol, 91 μL), NBS (0.07 mmol, 12.5 mg), 70 °C, 15 h. Purification: Not necessary. Yield: 200 mg of colourless oil (94%); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.16 (tt, *J* = 5.9, 2.6 Hz, 1H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.95–1.47 (m, 10H), 1.41–1.20 (m, 8H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (76 MHz, $CDCl_3$) δ 173.8, 76.8, 34.8, 32.8, 31.8, 29.2, 29.0, 25.2, 23.8, 22.7, 14.1; hRMS (ESI) for $C_{13}H_{24}O_2$: calculated m/z = 213.1855 (MH^+); found m/z = 213.1860 (MH^+).

4. Conclusions

In conclusion, a convenient and selective metal-free method for direct dehydrative esterification of free aromatic and aliphatic acids with different alcohols has been developed, using inexpensive and easy-to-handle *N*-bromosuccinimide as a moisture- and air-tolerant recyclable catalyst. The synthesis has been performed under neat reaction conditions without the need for simultaneous removal of water and excessive reagents. In spite of some scope limitations, the method provides good to excellent product yields and in the majority of cases, enables simple isolation procedure only by extraction. Even in the case of di- and tri-carboxy aliphatic acids, esterification has been successfully accomplished with the same amount of NBS catalyst as in the case of mono-carboxy alkyl acids. The applicability of the method has been successfully demonstrated also on steroidal carboxylic acids. The large-scale synthesis of methyl benzoate, methyl stearate and trimethyl citrate as examples of commercially significant esters has been performed with high to excellent yields (85–100%).

Supplementary Materials: The following are available online, ^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra of isolated final products.

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Sample Availability: Samples of the compounds are not available from the authors.

Chapter 6

1,3-Dibromo-5,5-dimethylhydantoin as a Precatalyst for Activation of Carbonyl Functionality

Activation of the carbonyl moiety is one of the most elementary techniques towards functionalisation of organic molecules in organic synthesis and is crucial for a plethora of industrial-scale condensation reactions. In esterification and aldol condensation, which represent two of the most important transformations, the susceptibility of the carbonyl group to nucleophile attack allows the formation of a variety of useful organic compounds. Accordingly, development and upgrade of the methods for addition-elimination reactions *via* activation of carbonyl functionality is a continuous necessity in the construction of organic backbones. In this chapter, an upgraded approach for direct esterification of carboxylic acids and alcohols and for aldol condensation of aldehydes using widely available, low-cost and metal-free 1,3-dibromo-5,5-dimethylhydantoin under neat reaction conditions is elaborated. The method is air- and moisture-tolerant, allowing a simple synthetic and isolation procedure for both reactions presented in this paper. Moreover, the reaction pathway for esterification was proposed and scale-up of certain industrially important derivatives performed.

Author's contribution

Klara Čebular performed the literature overview and co-planned, co-designed and performed the experiments. The author participated in the formal analysis of the obtained results and their interpretation, in writing of the original draft of the manuscript and in its revision and edit.

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1,3-Dibromo-5,5-dimethylhydantoin as a Precatalyst for Activation of Carbonyl Functionality

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Abstract: Activation of carbonyl moiety is one of the most rudimentary approaches in organic synthesis and is crucial for a plethora of industrial-scale condensation reactions. In esterification and aldol condensation, which represent two of the most important reactions, the susceptibility of the carbonyl group to nucleophile attack allows the construction of a variety of useful organic compounds. In this context, there is a constant need for development of and improvement in the methods for addition-elimination reactions via activation of carbonyl functionality. In this paper, an advanced methodology for the direct esterification of carboxylic acids and alcohols, and for aldol condensation of aldehydes using widely available, inexpensive, and metal-free 1,3-dibromo-5,5-dimethylhydantoin under neat reaction conditions is reported. The method is air- and moisture-tolerant, allowing simple synthetic and isolation procedures for both reactions presented in this paper. The reaction pathway for esterification is proposed and a scale-up of certain industrially important derivatives is performed.

Keywords: esterification; 1,3-dibromo-5,5-dimethylhydantoin; metal-free catalyst; aryl acids; alkyl acids

1. Introduction

(Trans)esterification is one of the most prominent transformations of carbonyl functionality in academia and industry due to the undeniable significance of the ester functional group in biological systems [1] and in the fabrication of a variety of products, such as cosmetics, plasticizers, pharmaceuticals, flavor chemicals, fine chemicals, adhesives, lubricants, electronic materials, etc. [2]. It is a vital reaction in the preparation of fatty acid methyl esters (FAME), which play a crucial role in producing detergents [3] and biodiesel fuel [4,5] and in microbial source tracking (MST) [6,7]. In developing active pharmaceutical ingredients (APIs), esterification is a valuable tool for modifying the physicochemical properties of drugs [8]. Esters with low molecular mass are widely used as fragrances and are components of essential oils [9] and pheromones [10], while certain steroidal esters are known as antifungal agents [11], as biocompatible and biodegradable polyesters for biomedical applications [12], or show antiproliferative and pro-apoptotic effects in cancer treatment [13]. Moreover, cholesterol esters and triglycerides belong to the main classes of lipids, which form the bulk of animal fats and vegetable oils. A particularly interesting cholesterol ester is cholesteryl acetate, since aside from being a component of gallstones, it has been readily exploited in constructing electronic displays [14]. On the other hand, bile acids play an important role in the digestion of lipids and in lipophilic vitamin reabsorbtion [15], and act as effective excipients (intestinal absorption enhancers, promoters, etc.) [16] (Figure 1).

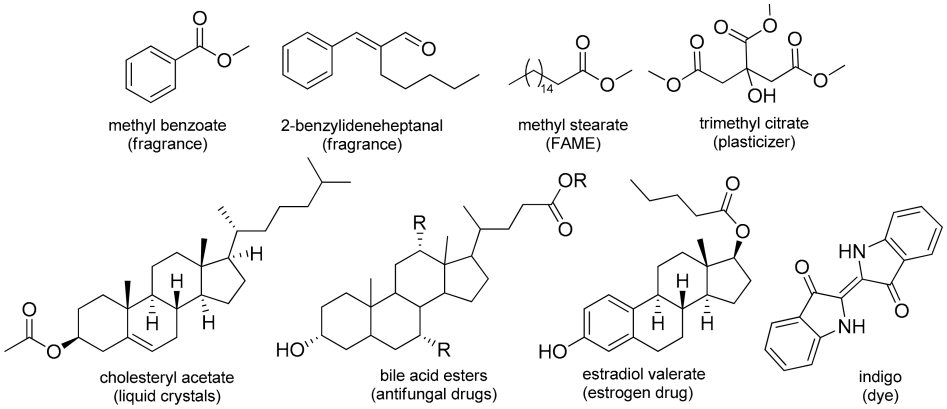


Figure 1. Structures of a selection of significant ester and aldol products.

The most extensively studied and commonly utilized esterification reaction is direct condensation between carboxylic acid and alcohol (Fischer esterification) [17]. Conventional approaches involve excessive reagents/dehydrative agents or use activated carboxylic acid derivatives in the presence of a stoichiometric base, leading to considerable amounts of byproducts and waste at the end of the process, and culminating in resource-consuming purification [18,19]. Consequently, catalytic direct esterification [20], lacking these disadvantages, has become the preferred method among researchers, employing a vast number of catalysts: Brønsted acids/bases [21,22], Lewis acids [23], metal catalysts [24], solid-supported catalysts [25,26], solid acids [27,28], ionic liquids [29,30], PPh_3-based catalysts [31], enzymes [32], zeolites [33], etc.

However, in the context of sustainable industrial processes, there is an omnipresent struggle between the economical and ecological aspects of production. Therefore, an ideal method for a condensation reaction should include the use of an easily manipulable, low-cost, non-metal, water- and air-tolerant catalyst under mild, solvent-free reaction conditions without the need for simultaneous water removal, stoichiometric amounts of activators or large excesses of reagents. Furthermore, the methodology should be applicable to a broad substrate scope with high selectivity, providing high product yields, allowing scaling-up, and involving a simple purification procedure.

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) belongs to the group of cost-effective *N*-halamine disinfectants, which are becoming increasingly popular due to their long-term stability in dry storage or in a wide pH range of aqueous solutions, their safety for humans and the environment, and their ability to rapidly kill most microorganisms [34]. Furthermore, relative to inorganic halogens, they are less corrosive, more stable, and relatively cheap [35]. In addition, DBDMH is among the more established, commercially available *N*-halo reagents that are gradually attracting attention for being safe, stable, easily-handled solids that can be utilized under mild conditions for highly selective organic transformations [36–39]. Their distinctive chemical properties, owing to the presence of an N-X bond, instil them with broad, synthetic usability, especially as a source of halenium ions (X^+) or halogen radicals ($X^\bullet$) [40]. Although DBDMH-mediated acetyl ester preparation has previously been reported, this method is limited only to acylation and includes the use of an activated carboxylic acid derivative (acetic anhydride) in the presence of a halogenated solvent (CH_2Cl_2) [41].

Our previous work described a convenient esterification method mediated by *N*-bromosuccinimide in substoichiometric amounts for direct esterification [42]. With this in mind, and in the context of our continued interest in improving and developing environmentally acceptable synthetic protocols [43–48], we now report the precatalytic activity of easily manipulable, metal-free DBDMH in the direct esterification of carboxylic acids and alcohols and in the aldol condensation of aldehydes.

2. Results and Discussion

2.1. Esterification

Initially, benzoic acid (**1**) was chosen as a model substrate to optimize the esterification reaction protocol. In the typical experimental procedure, the mixture of **1** and methanol (MeOH) was heated at 70 °C in the presence of different catalysts (Figure 2).

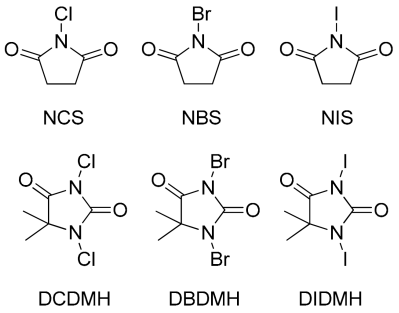
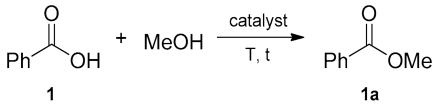


Figure 2. Structures of *N*-halosuccinimides and 1,3-dihalo-5,5-dimethylhydantoins (NCS: *N*-chlorosuccinimide, NBS: *N*-bromosuccinimide, NIS: *N*-iodosuccinimide, DCDMH: 1,3-dicholoro-5,5-dimethylhydantoin, DBDMH: 1,3-dibromo-5,5-dimethylhydantoin, DIDMH: 1,3-diiodo-5,5-dimethylhydantoin).

The results of this optimization are presented in Table 1. Among the studied catalysts (*N*-halosuccinimides, 1,3-dihalo-5,5-dimethylhydantoins, halogen mineral acids, molecular bromine and iodine), DBDMH exhibited the highest efficiency (Entry 3). In contrast, no conversion was noticed in the absence of catalyst (Entry 1). Furthermore, the effect of DBDMH loading was examined by changing its amount from a 3.5 molar percentage (mol%) to 7 mol% (Table 1, Entries 3, 7, and 8). No competing reaction was noticed, and although an excellent conversion was obtained even at 3.5 mol% (92%, Entry 8), a quantitative transformation to methyl benzoate was observed in the presence of 7 mol% of DBDMH (Entry 3). Therefore, further optimization was performed with 7 mol% of DBDMH. Furthermore, varying the temperature from 30 °C to 70 °C (Entries 3, 10, and 11) showed a considerable impact on esterification efficiency, with the optimal temperature being 70 °C (Entry 3). Under dry reaction conditions, the efficiency of esterification dropped for a substantial 20% (Entry 9), which suggests a water-assisted mechanism, as discussed below (Scheme 1).

To gain a clearer insight into the course of the reaction pathway, esterification of benzoic acid with methanol in the presence of 7 mol% of DBDMH under optimal reaction conditions was performed, with the reaction mixture being sampled every 10–15 min for the first 75 min of the reaction time and the spectra of each sample subsequently measured by ^{1}H-NMR (Figure 3). Moreover, the pH of the reaction mixture was also measured after 10, 30, and 60 min. The results presented in Figure 3 show the decomposition of DBDMH to 5,5-dimethylhydantoin (DMH) over the first 60 min. Interestingly, esterification started after the complete conversion of DBDMH to DMH, after 75 min. Furthermore, no conversion to the ester product was observed when a control experiment was performed by heating a mixture of benzoic acid and methanol under optimal reaction conditions at 70 °C in the presence of 7 mol% DMH, suggesting that the formation of bromine specie(s) during DBDMH decomposition is crucial for the esterification reaction and that the role of DBDMH is precatalytic rather than catalytic (Table 2, Entry 3). Figure 3 shows a considerable drop in pH value from 4.0–4.5 to 0–0.5 over 60 min, which stayed unchanged throughout the remainder of the reaction (24 h).

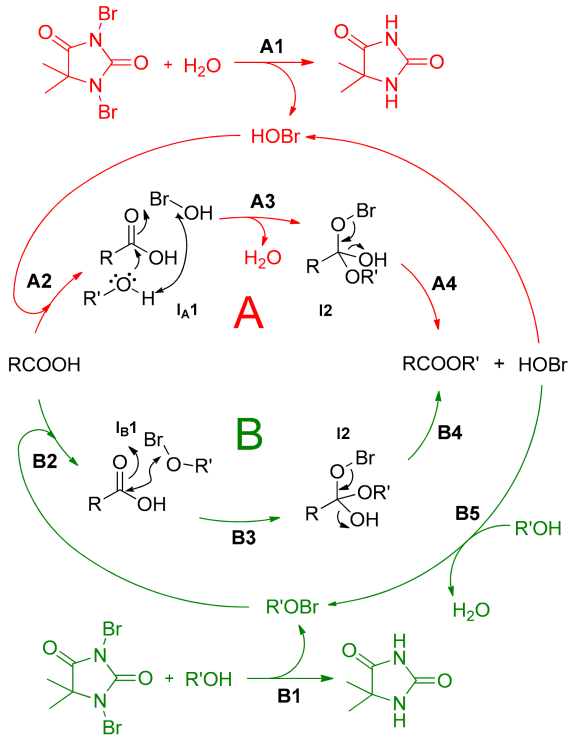
Table 1. Optimization of reaction conditions [1].



1 1a

Entry	Catalyst	Loading [mol%]	Temp. [°C]	Time [h]	Conv. [%] [2] (Yield [%])
1	/	/	70	20	0
2	DCDMH	7	70	20	88 (85)
3	DBDMH	7	70	20	100 (95)
4	DIDMH	7	70	20	30 (26)
5	HBr	7	70	20	84 (80) [3]
6	I_2	7	70	20	6 (3)
7	DBDMH	5	70	20	95 (90)
8	DBDMH	3.5	70	20	92 (88)
9	DBDMH	7	70	20	80 (77) [4]
10	DBDMH	7	50	20	75 (72)
11	DBDMH	7	30	20	0
12	DBDMH	7	70	14	90 (85)
13	DBDMH	7	70	8	86 (82)
14	DBDMH	7	70	6	79 (75)
15	DBDMH	7	70	4	70 (66)
16	DBDMH	7	70	2	15 (10)

[1] Reaction conditions: **1** (1.0 mmol), MeOH (0.5 mL), NXS, DXDMH, HCl (37%), HBr (48%), HI (57%), Br_2, I_2, T, t. [2] Conversions were determined by ^{1}H-NMR analysis of the crude reaction mixtures. [3] Data from reference [42]. [4] Freshly dried MeOH was used, and the reaction performed over anhydrous Na_2SO_4 and under nitrogen atmosphere.



(1) $5\ HOBr \rightleftharpoons 2\ Br_2 + 2\ H_2O + BrO_3^- + H^+$

(2) $Br_2 + H_2O \rightleftharpoons HOBr + HBr$

Scheme 1. Plausible reaction pathway.

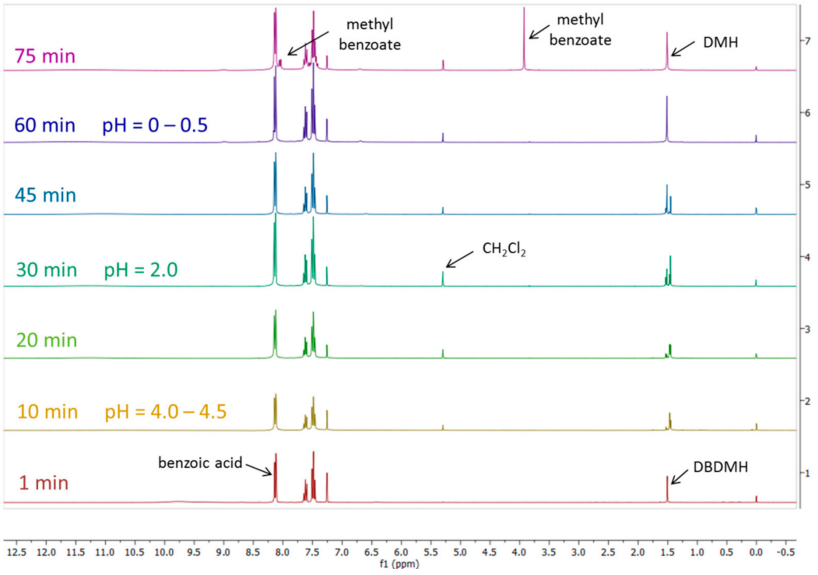


Figure 3. Timeline of the ^{1}H-NMR spectra and pH measurements for esterification of benzoic acid with methanol.

Table 2. pH measurements and conversion percentages of control esterification reactions [1,2].

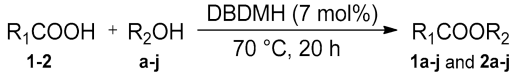
Entry	Components of the Mixture	pH [3]	Conv. [%]
1	MeOH	5.5	0
2	MeOH + DMH	5.5	0
3	MeOH + benzoic acid + DMH	3.5–4.0	0
4	MeOH + DBDMH	0.0–0.5	0
5	MeOH + benzoic acid	3.5–4.0	0
6	MeOH + benzoic acid + DBDMH	0.0–0.5	100 (95)
7	MeOH + benzoic acid + DBDMH + anh. Na_2SO_4 [4]	0.0–0.5	80 (77)
8	MeOH + DCDMH	3.0–3.5	0
9	MeOH + DIDMH	4.0–4.5	0
10	*n*-octanol	5.0	0
11	*n*-octanol + DBDMH [5]	0–0.5	<1% (octyl octanoate)
12	*n*-octanol + benzoic acid	5.0	0
13	*n*-octanol + benzoic acid/DBDMH	0–0.5	70 (65)

[1] Reaction conditions: carboxylic acid (1 mmol), MeOH (0.5 mL), precatalyst (0.07 mmol), 70 °C, 20 h; [2] Conversions were determined after 20 h by ^{1}H-NMR spectroscopy. [3] pH was measured after a reaction time of 1 h; [4] MeOH was dried with molecular sieves (4Å) and the reaction was performed under nitrogen atmosphere in the presence of Na_2SO_4; [5] Trace amounts of octyl octanoate were detected after 20 h.

These promising results encouraged us to investigate the efficiency of DBDMH in mediating the direct esterification of carboxylic acids with alcohols (Tables 3–7). In all cases, octanoic acid (**2**) showed significantly higher activity towards esterification than benzoic acid (**1**), yielding higher conversions (Table 3). Since, unlike in the case of octanoic acid, the carbonyl C-atom in the electron accepting carboxyl group of benzoic acid can receive electron density from resonance stabilization of the phenyl ring, benzoic acid is less reactive toward the nucleophile attack than octanoic acid. As reaction-limiting factors were found to include the nucleophilic character and steric properties of the substrate, different alcohols were tested (**a**–**j**, Table 3). The elongation of the alcohol alkyl chain (**a**, **d**, and **f**) had a stronger impact on the esterification efficiency of benzoic acid than on that of octanoic acid. In general, DBDMH mediation exhibited significantly higher conversions relative to *N*-bromosuccinimide (NBS), especially in the case of the secondary alcohols isopropanol (**c**) and cyclopentanol (**g**), as NBS mediation yielded only trace products or no conversion at all [42]. The reaction limitation was observed for the bulky tertiary alcohols *t*-BuOH (**e**) and adamantanol (**i**), as well as for phenol (**h**). However,

if the sterically-demanding adamantyl group was separated from the alcohol group with a CH_2 unit, the conversion increased to 79% for benzoic acid and 99% for alkyl acid (Table 3, **1j**, **2j**). The unreactivity in the case of the phenol molecule can be explained by the aromatic phenol structure, which possesses lower nucleophilicity due to the resonance delocalization of the oxygen electron pair in the OH group.

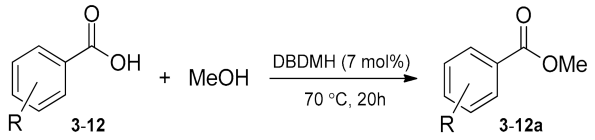
Table 3. The effect of alcohol structure on the esterification of benzoic acid (**1**) and octanoic acid (**2**) [1,2,3].



R_2OH	R_1 = Ph	R_1 = Heptyl
MeOH (**a**)	**1a**, 100% (95%)	**2a**, 100% (97%) [5]
FCH_2CH_2OH (**b**)	**1b**, 100% (96%) 4	**2b**, 98% (92%) [4]
i-PrOH (**c**)	**1c**, 29% (23%)	**2c**, 90% (86%)
n-BuOH (**d**)	**1d**, 82% (78%)	**2d**, 100% (95%) [6]
t-BuOH (**e**)	**1e**, 0%	**2e**, 0%
n-Octanol (**f**)	**1f**, 70% (65%)	**2f**, 91% (88%)
Cyclopentanol (**g**)	**1g**, 23% (21)	**2g**, 100% (94%) [6]
Phenol (**h**)	**1h**, 0%	**2h**, 0%
1-Adamantanol (**i**)	**1i**, 0%	**2i**, 0%
1-Adamantanemethanol (**j**)	**1j**, 79% (75%)	**2j**, 99% (94%)

[1] Reaction conditions: carboxylic acid (1 mmol), alcohol (1 mmol, 2 mmol, or 0.5 mL), DBDMH (0.07 mmol), 70 °C, 20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets indicate yields of isolated products. [4] Conversion (yield of isolated product) after 40 h. [5] Conversion (yield of isolated product) after 2 h. [6] Conversion (yield of isolated product) after 15 h.

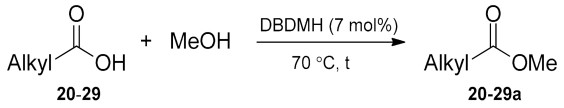
Table 4. Scope width of aromatic carboxylic acids tested under optimized esterification conditions [1,2,3].



Methyl Benzoates			
Entry	**R**	Compound	Conversion (Yield) [%]
1	4-NO_2	**3a**	100% (97%) [5]
2	4-F	**4a**	89% (85%) [6]
3	4-Me	**5a**	94% (90%) [6]
4	4-OMe	**6a**	74% (70%) [6]
5	3-NO_2	**7a**	100% (94%) [6]
6	3-F	**8a**	91% (87%)
7	3-Me	**9a**	100% (98%) [6]
8	3-OMe	**10a**	83% (78%) [6]
9	2-NO_2	**11a**	30% (25%)
10	2-F	**12a**	91% (85%)
11	2-Me	**13a**	82% (78%)
12	2-OMe	**14a**	0%
13	2-I	**15a**	62% (58%)
14	2,4-MeO	**16a**	0%
15	3,5-MeO	**17a**	0%
16	3,4-MeO	**18a**	70% (64%) [4,6]
17	methyl isonicotinate	**19a**	0%

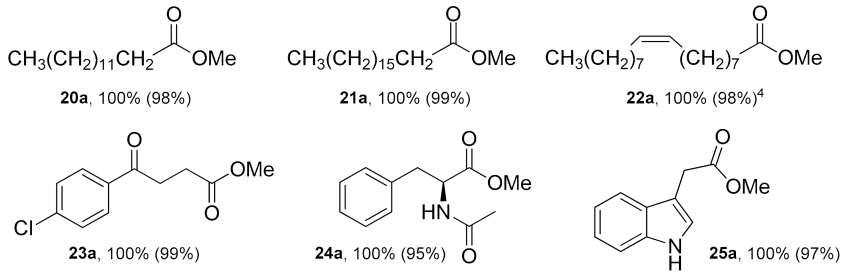
[1] Reaction conditions: carboxylic acid (1 mmol), MeOH (0.5 mL), DBDMH (0.07 mmol), 70 °C, 20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets stand for yields of isolated products. [4] Conversion (yield of isolated product) after 40 h. [5] A MeOH volume of 1.5 mL was used. [6] A MeOH volume of 2 mL was used.

Table 5. Scope of alkyl acids [1,2,3].



20-29 **20-29a**

Methyl alkyl esters



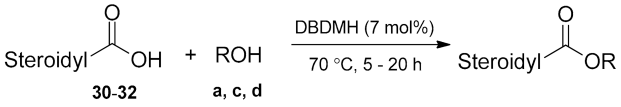
20a, 100% (98%) **21a**, 100% (99%) **22a**, 100% (98%)[4]

23a, 100% (99%) **24a**, 100% (95%) **25a**, 100% (97%)

26a, 100% (97%) **27a**, 100% (97%) **28a**, 100% (95%)[4] **29a**, 100% (94%)[4]

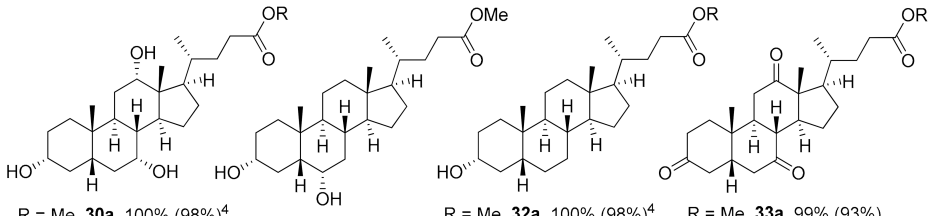
[1] Reaction conditions: carboxylic acid (1 mmol), MeOH (0.5 mL), DBDMH (0.07 mmol), 70 °C, 2–20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets indicate yields of isolated products. [4] A MeOH volume of 2 mL was used.

Table 6. Esterification of bile acids [1,2,3].



30-32 **a, c, d**

Methyl Esters of Cholic Acid Derivatives



R = Me, **30a**, 100% (98%)[4]
i-Pr, **30c**, 86% (80%)
n-Bu, **30d**, 87% (82%)
cholates

31a, 90% (85%)[4]
hyodeoxycholate

R = Me, **32a**, 100% (98%)[4]
i-Pr, **32c**, 59% (53%)
n-Bu, **32d**, 100% (90%)
litocholates

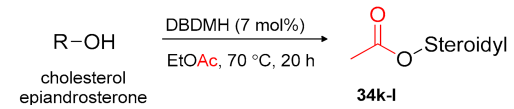
R = Me, **33a**, 99% (93%)
n-Bu, **33d**, 50% (44%)
dehydrocholates

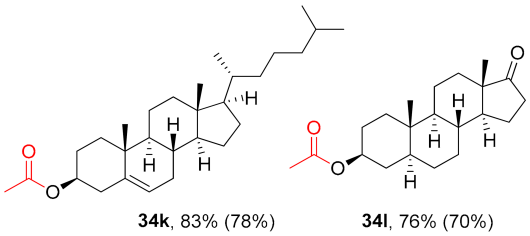
[1] Reaction conditions: carboxylic acid (0.25 mmol), alcohol (0.5–2 mL), DBDMH (0.018 mmol), 70 °C, 5–20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets indicate yields of isolated products. [4] A 2 mL volume of MeOH was used.

Moreover, a modest limitation of the substrate scope was observed for monosubstituted benzoic acids, as the reaction only failed in the case of 2-methoxybenzoic acid (Table 4) and hydroxy derivatives. The lower reactivity in case of ortho-substituted benzoic acids may be attributed to the steric hindrance of the ortho-positioned groups in the phenyl ring. The more the ortho-positioned group is sterically abundant, lower is the conversion. On the other hand, unreactivity of hydroxy-substituted derivatives is caused by the electron-donating properties of the OH group, which gives rise to low electron deficiency on the carbonyl C-atom, and consequently, lower susceptibility of carbonyl group to nucleophile attack. Bader charges for the carbon and oxygen atoms of the carbonyl group were

calculated and the analysis confirmed that the carbonyl C-atom in the case of *p*-OH-benzoic acid was not as positively charged, as in the case of benzoic acid (Figure S1 and Table S1). When benzoic acid derivatives bore multiple electron-rich moieties on the aromatic ring, esterification was more limited, as only 3,4-dimethoxybenzoic acid produced an acceptable yield (Table 4, Compound **18a**). In the case of isonicotinic acid (Product **19a**), the unreactivity probably originated from the higher basicity and higher nucleophilicity of the nitrogen atom in the pyridine ring relative to the basicity (nucleophilicity) of the carbonyl oxygen atom in the carboxyl group. The nitrogen atom in the pyridine ring could therefore take a role of a Lewis base in a strong halogen bond interaction. [49] In net effect, it could therefore act as a Br^+ scavenger, preventing the activation of carboxylic acid toward the nucleophile (alcohol) attack in the esterification reaction.

Table 7. Transesterification of cholesterol and epiandrosterone [1,2,3].



Cholesteryl Acetate and Epiandrosteryl Acetate

34k, 83% (78%) **34l**, 76% (70%)

[1] Reaction conditions: steroidal alcohol (0.25–0.5 mmol), EtOAc (1 mL), DBDMH (0.018–0.035 mmol), 70 °C, 20 h. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets stand for yields of isolated products.

The commercial importance of certain methyl esters in biodiesel production (FAME) and perfumery (methyl benzoate) encouraged us to test the esterification of different types of alkyl carboxylic acids with MeOH under optimal reaction conditions in the presence of DBDMH (Table 5). No limitations were observed, and excellent yields were achieved, even in the case of polycarboxy derivatives.

In addition, the esterification of a selection of relevant bile acids was conducted to verify the synthetic applicability of this method on larger and more complex structures (Table 6). Esterification with methanol (**a**) and *n*-butanol (**d**) predominantly resulted in excellent yields, while the use of the secondary alcohol isopropanol (**c**) resulted in fair conversion.

Moreover, the results regarding the acetylation of cholesterol and epiandrosterone are presented in Table 7. Due to the high lipophilicity, and consequently, low solubility of these steroid alcohols in acetic acid, no esterification took place, and ethyl acetate was used as a reaction medium to obtain ester derivatives **34k** and **34l** in high yields. Using this approach, we also managed to demonstrate the potential of DBDMH as mediator in transesterification reactions. Additionally, to confirm the synthetic value of the presented methodology, scaled-up syntheses of methyl benzoate (**1a**), methyl stearate (**21a**), methyl citrate (**29a**), and cholic acid methyl ester (**30a**) up to 30 mmol were performed with excellent yields (93–100%).

The disinfection agency of DBDMH is known to originate from its ability to act as a source of Br^+ in the presence of water through the release of hypobromous acid (HOBr), which further reacts as an oxidant in the process of disinfection [34]. However, as the substoichiometric amounts of DBDMH (7 mol%) used in the esterification method discussed herein were sufficient for high-yield, direct esterification between carboxylic acid and alcohol, Br^+ clearly acted as a catalytic species rather than an oxidant.

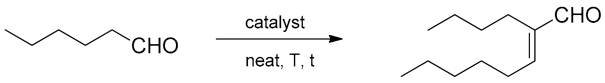
Based on the results of the control experiments presented in Table 2 and Figure 3, the proposed reaction pathway is presented in Scheme 1. In general, DBDMH in the presence of traces of water decomposes to form HOBr (**A1**), which catalyses the esterification reaction and regenerates *via* path **A** (steps **A2**–**A4**, depicted in red colour). However, as the reaction yields 80% conversion even under dry starting reaction conditions (Table 2, Entry 7), the initial DBDMH decomposition most probably originates from its reaction with alcohol to form alkyl hypobromite [50], which further promotes the esterification reaction via path **B** (steps **B2**–**B4**, depicted in green colour). As a consequence of water formation during the esterification reaction (step **A3** or/and **B5**), the reaction can further proceed both ways simultaneously, where the formation of HOBr acts as the ultimate driving force of the reaction.

As already mentioned, a considerable drop in pH from 4.0–4.5 to 0–0.5 was measured during the reaction, which could not be attributed to the acidity of HOBr because of its relatively high pK_a value (pK_a = 8.65). At the same time, the formation of a distinctive orange color and bromine odor was observed during the reaction, which readily disappeared upon introduction of a sodium thiosulphate solution, $NaS_2O_{3(aq)}$, to the reaction mixture. All of this could be explained by the instability of HOBr and its decomposition at pH below 4 to form bromine (Br_2) and bromic acid ($HOBr_3$) with a considerably lower pK_a of −2 (Scheme 1, Equation 1) [51]. Bromine is well-known to form HOBr and HBr in reactions with water through an equilibrium reaction (Scheme 1, Equation 2), thereby allowing the regeneration of HOBr for subsequent esterification catalysis. Therefore, the water formed through the esterification reaction is more than only an inevitable side product, it is an assisting component in catalysis, due to this equilibrium reaction according to Le Chatelier's principle. The hypothesis of water-assistance in the proposed mechanism is supported by the fact that only an 80% conversion to the ester product was observed when the reaction was performed in the presence of a drying agent (Na_2SO_4), which is in contrast to the general requirement for water removal for efficient transformation in an acid-catalyzed Fischer esterification methodology (Table 2, Entry 7). However, if the reaction was performed in water as a solvent, the hydrolysis of the ester product due to the carboxylic acid/ester equilibrium dominated the beneficial increased concentration of HOBr and the reaction resulted in no conversion. Furthermore, to eliminate the possibility of classic Brønsted acid catalysis acting as the major driving force of the quantitative esterification reaction (by the *in-situ* formed $HBrO_3$ and HBr), the reaction was conducted in the presence of 7 mol% of hydrobromic acid (pK_a = −9), and only 84 percent conversion to methyl benzoate was noticed (Table 1, Entry 9).

2.2. Aldol Condensation

To furtherly investigate possible DBDMH mediation in the activation of the carbonyl moiety, aldol condensation as an additional reaction model was chosen. Aldol condensation remains one of the most versatile, effective, and cheap methods for C–C bond formation in organic synthesis, widely employed in industry for the preparation of indigo dye as well as in preclinical and clinical drug-discovery research [52,53]. It also serves as a powerful tool in the fragrance industry for synthesising aromatic compounds, such as 2-benzylideneheptanal (jasmine odor), 2-methyl-3-(4-isopropylphenyl)propanal (cyclamen odor), and 2-methyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)butanol (sandalwood odor) [54]. To optimize the reaction conditions, hexanal was used as a model substrate for self-aldol condensation of aldehydes, and the results of the optimization are presented in Table 8. The reaction proceeded under neat reaction conditions and was found to be time sensitive, as prolonging the reaction time resulted in the formation of polymeric material (Table 8, Entries 5–7). Furthermore, the optimal reaction conditions were then applied in studies to examine the scope of the methodology (Table 9). Excellent conversions and regioselectivity were obtained in the aldol condensation of alkyl aldehydes, and it was observed that chain elongation did not exhibit a significant influence on reaction conversion. Finally, the synthesis of the commercially-important product (*E*)-2-benzylideneheptanal (jasmine aldehyde, Scheme 2) as an example of cross-aldol condensation was performed, with quantitative conversion, yet with low yields, as a consequence of difficult separation resulting from the presence of excessive amounts of benzaldehyde reagent (3:1).

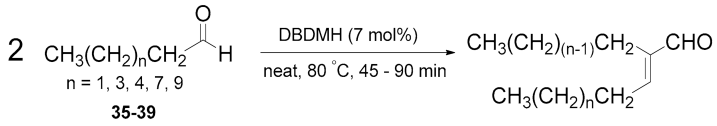
Table 8. Catalyst, catalyst loading, temperature, and time optimization for aldol condensation of hexanal [1].

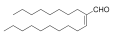
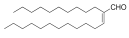


Entry	Catalyst	Loading [mol%]	Temperature [°C]	Time	Conv. [%] [2]
1	/	/	70	17 h	0
2	NCS	7	70	17 h	21
3	NBS	7	70	1 h	58
4	NIS	7	70	1 h	58
5	DBDMH	7	70	1 h	90 [3]
6	DBDMH	7	80	1 h	99 [3]
7	DBDMH	7	60	1 h	84 [3]
8	DBDMH	7	80	45 min	100
9	DBDMH	7	80	30 min	97
10	DBDMH	7	80	15 min	91
11	DBDMH	7	80	10 min	76
12	DBDMH	7	80	5 min	62
13	DBDMH	5	80	45 min	94
14	DBDMH	3	80	45 min	90

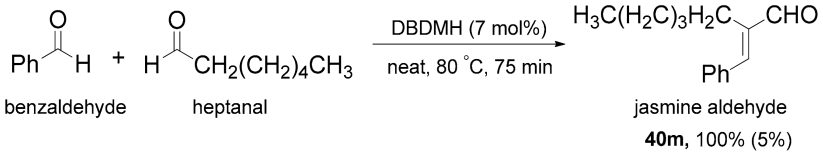
[1] Reaction conditions: hexanal (2.0 mmol), DBDMH, T, t. [2] Conversions were determined by ^{1}H-NMR analysis of the crude reaction mixtures. [3] Considerable amounts of polymeric material were detected in the reaction mixture.

Table 9. Effect of chain elongation on aldol condensation efficiency [1,2,3].



Product	n	Aldehyde	Product Structure	Conversion [%] (Yield [%])
35m	1	Butanal		94 (90)
36m	3	Hexanal		100 (94)
37m	4	Heptanal		100 (95)
38m	7	Decanal		94 (90)
39m	9	Dodecanal		97 (92)

[1] Reaction conditions: aldehyde (2.0 mmol), DBDMH (7 mol%), neat, 80 °C, 45–90 min. [2] Conversions were determined by ^{1}H-NMR spectroscopy. [3] The values in brackets indicate yields of isolated products.



Scheme 2. Synthesis of (*E*)-2-benzylideneheptanal (jasmine aldehyde).

3. Materials and Methods

3.1. General Information

All reactions were performed in a Mettler-Toledo Easymax 102 Advanced Synthesis Workstation, using closed 25 mL vials. NMR spectra were recorded on a Varian Inova 300 spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C, 285 MHz ^{19}F) at 25 °C. ^{1}H-NMR spectra were obtained as solutions in $CDCl_3$ with TMS as an internal standard. ^{19}F-NMR spectra were obtained as solutions in $CDCl_3$ with $CFCl_3$ as an

internal standard. pH was measured with Whatman Panpeha pH indicator strips (pH range 0–14). All chemicals used for synthetic procedures were obtained from commercial sources and were of reagent grade purity or better (Merck, Darmstadt, Germany; Sigma Aldrich, St. Louis, MO, USA; Carlo Erba, Milano, Italy; Fluka, Seelze, Germany, Fisher Scientific, Waltham, MA, USA; Apollo Scientific, Bredbury, United Kingdom; etc.). Reactions were monitored by thin layer chromatography (TLC) with silica gel coated plates (Silica gel/TLC cards; DC-Alufolien-Kieselgel; with 60 Å medium pore diameter; Sigma Aldrich), and detection was conducted by UV absorption (254 nm, Camag, Muttenz, Switzerland). Purification of certain products was conducted on preparative silica gel glass plates (PLC Kieselgel 60 F254 with 2 mm layer thickness). Density functional theory (DFT) calculations were performed with the PWscf (Plain-Wave Self-Consistent Field) code from the Quantum ESPRESSO distribution [55,56], using the generalized gradient approximation (GGA) of Perdew–Burke–Ernzerhof (PBE) [57]. Bader charge analysis was performed by generating charge densities with single point self-consistent-field calculations of Ultra-Soft Pseudopotential (US-PP) optimized [58] structures using the PAW (projector-augmented-wave) potentials [59] and 1000 Ry kinetic energy cutoff for charge density, and then computing the Bader charges using the Bader program [60,61].

3.2. Experimental Procedures

3.2.1. General Procedure for the Esterification between Carboxylic Acids and Alcohols

The mixture of carboxylic acid, alcohol, and 1,3-dibromo-5,5-dimethylhydantoin was stirred in a 25 mL reactor tube at 70 °C for 2–40 h. After reaction completion, the mixture was cooled to room temperature and the alcohol was evaporated under reduced pressure. The isolation procedure was as follows, except where noted differently in the Supporting Information. The residue was dissolved in 10 mL ethyl acetate and washed with a mixture of 1 mL saturated $NaHCO_{3(aq)}$, 1 mL saturated $Na_2S_2O_{3(aq)}$, and 10 mL distilled water, and the water phase was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure.

3.2.2. General Procedure for the Self-aldol Condensation of Aldehydes

The mixture of aldehyde (2.0 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 45–90 min. After reaction completion, the mixture was cooled to room temperature and dissolved in 10 mL EtOAc. The solution was washed with the mixture of 1 mL saturated $Na_2S_2O_{3(aq)}$, 1 mL saturated $NaHCO_{3(aq)}$, and 10 mL distilled water. The water phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, dried with Na_2SO_4, and the solvent was evaporated under reduced pressure.

4. Conclusions

In summary, the precatalytic potential of cost-effective, accessible, and easily manipulable 1,3-dibromo-5,5-dimethylhydantoin as an air-tolerant mediator for the activation of carbonyl moieties has been demonstrated by developing a metal-free methodology for direct dehydrative esterification of carboxylic acids with alcohols, as well as for aldol condensation of aldehydes (self- and cross-condensation). This approach allows neat reaction conditions and does not need simultaneous water removal or stoichiometric amounts of activators. The esterification method using 1,3-dibromo-5,5-dimethylhydantoin provides good yields for a wide range of substrates. It was also successfully applied to certain significant steroidal backbones, such as cholesterol, bile acids, and epiandrosterone. Scaled-up synthesis of some commercially-interesting esters was successfully accomplished with high-to-excellent yields, and an esterification mechanism has been proposed. The effects of chain extension on self-aldol condensation products have been presented.

Supplementary Materials: The following are available online, detailed experimental data, ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra of isolated final products.

Author Contributions: Conceptualization, S.S; Formal analysis, K.Č., B.Đ.B. and S.S; Investigation, K.Č., B.Đ.B. and S.S; Methodology, K.Č., B.Đ.B. and S.S; Supervision, S.S; Writing–original draft, K.Č. and B.Đ.B.; Writing–review & editing, K.Č, B.Đ.B. and S.S.

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Sample Availability: Samples of the compounds are not available from the authors.

Experimental data

Scale-up procedure for preparation of methyl benzoate (1a) and isolation of 5,5-dimethylhydantoin

The mixture of benzoic acid (30 mmol, 3.66 g), MeOH (15 mL) and 1,3-dibromo-5,5-dimethylhydantoin (2.10 mmol, 0.60 g) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate and washed with water (3 x 30 mL). The water layers were combined, concentrated to the volume of 8 mL by rotary evaporation and again extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to yield 5,5-dimethylhydantoin. The organic layer from the first washing of the crude reaction mixture was washed with the mixture of 20 mL of saturated $NaHCO_{3\ (aq)}$, 20 mL of 10% $Na_2S_2O_{3\ (aq)}$ and 100 mL of distilled water. The water layer was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl benzoate as colourless oil.
Yield (methyl benzoate): 3.88 g, 95%.
Yield (5,5-dimethylhydantoin) [224]: 227 mg, 85%.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.07 (s, 1H), 1.42 (s, 6H).
^{13}C NMR (76 MHz, $CDCl_3$) δ 179.0, 157.0, 60.0, 24.8.
HRMS (ESI) for $C_5H_8N_2O_2$: calculated m/z = 129.0664 (MH^+); found m/z = 129.0666 (MH^+).

Scale-up procedure for preparation of methyl citrate (29a)

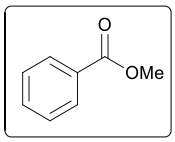
The mixture of citric acid (30 mmol, 5.76 g), MeOH (60 mL) and DBDMH (0.70 mmol, 0.600 g) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate, washed with the mixture of 10 mL of saturated $NaHCO_{3\ (aq)}$, 10 mL of saturated $Na_2S_2O_{3\ (aq)}$ and 50 mL of distilled water and the water phase was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl citrate as a white solid. Yield: 6.53 g, 93%.

Scale-up procedure for preparation of methyl stearate (21a)

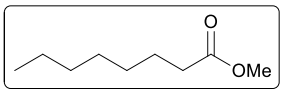
The mixture of stearic acid (30 mmol, 8.53 g), MeOH (15 mL) and DBDMH (0.70 mmol, 0.600 g) was stirred in a 25 mL reactor tube at 70 °C for 2 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate, washed with the mixture of 20 mL of saturated $NaHCO_{3\ (aq)}$, 20 mL of 10% $Na_2S_2O_{3\ (aq)}$ and 100 mL of distilled water and the water phase was extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, washed with distilled water (2 x 20 mL), dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish methyl stearate as a white solid. Yield: 8.96 g, 100%.

Scale-up procedure for preparation of cholic acid methyl ester (30a)

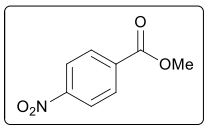
The mixture of cholic acid (2.0 mmol, 0.814 g), MeOH (8 mL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 70 °C for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and alcohol was evaporated under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate, washed with the mixture of 5 mL of saturated $NaHCO_{3\,(aq)}$, 5 mL of 10% $Na_2S_2O_{3\,(aq)}$ and 20 mL of distilled water and the water phase was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with distilled water (2 x 20 mL), dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to furnish cholic acid methyl ester as white solid. Yield: 0.845 g, 100%.



Methyl benzoate (1a) [225]
Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), MeOH (0.5 mL), DBMDH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 129 mg, 95%; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 2H), 7.59 – 7.51 (m, 1H), 7.43 (ddt, J = 8.2, 6.8, 1.1 Hz, 2H), 3.91 (s, 3H); **^{13}C NMR** (76 MHz, CDCl3) δ 167.2, 133.0, 130.3, 129.7, 128.4, 52.2; **HRMS** (ESI) for $C_8H_8O_2$: calculated m/z = 137.0603 (MH^+); found m/z = 137.0606 (MH^+).



Methyl octanoate (2a) [226]
Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 µL), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 2 h.
Purification: Not necessary.
Yield: 153 mg, 97% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.69 – 1.56 (m, 2H), 1.35 – 1.25 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.5, 51.5, 34.2, 31.8, 29.2, 29.0, 25.1, 22.7, 14.2; **HRMS** (ESI) for $C_9H_{18}O_2$: calculated m/z = 159.1385 (MH^+); found m/z = 159.1389 (MH^+).

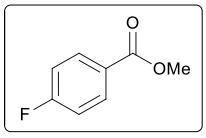


Methyl 4-nitrobenzoate (3a) [225]
Reaction conditions: According to the general procedure; 4-nitrobenzoic acid (1 mmol, 167.1 mg), MeOH (1.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 176 mg, 97% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 – 8.19 (m, 4H), 3.99 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 165.2, 150.6, 135.6, 130.8, 123.6, 52.9. **HRMS** (ESI) for $C_8H_7NO_4$: calculated m/z = 182.0453 (MH^+); found m/z = 182.0457 (MH^+).

Methyl 4-fluorobenzoate (4a) [227]

Reaction conditions: According to the general procedure; 4-fluorobenzoic acid (1 mmol, 140.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Not necessary.



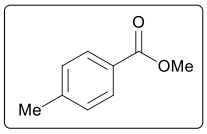
Yield: 131 mg, 85% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (ddd, J = 10.1, 5.2, 2.5 Hz, 2H), 7.13 – 7.03 (m, 2H), 3.89 (s, 3H); **^{13}C NMR** (76 MHz, CDCl3) δ 166.2, 165.8 (d, J = 253.5 Hz) 132.2 (d, J = 9.4 Hz), 126.5 (d, J = 3.0 Hz), 115.6 (d, J = 22.0 Hz), 52.2; **^{19}F NMR** (285 MHz, CDCl3) δ -106.34 (tt, J = 8.5, 5.4 Hz); **HRMS** (ESI) for $C_8H_7FO_2$: calculated m/z = 155.0508 (MH^+); found m/z = 155.0505 (MH^+).

Methyl 4-methylbenzoate (5a) [227]

Reaction conditions: According to the general procedure; 4-methylbenzoic acid (1 mmol, 136.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Not necessary.



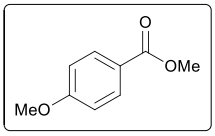
Yield: 135 mg, 90% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.86 (m, 2H), 7.22 (d, J = 8.2 Hz, 2H), 3.88 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 167.2, 143.6, 129.6, 129.1, 127.5, 52.0, 21.7; **HRMS** (ESI) for $C_9H_{10}O_2$: calculated m/z = 151.0759 (MH^+); found m/z = 151.0755 (MH^+).

Methyl 4-methoxybenzoate (6a) [228]

Reaction conditions: According to the general procedure; 4-methoxybenzoic acid (1 mmol, 152.2 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Not necessary.



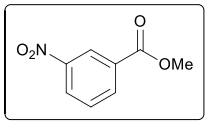
Yield: 116 mg, 70% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.89 (m, 2H), 7.00 – 6.83 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.8, 163.3, 131.5, 122.6, 113.6, 55.3, 51.8; **HRMS** (ESI) for $C_9H_{10}O_3$: calculated m/z = 167.0708 (MH^+); found m/z = 167.0712 (MH^+).

Methyl 3-nitrobenzoate (7a) [228]

Reaction conditions: According to the general procedure; 3-nitrobenzoic acid (1 mmol, 167.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.

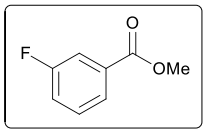
Purification: Not necessary.



Yield: 141 mg, 78% yield; yellow solid;

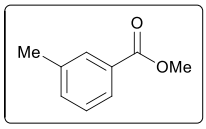
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 – 8.75 (m, 1H), 8.50 – 8.30 (m, 2H), 7.68 (t, J = 8.0 Hz, 1H), 4.00 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 165.0, 148.3, 135.3, 131.9, 129.7, 127.4, 124.6, 52.8; **HRMS** (ESI) for $C_8H_7NO_4$: calculated m/z = 182.0453 (MH^+); found m/z = 182.0457 (MH^+).

Methyl 3-fluorobenzoate (8a) [229]
Reaction conditions: According to the general procedure; 3-fluorobenzoic acid (1 mmol, 140.1 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 128 mg, 83% yield; colourless oil;



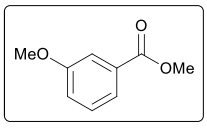
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dt, J = 7.7, 1.2 Hz, 1H), 7.71 (ddd, J = 9.4, 2.6, 1.5 Hz, 1H), 7.41 (td, J = 8.0, 5.6 Hz, 1H), 7.25 (tdd, J = 8.3, 2.5, 1.0 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.0 , 162.6 (d, J = 246.6 Hz), 132.4 (d, J = 7.6 Hz), 130.1 (d, J = 7.6 Hz), 125.4 (d, J = 2.9 Hz), 120.1 (d, J = 21.4 Hz), 116.6 (d, J = 23.0 Hz), 52.4; **^{19}F NMR** (285 MHz, $CDCl_3$) δ -112.92 (ddd, J = 9.4, 8.4, 5.6 Hz); **HRMS** (ESI) for $C_8H_7FO_2$: calculated m/z = 155.0508 (MH^+); found m/z = 155.0511 (MH^+).

Methyl 3-methylbenzoate (9a) [227]
Reaction conditions: According to the general procedure; 3-methylbenzoic acid (1 mmol, 136.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 147 mg, 98% yield; colourless oil;



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 1H), 7.39 – 7.28 (m, 1H), 3.91 (s, 2H), 2.40 (s, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 167.3, 138.2, 133.7, 130.2, 130.2, 128.3, 126.8, 52.1, 21.3; **HRMS** (ESI) for $C_9H_{10}O_2$: calculated m/z = 151.0759 (MH^+); found m/z = 151.0762 (MH^+).

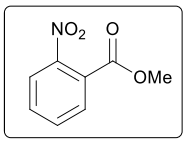
Methyl 3-methoxybenzoate (10a) [230]
Reaction conditions: According to the general procedure; 3-methoxybenzoic acid (1 mmol, 152.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 130 mg, 78% yield; yellow oil;



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.53 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.09 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 167.0, 159.6, 131.5, 129.4, 122.0, 119.5, 114.0, 55.4, 52.2; **HRMS** (ESI) for $C_9H_{10}O_3$:

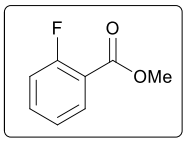
calculated m/z = 167.0708 (MH^+); found m/z = 167.0717 (MH^+).

Methyl 2-nitrobenzoate (11a) [231]



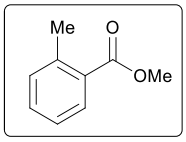
Reaction conditions: According to the general procedure; 2-nitrobenzoic acid (1 mmol, 167.1 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 45 mg, 25% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.4, 1.9 Hz, 1H), 7.78 – 7.59 (m, 3H), 3.93 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ δ 166.0, 148.3, 133.0, 131.9, 129.9, 127.6, 124.0, 53.3; **HRMS** (ESI) for $C_8H_7NO_4$: calculated m/z = 182.0453 (MH^+); found m/z = 182.0456 (MH^+).

Methyl 2-fluorobenzoate (12a) [231]

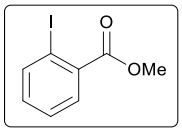


Reaction conditions: According to the general procedure; 2-fluorobenzoic acid (1 mmol, 140.1 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 131 mg, 85% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (td, J = 7.6, 1.9 Hz, 1H), 7.57 – 7.45 (m, 1H), 7.20 (td, J = 7.6, 1.1 Hz, 1H), 7.13 (ddd, J = 10.9, 8.3, 1.1 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 164.96 (d, J = 2.9 Hz), 162.00 (d, J = 259.7 Hz), 134.55 (d, J = 9.0 Hz), 132.20, 124.02 (d, J = 3.5 Hz), 118.72 (d, J = 10.1 Hz), 117.03 (d, J = 22.5 Hz), 52.36; **^{19}F NMR** (285 MHz, $CDCl_3$) δ -109.58 (ddd, J = 10.9, 7.3, 4.9 Hz); **HRMS** (ESI) for $C_8H_7FO_2$: calculated m/z = 155.0508 (MH^+); found m/z = 155.0505 (MH^+).

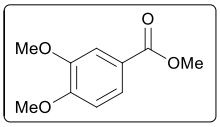
Methyl 2-methylbenzoate (13a) [231]



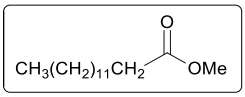
Reaction conditions: According to the general procedure; 2-methylbenzoic acid (1 mmol, 136.1 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 117 mg, 78% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.1, 1.5 Hz, 1H), 7.37 (td, J = 7.5, 1.5 Hz, 1H), 7.28 – 7.14 (m, 2H), 3.87 (s, 3H), 2.59 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 168.1, 140.2, 132.0, 131.7, 130.6, 129.6, 125.7, 51.8, 21.8; **HRMS** (ESI) for $C_9H_{10}O_2$: calculated m/z = 151.0759 (MH^+); found m/z = 151.0757 (MH^+).



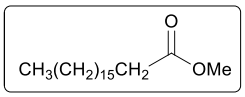
Methyl 2-iodobenzoate (15a) [232]
Reaction conditions: According to the general procedure; 2-iodobenzoic acid (1 mmol, 248.0 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 152 mg, 58% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.9, 1.1 Hz, 1H), 7.76 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (td, J = 7.6, 1.1 Hz, 1H), 7.11 (td, J = 7.7, 1.7 Hz, 1H), 3.90 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.9, 141.3, 135.1, 132.7, 130.9, 127.9, 94.1, 52.5; **HRMS** (ESI) for $C_8H_7IO_2$: calculated m/z = 262.9569 (MH^+); found m/z = 262.9563 (MH^+).



Methyl 3,4-dimethoxybenzoate (18a) [233]
Reaction conditions: According to the general procedure; 3,4-dimethoxybenzoic acid (1 mmol, 182.2 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 40 h.
Purification: Not necessary.
Yield: 126 mg, 64% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 3.93 (s, 6H), 3.89 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.8, 152.9, 148.6, 123.5, 122.6, 111.9, 110.2, 55.9, 55.9, 51.9; **HRMS** (ESI) for $C_{10}H_{12}O_4$: calculated m/z = 197.0814 (MH^+); found m/z = 197.0809 (MH^+).



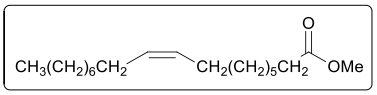
Methyl myristate (20a) [226]
Reaction conditions: According to the general procedure; myristic acid (1 mmol, 228.4 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 2 h.
Purification: Not necessary.
Yield: 238 mg, 98% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.74 – 1.52 (m, 2H), 1.26 (s, 20H), 0.88 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.5, 51.5, 34.2, 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.2, 11.2; **HRMS** (ESI) for $C_{15}H_{30}O_2$: calculated m/z = 243.2324 (MH^+); found m/z = 243.2318 (MH^+).



Methyl stearate (21a) [234]
Reaction conditions: According to the general procedure; stearic acid (1 mmol, 284.5 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 2 h.
Purification: Not necessary.

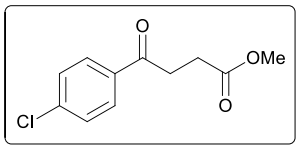
Yield: 296 mg, 99% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.69 – 1.55 (m, 2H), 1.37 – 1.20 (m, 28H), 0.88 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.5, 51.6, 34.3, 32.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.8, 14.3; **HRMS** (ESI) for $C_{19}H_{38}O_2$: calculated m/z = 299.2950 (MH^+); found m/z = 299.2957 (MH^+).

Methyl oleate (22a) [234]
Reaction conditions: According to the general procedure; oleic acid (1 mmol, 315.6 µL), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 5 h.
Purification: Not necessary.



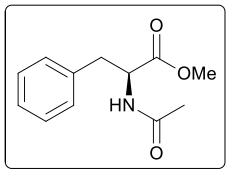
Yield: 291 mg, 98% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (ddd, J = 5.6, 3.5, 2.1 Hz, 2H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.10 – 1.91 (m, 4H), 1.71 – 1.54 (m, 2H), 1.42 – 1.17 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.4, 130.1, 129.9, 51.5, 34.2, 32.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.3, 29.2, 27.3, 27.3, 25.1, 22.8, 14.2; **HRMS** (ESI) for $C_{19}H_{36}O_2$: calculated m/z = 297.2794 (MH^+); found m/z = 297.2798 (MH^+).

Methyl 4-(4-chlorophenyl)-4-oxobutanoate (23a) [235]
Reaction conditions: According to the general procedure; 3-(4-chlorobenzoyl)propionic acid (1 mmol, 212.6 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.



Yield: 224 mg of white solid (99%);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 2H), 7.41 – 7.33 (m, 2H), 3.64 (s, 3H), 3.22 (t, J = 6.6 Hz, 2H), 2.70 (t, J = 6.6 Hz, 2H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 196.8, 173.2, 139.6, 134.8, 129.4, 128.9, 51.8, 33.3, 27.9; **HRMS** (ESI) for $C_{12}H_{18}O_2$: calculated m/z = 249.0294 (MNa^+); found m/z = 249.0297 (MNa^+).

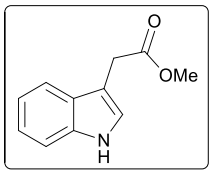
(*S*)-Methyl 2-acetamido-3-phenylpropanoate (24a) [236]
Reaction conditions: According to the general procedure; *N*-acetyl-*L*-phenylalanine (1 mmol, 207.2 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.



Yield: 210 mg of white solid (95%);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 3H), 7.18 – 7.05 (m, 2H), 6.38 (d, J = 7.5 Hz, 1H), 4.95 – 4.77 (m, 1H), 3.69 (s, 3H), 3.21 – 2.93 (m, 2H), 1.95 (s, 3H); **^{13}C NMR** (76 MHz,

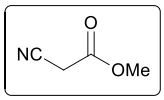
$CDCl_3$) δ 172.2, 169.8, 136.0, 129.2, 128.5, 127.0, 53.2, 52.2, 37.8, 22.9; **HRMS** (ESI) for $C_{12}H_{15}NO_3$: calculated m/z = 222.1130 (MH^+); found m/z = 222.1135 (MH^+).

Methyl 2-(1H-indol-3-yl)acetate (25a) [237]



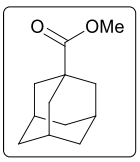
Reaction conditions: According to the general procedure; Heteroauxin (1 mmol, 175.2 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: Yield: 183 mg of brown oil (97%);
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.56 (dd, J = 6.7, 1.6 Hz, 2H), 7.24 – 6.98 (m, 3H), 6.84 (d, J = 2.4 Hz, 1H), 3.72 (s, 2H), 3.63 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.0, 136.1, 127.1, 123.4, 122.0, 119.5, 118.6, 111.4, 107.8, 52.0, 31.1; **HRMS** (ESI) for $C_{11}H_{11}NO_2$: calculated m/z = 190.0868 (MH^+); found m/z = 190.0865 (MH^+).

Methyl 2-cyanoacetate (26a) [238]



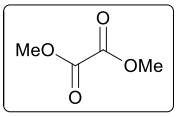
Reaction conditions: According to the general procedure; Cyanoacetic acid (1 mmol, 85.1 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: Yield: 96 mg of colourless oil (97%);
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.46 (s, 2H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 163.6, 113.2, 53.5, 24.4; **HRMS** (ESI) for $C_4H_5NO_2$: calculated m/z = 100.0399 (MH^+); found m/z = 100.0398 (MH^+).

Adamantane-1-carboxylic acid methyl ester (27a) [229]



Reaction conditions: According to the general procedure; 1-adamantanecarboxylic acid (1 mmol, 180.2 mg), MeOH (0.5 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 188 mg, 97% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.01 – 1.92 (m, 3H), 1.88 – 1.80 (m, 6H), 1.74 – 1.59 (m, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 178.08, 51.44, 40.64, 38.81, 36.46, 27.91; **HRMS** (ESI) for $C_{12}H_{18}O_2$: calculated m/z = 195.1385 (MH^+); found m/z = 195.1382 (MH^+).

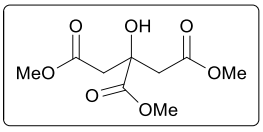
Dimethyl oxalate (28a) [239]



Reaction conditions: According to the general procedure; oxalic acid (1 mmol, 90.0 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 15 h.

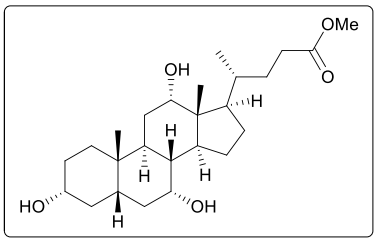
Purification: Not necessary.
Yield: 112 mg, 95% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 6H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 157.8, 53.5; **HRMS** (ESI) for $C_4H_6O_4$: calculated m/z = 119.0344 (MH^+); found m/z = 119.0342 (MH^+).

Trimethyl citrate (29a) [240]
Reaction conditions: According to the general procedure; malonic acid (1 mmol, 210.1 mg), MeOH (2 mL), DBDMH (0.070 mmol, 20.0 mg), 70 °C, 20 h.

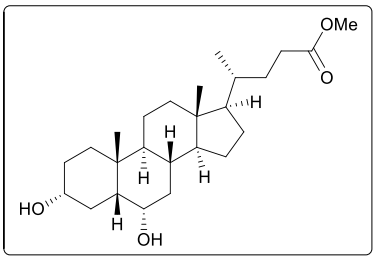


Purification: Not necessary.
Yield: 220 mg, 94% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (s, 1H), 3.81 (s, 3H), 3.67 (s, 6H), 2.89 (d, J = 15.6 Hz, 2H), 2.79 (d, J = 15.6 Hz, 2H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.8, 170.2, 73.3, 53.2, 52.0, 43.1; **HRMS** (ESI) for $C_9H_{14}O_7$: calculated m/z = 235.0818 (MH^+); found m/z = 235.0815 (MH^+).

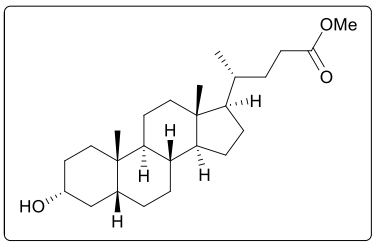
Cholic acid methyl ester (30a) [241]
The mixture of cholic acid (0.25 mmol, 102.1 mg), MeOH (2 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.



Purification: Not necessary.
Yield: 104 mg, 98% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 1H), 3.83 (s, 1H), 3.66 (s, 3H), 3.55 (s, 3H), 3.49 – 3.32 (m, 1H), 2.48 – 1.07 (m, 24H), 0.98 (d, J = 5.8 Hz, 3H), 0.88 (s, 3H), 0.67 (s, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.7, 72.9, 71.7, 68.3, 51.3, 46.8, 46.2, 41.4, 41.4, 39.3, 39.3, 35.2, 35.2 34.6, 34.6, 31.0, 30.8, 30.2, 28.0, 27.4, 26.1, 23.1, 22.3, 17.2, 12.3; **HRMS** (ESI) for $C_{25}H_{42}O_5$: calculated m/z = 423.3110 (MH^+); found m/z = 423.3128 (MH^+).



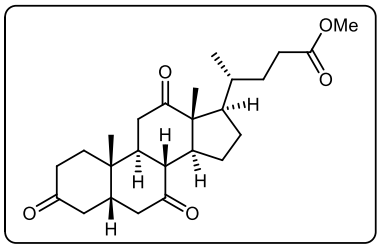
Hyodeoxycholic acid methyl ester (31a) [242]
The mixture of hyodeoxycholic acid (0.25 mmol, 98.1 mg), MeOH (2 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Not necessary.
Yield: 86 mg, 85% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 – 3.96 (m, 1H), 3.66 (s, 3H), 3.64 – 3.52 (m, 1H), 2.82 (s, 2H), 2.45 – 2.29 (m, 1H), 2.29 – 2.13 (m, 1H), 2.03 – 1.54 (m, 10H), 1.50 – 1.03 (m, 14H), 0.93 (s, 3H), 0.90 (s, 3H), 0.64 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.8, 71.5, 68.0, 56.3, 56.1, 51.6, 48.6, 42.9, 40.1, 40.0, 36.0, 35.7, 35.5, 34.9, 34.9, 31.2, 31.0, 30.2, 29.4, 28.2, 24.3, 23.6, 20.9, 18.3, 12.1; **HRMS** (ESI) for $C_{25}H_{42}O_4$: calculated m/z = 371.2950 (M-H_2O+H^+); found m/z = 371.2951 (M-H_2O+H^+).



Litocholic acid methyl ester (32a) [243]
The mixture of litocholic acid (0.25 mmol, 94.1 mg), MeOH (2 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Not necessary.
Yield: 96 mg, 98% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.60 (dt, J = 10.8, 4.7 Hz, 1H), 2.35 (ddd, J = 15.2, 10.1, 5.1 Hz, 1H), 2.29 – 2.15 (m, 1H), 2.06 (s, 1H), 2.00 – 1.00 (m, 26H), 0.92 (s, 3H), 0.90 (s, 3H), 0.64 (s, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.8, 71.8, 56.5, 56.0, 51.5, 42.8, 42.2, 40.5, 40.2, 36.5, 35.9, 35.4, 35.4, 34.6, 31.1, 31.0, 30.5, 28.2, 27.3, 26.5, 24.3, 23.4, 20.9, 18.3, 12.1;

HRMS (ESI) for $C_{25}H_{42}O_3$: calculated m/z = 371.3107 (M-H_2O+H^+); found m/z = 373.3102 (M-H_2O+H^+).

Dehydrocholic acid methyl ester (33a) [244]



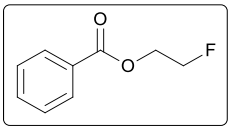
The mixture of dehydrocholic acid (0.25 mmol, 101.6 mg), MeOH (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 5 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and first washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water and then with 10 mL of 10% $HCl_{(aq)}$. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

Purification: Not necessary.

Yield: 97 mg, 93% yield; white solid;

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.01 – 2.75 (m, 3H), 2.51 – 1.16 (m, 21H), 1.41 (s, 3H), 1.08 (s, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 212.0, 209.1, 208.8, 174.5, 56.9, 51.8, 51.5, 49.0, 46.9, 45.7, 45.6, 45.0, 42.8, 38.7, 36.5, 36.1, 35.6, 35.3, 31.3, 30.5, 27.7, 25.2, 22.0, 18.7, 11.9; **HRMS** (ESI) for $C_{25}H_{36}O_5$: calculated m/z = 417.2641 (MH^+); requires m/z = 417.2644 (MH^+).

2-Fluoroethyl benzoate (1b) [245]



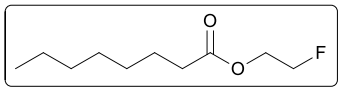
Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), 2-fluoroethanol (0.5 mL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 40 h.

Purification: Preparative TLC (CH_2Cl_2/MeOH = 200 : 1)

Yield: 161 mg, 96% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 – 7.86 (m, 2H), 7.60 – 7.52 (m, 1H), 7.49 – 7.37 (m, 2H), 4.85 – 4.44 (m, 4H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.4, 133.3, 129.8, 128.5, 81.5 (d, J = 170.6 Hz), 63.9 (d, J = 20.2 Hz); **^{19}F NMR** (285 MHz, CDCl3) δ 5.03 (tt, J = 47.4, 28.6 Hz); **HRMS** (ESI) for $C_9H_9FO_2$: calculated m/z = 169.0665 (MH^+); found m/z = 169.0668 (MH^+).

2-Fluoroethyl octanoate (2b) [246]

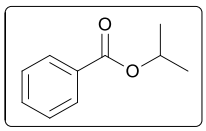


Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 μL), 2-fluoroethanol (0.5 mL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Not necessary.

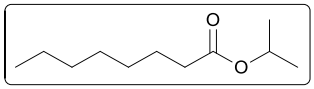
Yield: 175 mg, 92% yield; yellow oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 – 4.20 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.42 – 1.19 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.7, 81.5 (d, J = 170.3 Hz), 63.2 (d, J = 20.1 Hz), 34.2, 31.7, 29.1, 29.0, 25.0, 22.7, 14.1. **^{19}F NMR** (285 MHz, CDCl3) δ 4.86 (tt, J = 47.4, 28.7 Hz); **HRMS** (ESI) for $C_{10}H_{19}FO_2$: calculated m/z = 191.1447 (MH^+); found m/z = 191.1446 (MH^+).

Isopropyl benzoate (1c) [247]
Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), isopropanol (0.5 mL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.



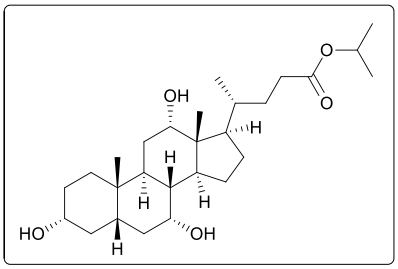
Yield: 38 mg, 23% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 – 7.99 (m, 2H), 7.59 – 7.50 (m, 1H), 7.47 – 7.38 (m, 2H), 5.26 (hept, J = 6.3 Hz, 1H), 1.37 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.3, 132.8, 131.1, 129.6, 128.4, 68.5, 22.1.

Isopropyl octanoate (2c) [248]
Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 μL), isopropanol (0.5 mL DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.



Yield: 160 mg, 86% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (hept, J = 6.3 Hz, 1H), 2.25 (t, J = 7.5 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.35 – 1.25 (m, 8H), 1.23 (d, J = 6.3 Hz, 6H), 0.88 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.4, 67.3, 34.8, 31.7, 29.2, 29.0, 25.1, 22.7, 21.9, 14.1; **HRMS** (ESI) for $C_{11}H_{22}O_2$: calculated m/z = 187.1698 (MH^+); found m/z = 187.1703 (MH^+).

Cholic acid isopropyl ester (30c) [249]



The mixture of cholic acid (0.25 mmol, 102.1 mg), *i*-PrOH (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and *i*-PrOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined,

dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

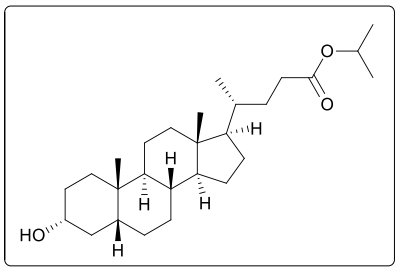
Purification: Not necessary.

Yield: 97 mg, 86% yield; white solid;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (hept, J = 6.1 Hz, 1H), 3.96 (s, 1H), 3.84 (s, 1H), 3.53 – 3.35 (m, 1H), 3.11 (s, 3H), 2.43 – 1.31 (m, 24H), 1.22 (d, J = 6.3 Hz, 6H), 0.98 (d, J = 6.0 Hz, 3H), 0.88 (s, 3H), 0.67 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.0, 73.2, 72.0, 68.6, 67.5, 47.2, 46.6, 41.7, 41.6, 39.6, 35.4, 35.4, 34.9, 34.8, 31.8, 31.1, 30.5, 28.3, 27.6, 26.4, 23.3, 22.6, 22.0, 17.4, 12.6, 11.1; **HRMS** (ESI) for $C_{27}H_{46}O_5$: calculated m/z = 451.3424 (MH^+); found m/z = 451.3436 (MH^+).

Litocholic acid isopropyl ester (32c) [243]

The mixture of litocholic acid (0.25 mmol, 94.1 mg), *i*-PrOH (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and *i*-PrOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 2 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.



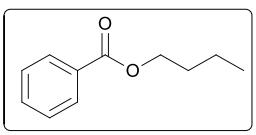
Purification: Not necessary.

Yield: 55 mg, 53% yield; white solid;

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 – 4.93 (m, 1H), 3.71 – 3.56 (m, 1H), 2.44 – 2.10 (m, 2H), 2.02 – 1.27 (m, 21H), 1.27 – 1.18 (m, 6H), 1.19 – 0.97 (m, 6H), 0.95 – 0.87 (m, 6H), 0.64 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.0, 72.0, 67.4, 56.6, 56.1, 42.8, 42.2, 40.5, 40.3, 36.5, 35.9, 35.5, 35.4, 34.7, 31.8, 31.1, 30.6, 28.3, 27.3, 26.5, 24.3, 23.5, 22.0, 20.9, 18.4, 12.1; **HRMS** (ESI) for $C_{27}H_{46}O_3$: calculated m/z = 419.3498 (MH^+); found m/z = 419.3523 (MH^+).

***n*-Butyl benzoate (1d)** [250]

Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), *n*-butanol (0.5 mL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.



Purification: Preparative TLC (CH_2Cl_2/MeOH = 200 : 1)

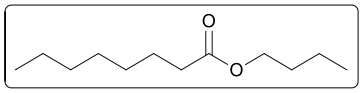
Yield: 139 mg, 78% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H), 7.58 – 7.49 (m, 1H), 7.42 (t, J = 7.5 Hz, 2H), 4.32 (t, J = 6.6 Hz, 2H), 1.84

– 1.66 (m, 2H), 1.56 – 1.39 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (76 MHz, CDCl3) δ 166.7, 132.8, 130.6, 129.6, 128.4, 64.9, 30.9, 19.4, 13.8; **HRMS** (ESI) for $C_{11}H_{14}O_2$: calculated m/z = 179.1072 (MH^+); found m/z = 179.1070 (MH^+).

***n*-Butyl octanoate (2d)** [251]

Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 µL), *n*-butanol (1 mmol, 92 µL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 15 h.



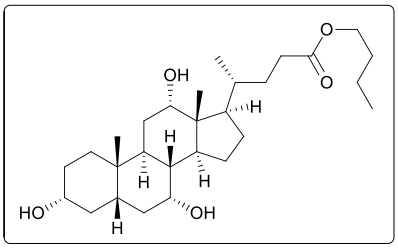
Purification: Not necessary.

Yield: 190 mg, 95% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J = 6.6 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.70 – 1.52 (m, 4H), 1.47 – 1.21 (m, 10H), 0.94 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.0, 64.1, 34.4, 31.8, 30.8, 29.2, 29.0, 25.1, 22.7, 19.2, 14.1, 13.7; **HRMS** (ESI) for $C_{12}H_{24}O_2$: calculated m/z = 201.1855 (MH^+); found m/z = 201.1857 (MH^+).

Cholic acid *n*-butyl ester (30d) [252]

The mixture of cholic acid (0.25 mmol, 102.1 mg), *n*-butanol (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and MeOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

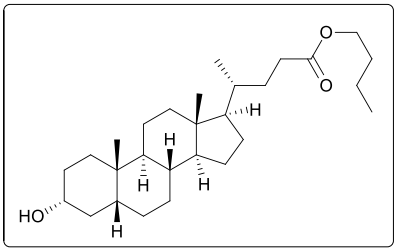


Purification: Not necessary.

Yield: 95 mg, 82% yield; white solid;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, *J* = 6.6 Hz, 2H), 3.96 (s, 1H), 3.84 (s, 1H), 3.53 – 3.35 (m, 1H), 3.22 (s, 3H), 2.44 – 0.78 (m, 37H), 0.67 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.6, 73.2, 72.0, 68.6, 64.2, 47.1, 46.5, 41.7, 41.6, 39.6, 39.6, 35.4, 35.4, 34.9, 34.8, 31.5, 31.1, 30.8, 30.5, 28.3, 27.6, 26.4, 23.3, 22.6, 19.3, 17.4, 13.8, 12.6. **HRMS** (ESI) for $C_{28}H_{48}O_5$: calculated m/z = 465.3580 (MH^+); found m/z = 465.3576 (MH^+).

Litocholic acid *n*-butyl ester (32d) [253]



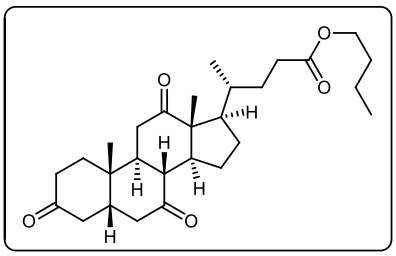
The mixture of litocholic acid (0.25 mmol, 94.1 mg), *n*-BuOH (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and *n*-BuOH was evaporated under the reduced pressure. The residue was dissolved in ethyl acetate and washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

Purification: Not necessary.

Yield: 97 mg, 90% yield; white solid;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 6.7 Hz, 2H), 3.72 – 3.53 (m, 1H), 2.41 – 2.15 (m, 2H), 2.06 (s, 1H), 2.02 – 0.86 (m, 39H), 0.64 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.6, 72.0, 64.2, 56.6, 56.1, 42.8, 42.2, 40.5, 40.3, 36.5, 36.0, 35.5, 35.5, 34.7, 31.4, 31.1, 30.8, 30.6, 28.3, 27.3, 26.5, 24.3, 23.5, 20.9, 19.3, 18.4, 13.8, 12.1; **HRMS** (ESI) for $C_{28}H_{48}O_3$: calculated m/z = 415.3576 (M-H_2O+H^+); found m/z = 415.3577 (M-H_2O+H^+).

Dehydrocholic acid *n*-butyl ester (33d) [254]



The mixture of dehydrocholic acid (0.25 mmol, 101.6 mg), *n*-BuOH (0.5 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and *n*-BuOH was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and first washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 2 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water and then with 10 mL of 10% $HCl_{(aq)}$. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

Purification: Not necessary.

Yield: 50 mg, 44% yield; white solid;

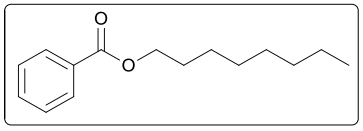
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J = 6.6 Hz, 2H), 3.03 – 2.76 (m, 3H), 2.53 – 1.18 (m, 28H), 1.07 (s, 3H), 0.93 (t, J = 7.3 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (76 MHz, $CDCl_3$) δ 212.0, 209.1, 208.8, 174.3, 64.2, 57.0, 51.9, 49.1, 46.9, 45.8, 45.6, 45.1, 42.9, 38.7, 36.6, 36.1, 35.6, 35.4, 31.6, 30.8, 30.6, 27.7, 25.2, 22.0, 19.2, 18.7, 13.8, 11.9; **HRMS** (ESI) for $C_{28}H_{42}O_5$:

calculated m/z = 459.3110 (MH^+); requires m/z = 459.3109 (MH^+).

***n*-Octyl benzoate (1f)** [226]

Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), *n*-octanol (1 mmol, 158 µL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Preparative TLC (CH_2Cl_2/Hexane = 1 : 1)



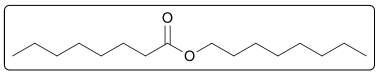
Yield: 152 mg, 65% yield; white solid;

^{1}H NMR (300 MHz, CDCl3) δ 8.10 – 8.00 (m, 2H), 7.59 – 7.51 (m, 1H), 7.47 – 7.39 (m, 2H), 4.31 (t, J = 6.7 Hz, 2H), 1.83 – 1.70 (m, 2H), 1.51 – 1.21 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.8, 132.9, 130.7, 129.7, 128.4, 65.3, 31.9, 29.4, 29.3, 28.9, 26.2, 22.8, 14.2; **HRMS** (ESI) for $C_{15}H_{22}O_2$: calculated m/z = 235.1698 (MH^+); found m/z = 235.1697 (MH^+).

***n*-Octyl octanoate (2f)** [255]

Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 µL), *n*-octanol (1 mmol, 158 µL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.

Purification: Preparative TLC (CH_2Cl_2/MeOH = 200 : 1)



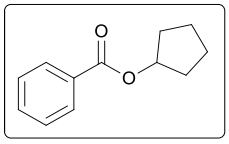
Yield: 226 mg, 88% yield; colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (t, J = 6.7 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.68 – 1.54 (m, 4H), 1.39 – 1.19 (m, 18H), 0.88 (t, J = 6.3 Hz, 6H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.9, 64.4, 34.4, 31.9, 31.8, 29.3, 29.3, 29.2, 29.0, 28.8, 26.0, 25.1, 22.7, 22.7, 14.1, 14.1; **HRMS** (ESI) for $C_{16}H_{32}O_2$: calculated m/z = 257.2481 (MH^+); found m/z = 257.2486 (MH^+).

Cyclopentyl benzoate (1g) [256]

Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), cyclopentanol (1.1 mmol, 100 µL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.

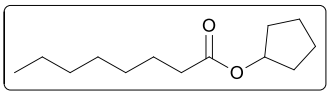
Purification: Column chromatography (EtOAc/Hexane = 1:10)



Yield: 36 mg, 19% yield; colourless oil;

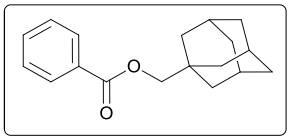
^{1}H NMR (300 MHz, CDCl3) δ 8.02 (dt, *J* = 7.1, 1.4 Hz, 2H), 7.57 – 7.49 (m, 1H), 7.46 – 7.37 (m, 2H), 5.41 (tt, *J* = 6.1, 2.8 Hz, 1H), 2.12 – 1.51 (m, 8H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.4, 132.7, 131.0, 129.6, 128.3, 77.7, 32.9, 23.9; **HRMS** (ESI) for $C_{12}H_{14}O_2$: calculated m/z = 213.0891 (MNa^+); found m/z = 213.0894 (MNa^+).

Cyclopentyl octanoate (2g) [257]



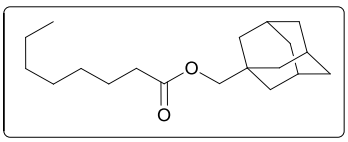
Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 µL), cyclopentanol (1 mmol, 91 µL), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 15 h.
Purification: Not necessary.
Yield: 200 mg, 94% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (tt, J = 5.9, 2.6 Hz, 1H), 2.25 (t, J = 7.5 Hz, 2H), 1.95 – 1.47 (m, 10H), 1.41 – 1.20 (m, 8H), 0.88 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 173.8, 76.8, 34.8, 32.8, 31.8, 29.2, 29.0, 25.2, 23.8, 22.7, 14.1; **HRMS** (ESI) for $C_{13}H_{24}O_2$: calculated m/z = 213.1855 (MH^+); found m/z = 213.1860 (MH^+).

Adamantan-1-ylmethyl benzoate (1j) [258]

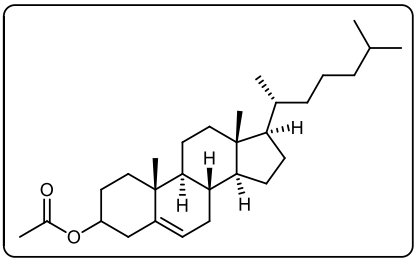


Reaction conditions: According to the general procedure; benzoic acid (1 mmol, 122.1 mg), 1-adamantanemethanol (2.0 mmol, 332.5 mg), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Column chromatography (EtOAc/Hexane = 1:10)
Yield: 203 mg, 75% yield; white solid;
^{1}H NMR (300 MHz, CDCl3) δ 8.06 (dt, J = 7.1, 1.4 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.49 – 7.40 (m, 2H), 3.92 (s, 2H), 2.32 – 1.28 (m, 15H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 166.8, 132.9, 130.7, 129.6, 128.4, 74.5, 39.5, 37.1, 33.6, 28.2; **HRMS** (ESI) for $C_{18}H_{22}O_2$: calculated m/z = 271.1698 (MH^+); found m/z = 271.1704 (MH^+).

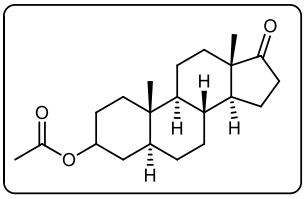
Adamantan-1-ylmethyl octanoate (2j) [259]



Reaction conditions: According to the general procedure; octanoic acid (1 mmol, 158.5 µL), 1-adamantanemethanol (2.0 mmol, 332.5 mg), DBDMH (0.07 mmol, 20.0 mg), 70 °C, 20 h.
Purification: Not necessary.
Yield: 275 mg, 94% yield; colourless oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 2H), 2.31 (t, J = 7.5 Hz, 2H), 2.07 – 1.87 (m, 3H), 1.84 – 1.21 (m, 22H), 0.94 – 0.80 (m, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 174.2, 73.9, 39.4, 37.1, 34.5, 33.3, 31.8, 29.3, 29.1, 28.2, 25.2, 22.7, 14.2; **HRMS** (ESI) for $C_{19}H_{32}O_2$: calculated m/z = 293.2481 (MH^+); found m/z = 293.2486 (MH^+).

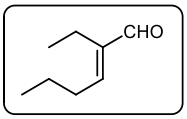


3β-O-Acetyl-cholesterol (34k) [260]
The mixture of cholesterol (0.25 mmol, 96.6 mg), EtOAc (1 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and additional 10 mL of ethyl acetate was added. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 2 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Column chromatography (EtOAc/Hexane = 1:5)
Yield: 84 mg, 78% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J = 4.6 Hz, 1H), 4.73 – 4.48 (m, 1H), 2.32 (d, J = 7.6 Hz, 2H), 2.03 (s, 3H), 2.01 – 0.79 (m, 38H), 0.68 (s, 3H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 170.6, 139.8, 122.8, 74.1, 56.8, 56.3, 50.2, 42.4, 39.9, 39.7, 38.3, 37.1, 36.7, 36.3, 35.9, 32.0, 32.0, 28.4, 28.1, 27.9, 24.4, 24.0, 23.0, 22.7, 21.6, 21.2, 19.4, 18.9, 12.0.



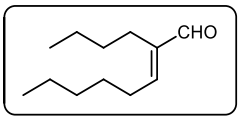
3β-Acetyloxy-5α-androstan-17-on (34l) [261]
The mixture of epi-androsterone (0.5 mmol, 145.2 mg), EtOAc (1 mL) and DBDMH (0.018 mmol, 5.1 mg) was stirred in a 25 mL reactor tube at 70 °C for 20 h. After the completion of the reaction, the mixture was cooled to room temperature and additional 10 mL of ethyl acetate was added. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 2 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Column chromatography (EtOAc/Hexane = 1:3)
Yield: 116 mg, 70% yield; white solid;
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (ddd, J = 16.3, 11.2, 4.9 Hz, 1H), 2.43 (dd, J = 18.7, 8.7 Hz, 1H), 2.10 (t, J = 9.0 Hz, 1H), 2.02 (s, 3H), 1.98 – 0.92 (m, 19H), 0.86 (s, 3H), 0.85 (s, 3H), 0.71 (tt, J = 12.1, 6.0 Hz, 1H); **^{13}C NMR** (76 MHz, $CDCl_3$) δ 170.7, 73.6, 54.4, 51.5, 47.9, 44.8, 36.8, 35.9, 35.7, 35.1, 34.0, 31.6, 30.9, 28.4, 27.5, 21.9, 21.5, 20.6, 13.9, 12.3; **HRMS** (ESI) for $C_{21}H_{32}O_3$: calculated m/z = 333.2430 (MH^+); found m/z = 333.2417 (MH^+).

(*E*)-2-ethylhex-2-enal (35m) [262]



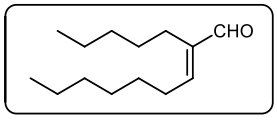
The mixture of butanal (2.0 mmol, 180.2 µL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 45 min. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Not necessary.
Yield: 114 mg, 90% yield; dark oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 6.43 (t, $J = 7.5$ Hz, 1H), 2.40 – 2.22 (m, 4H), 1.55 (m, 2H), 0.98 (t, $J = 7.4$ Hz, 3H), 0.97 (t, $J = 7.6$ Hz, 3H); **^{13}C NMR** (76 MHz, CCl_3) δ 195.2, 154.7, 145.5, 30.8, 22.1, 17.4, 14.0, 13.4.

(*E*)-2-butyloct-2-enal (36m) [263]



The mixture of hexanal (2.0 mmol, 244.2 µL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 45 min. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.
Purification: Not necessary.
Yield: 171 mg, 94% yield; dark oil;
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.45 (t, $J = 7.4$ Hz, 1H), 2.35 (q, $J = 7.4$ Hz, 2H), 2.24 (t, $J = 7.3$ Hz, 2H), 1.60 – 1.15 (m, 10H), 0.91 (td, $J = 6.9$, 4.4 Hz, 6H); **^{13}C NMR** (76 MHz, CCl_3) δ 195.4, 155.4, 143.9, 31.6, 31.0, 28.9, 28.4, 23.8, 22.8, 22.5, 14.0, 13.9.

(*E*)-2-pentylnon-2-enal (37m) [264]



The mixture of heptanal (2.0 mmol, 279.6 µL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 1.5 h. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried

with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

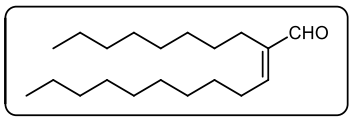
Purification: Not necessary.

Yield: 200 mg, 95% yield; dark oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.54 – 6.27 (m, 1H), 2.35 (q, J = 7.4 Hz, 2H), 2.28 – 2.17 (m, 2H), 1.75 – 1.12 (m, 14H), 0.99 – 0.74 (m, 6H); **^{13}C NMR** (76 MHz, CCl_3) δ 195.3, 155.3, 143.9, 31.9, 31.6, 29.1, 28.9, 28.7, 28.5, 24.0, 22.6, 22.5, 14.0, 13.9.

(*E*)-2-octyldodec-2-enal (38m) [265]

The mixture of decanal (2.0 mmol, 376.6 µL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 1.5 h. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.



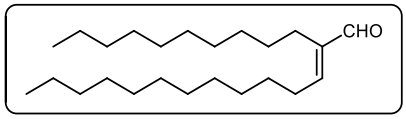
Purification: Not necessary.

Yield: 265 mg, 90% yield; dark oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H), 6.50 – 6.37 (m, 1H), 2.35 (q, J = 7.4 Hz, 2H), 2.26 – 2.20 (m, 2H), 1.68 – 1.12 (m, 26H), 0.88 (q, J = 4.5 Hz, 6H); **^{13}C NMR** (76 MHz, CCl_3) δ 195.3, 155.3, 143.9, 31.9, 30.3, 29.8, 29.6, 29.5, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 28.8, 28.8, 24.1, 22.7, 14.1, 14.1.

(*E*)-2-decyltetradec-2-enal (39m)[266]

The mixture of dodecanal (2.0 mmol, 443.6 µL) and DBDMH (0.14 mmol, 40 mg) was stirred in a 25 mL reactor tube at 80 °C for 1.5 h. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.



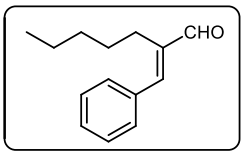
Purification: Not necessary.

Yield: 340 mg, 92% yield; dark oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 6.43 (t, J = 7.4 Hz, 1H), 2.42 – 2.27 (m, 2H), 2.27 – 2.15 (m, 2H), 1.70 – 1.01 (m, 34H), 0.88 (t, J = 6.4 Hz, 6H); **^{13}C NMR** (76 MHz, CCl_3) δ

195.3, 155.3, 144.0, 32.0, 29.8, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.5, 29.4, 29.4, 29.2, 29.0, 28.9, 28.9, 28.8, 28.7, 24.1, 22.8, 14.2, 14.2.

(*E*)-2-benzylideneheptanal (40m)[264]



Heptanal (1.0 mmol, 140.0 μL) was added dropwise to the mixture of benzaldehyde (3.0 mmol, 306.1 μL) and DBDMH (0.07 mmol, 20 mg), stirring in a 25 mL reactor tube at 80 °C over a time period of 20 min and the reaction mixture was heated for additional 45 min. After the completion of the reaction, the mixture was cooled to room temperature and dissolved in 10 mL of EtOAc. The solution was washed with the mixture of 1 mL of saturated $Na_2S_2O_{3(aq)}$, 1 mL of saturated $NaHCO_{3(aq)}$ and 10 mL of distilled water. The water phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried with Na_2SO_4 and the solvent was evaporated under the reduced pressure.

Purification: Preparative TLC (Hexane/EtOAc = 9 : 1)

Yield: 10 mg, 5% yield; yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.55 – 7.35 (m, 5H), 7.21 (s, 1H), 2.59 – 2.46 (m, 2H), 1.55 – 1.43 (m, 2H), 1.43 – 1.29 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); **^{13}C NMR** (76 MHz, CCl_3) δ 195.9, 149.9, 143.6, 135.2, 129.8, 129.7, 128.9, 32.2, 28.1, 24.9, 22.6, 14.2.

Chapter 7

Conclusions

In conclusion, new methods for important organic transformations, such as direct dehydrative C-C coupling, direct esterification of carboxylic acids and alcohols and aldol condensation of aldehydes were developed, using environmentally friendlier non-metal catalysts, such as iodine, *N*-halosuccinimides and dibromantin.

In the first part of the thesis, the method for direct dehydrative C-C coupling of alcohols and alkenes catalyzed by iodine is described. Iodine proved as an efficient Lewis acid catalyst for coupling of various benzylic alcohols with phenyl-substituted alkenes, such as 1,1-diphenylethene and allowing relatively low temperatures and furnishing polysubstituted olefins in high yields. During the optimization of reaction conditions, the solvent-free reaction conditions proved to be equally efficient than the use of Solkane® or *n*-hexane. Besides that, only 10 mol% excess of the alcohol was needed for high conversions of the starting material. Based on the control experiments, the mechanism, involving the formation of the carbocation intermediate was proposed and a scale-up protocol performed to confirm the synthetic practicability of the methodology. Unfortunately, the dehydrative cross-coupling of styrene with alcohols was unsuccessful, as a considerable amount of polymeric material was formed. As some alcohols may act as cheaper or more widely available starting materials than alkenes and since the tertiary alcohols are well known to readily undergo elimination reaction in the presence of Brønsted or Lewis acids, we subsequently investigated and confirmed the possibility to use tertiary alcohols as a convenient replacement for the alkene component in the reaction system.

In the second part, the newly developed methodology for the direct esterification of carboxylic acids and alcohols is presented. *N*-halosuccinimides, particularly *N*-bromosuccinimide (NBS), proved as a convenient, easily-handled and inexpensive bench-top mediator, which allows mild neat reaction conditions and relatively low temperatures (70 °C) without the need for the inert atmosphere. The approach provides comprehensive esterification of substituted benzoic acids as well as of mono-, di- and tri-carboxy alkyl derivatives. Relative to aromatic acids, significantly higher activity of alkyl acids has been observed. The reaction limitation was observed in the case of esterification of tertiary alcohols, phenol and in the case of *p*-methoxy substituted benzoic acid. The efficacy of the method was elaborated also on more complex structural backbones, such as bile acids (cholic acid and dehydrocholic acid). The method is metal-free, enables a catalyst recyclation and allows for a simple synthetic and isolation procedure as well as for the scale-up of aromatic and alkyl esters with yields up to 100%.

The last section is dedicated to the upgrade of the NBS-mediated esterification protocol by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as an accessible, affordable, and metal-free precatalyst. The method approves an expansion of the esterification scope of carboxylic acids, while maintaining all other advantages of NBS-mediated reaction system.

Moreover, the reaction pathway for esterification was proposed and a scale-up of certain industrially important derivatives performed. Finally, to show a general ability of DBDMH acting as the activator of the carbonyl functionality, the methodology was expanded also to the aldol condensation of aldehydes.

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Publications Related to the Thesis

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K. Čebular and S. Stavber, "Molecular iodine as a mild catalyst for cross-coupling of alkenes and alcohols," *Pure and Applied Chemistry,* vol. 90, no. 2, pp. 377-386, 2018.

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