ChemPubSoc Europe

DOI: 10.1002/ejoc.201901495

EurJOC European Journal of Organic Chemistry

Minireview

YourJOC Talents | *Very Important Paper* |

VIP

Lewis Base Catalysis Promoted Nucleophilic Substitutions – Recent Advances and Future Directions

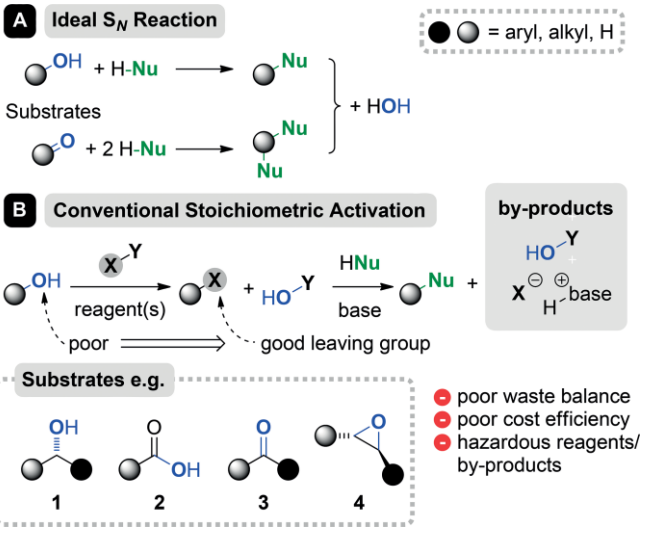
Peter H. Huy*[a]

Abstract: Nucleophilic substitutions (S_N) account for the most essential and frequently applied chemical transformations. S_N-reactions allow forging C–C, C–O, C–N and C–Cl bonds, for example, from natural abundant starting materials such as alcohols and carboxylic acids. Products of S_N-reactions are ubiquitous and find *inter alia* applications as pharmaceuticals, plant protection agents and polymers. However, conventional S_N-type approaches are restricted frequently by the necessity of hazardous reagents and by-products, a poor waste-balance and therefore sustainability and high levels of costs, which especially impedes application in large scale synthesis. In order to provide solutions to these limitations, the development of novel catalytic methods for S_N-transformations has evolved into a flourishing and reviving area of research. The current review enables an overview of modern strategies for catalytic nucleophilic substitutions, presents as main topic the state-of-the-art with respect to S_N-methods that are promoted by Lewis bases and points out potential future directions for further innovations.

1. Introduction

1.1. Catalysis in Nucleophilic Substitutions

Nucleophilic substitutions (S_N) enable straightforward C–C, C–O, C–N, and C-X bond formation, for instance, utilizing readily available starting materials (Scheme 1, X = halogen).[1–7] As the consequence S_N-type reactions account for the most fundamental and widely-spread transformations in chemistry. Of particular importance are hydroxyl group-containing starting materials such as alcohols **1** and carboxylic acids **2** (Scheme 1). Both are of high natural abundance and can also be derived from renewable feedstocks.[8] Products arising from S_N-chemistry are omnipresent like in drugs, proteins, and materials (e.g. polymers).



Scheme 1. **A** Ideal and **B** conventional S_N-reactions.

In an "ideal" S_N-transformation, only water would be formed as by-product (Scheme 1 **A**). However, the hydroxyl group is an

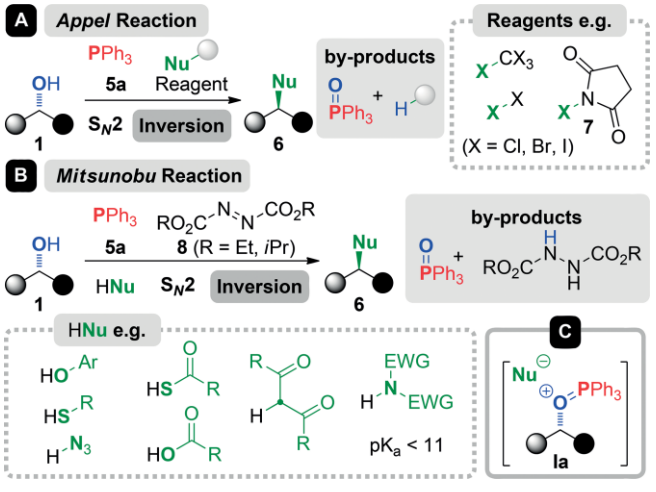
[a] *Saarland University, Institute for Organic Chemistry, P. O. Box 151150, 66041 Saarbruecken, Germany*
E-mail: peter.huy@uni-saarland.de
https://www.peterhuylab.de
ORCID(s) from the author(s) for this article is/are available on the WWW under https://doi.org/10.1002/ejoc.201901495.

Peter Huy obtained his Ph.D. in chemistry at the University of Cologne in 2010 working with Prof. Hans-Guenther Schmalz on the stereoselective synthesis of diproline peptido mimetics. Subsequently, he performed a postdoctoral research project on the synthesis of N-heterocycles from amino acids in the group of Prof. Ari Koskinen at the Aalto University in Helsinki (2011–2012), which has been funded by the DAAD. After a second postdoctoral stint in the group of Prof. Ben List at the Max-Planck Institute for Carbon Research in Muehlheim at Ruhr (2013), he joined Saarland university to initiate his independent research career in 2014. Distinguished with a Liebig-fellowship his group is dedicated towards homogeneous catalysis and natural product synthesis.

intrinsically poor leaving group, which is explained by its high Brønsted basicity. Hence, the displacement of OH groups by nucleophiles conventionally affords a preceding activation step (Scheme 1 **B**). Thereby, the hydroxyl function is transformed into a good leaving group, which is derived from weak Brønsted bases. This additional derivatization requires at least one stoichiometric reagent, which results in the formation of by-products with considerably higher molecular masses than water.

Therefore, the majority of the conventional S_N-protocols is impaired by a rather poor waste-balance and consequently also sustainability[9] and cost-efficiency.

Actually, many of the catalytic methods delineated in this review have been inspired by the renowned Appel[10] and Mitsunobu[6,11] reaction (Scheme 2). These two classical S_N-approaches illustrate the challenges that have to be faced very well. Appel reactions furnish haloalkanes of type **6** from alcohols **1**, which is promoted by triphenylphosphine (**5a**) and an electrophilic halogenation reagent (Scheme 2 **A**). Besides carbon tetrachloride and -bromide also elemental halogens and *N*-halosuccinimides (**7**) are widely-used as oxidation agents.

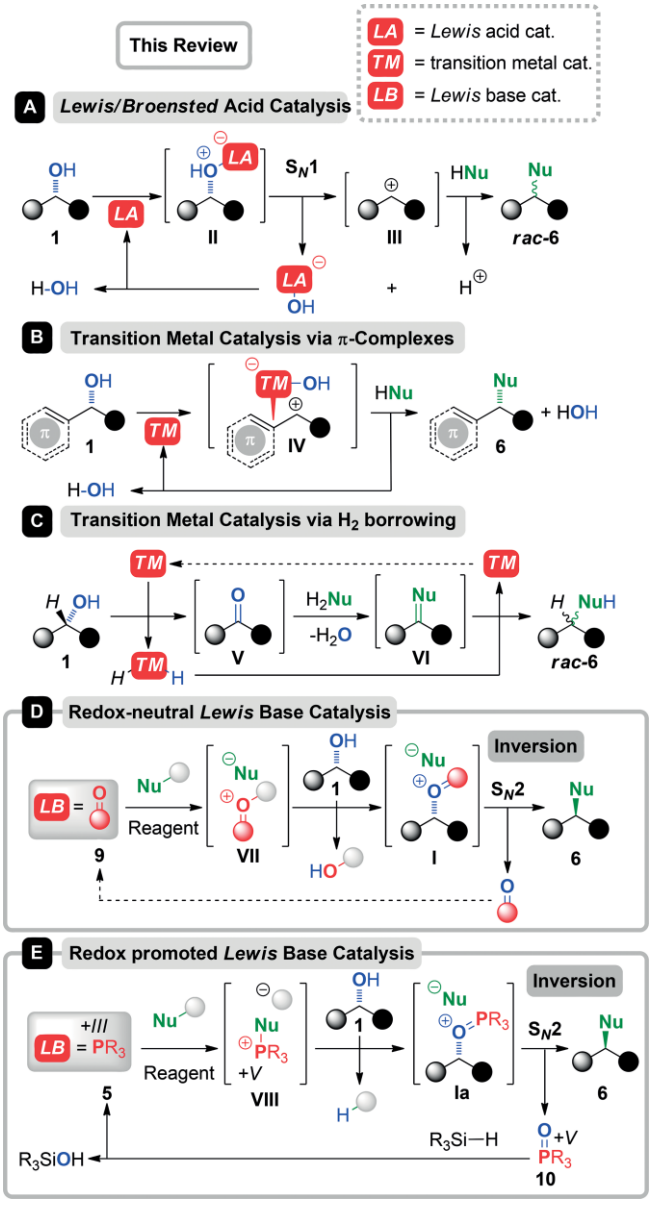


Scheme 2. Classical S_N-methods for alcohols (EWG = electron withdrawing group).

The Mitsunobu reaction on the other hand facilitates condensations of alcohols with a broad scope of O, S, C, and N-nucleophiles with a $pK_a \leq 11$, which necessitates PPh_3 and an diazodicarboxylate of type **8** as reagents (Scheme 2 **B**).

Since only neutral by-products evolve, these methods exhibit high levels of functional group compatibility. As an additional important aspect, enantioenriched alcohols **1** are transformed under so-called stereochemical Walden inversion into non-racemic products of type **6**,[12] which is ascribed to a concerted bimolecular nucleophilic substitution (S_N2) mechanism. Both named reactions have alkoxyphosphonium salts **Ia** as key intermediate in common, in which the hydroxyl group has been converted in a neutral leaving group ($O{=}PPh_3$, Scheme 2 **C**). However, the generation of two by-products, which is accountable for a poor waste-balance and thus cost-efficiency, the hazardous nature of diazo agents such as **8** and the often tedious separation of triphenylphosphane oxide impede the application of these highly-useful protocols in particular in larger scales severely.[6b]

Against this background, the development of more effective and "greener" methods for S_N-type transformations is a challenging and highly attractive goal for academic research. Additionally, the chemical industry declared a high demand for novel S_N-protocols that exhibit a minimized ecological footprint.[13] To accomplish these goals, several strategies for catalytic nucleophilic substitutions relying on closed-shell intermediates have been devised. The most important concepts for the transformation of alcohols are summarized in Scheme 3, which also includes simplified reaction mechanisms.



Scheme 3. Modern strategies for catalytic nucleophilic substitutions employing alcohols.

Lewis and Brønsted acid catalysis pave the way for the formation of C–C, C–N, C–O, and C–S bonds in high versatility and optimal atom efficiency, as water is liberated as exclusive by-

product (Scheme 3 **A**).[1,2,14] At the outset, complexation and protonation, respectively, of **1**, which results in intermediate **II**, allow for catalytic activation of the OH group. According to a two-step unimolecular nucleophilic substitution (S_N1) mechanism, the successive displacement proceeds via achiral carbenium ions of type **III**. As a consequence, enantioenriched substrates **1** give rise to racemic products. For this approach mainly electron-rich alcohols, which engender stabilized type **III** cations, are appropriate.

Transition metal catalysis allows for S_N-reactions addressing allylic, propargylic and certain benzylic alcohols of type **1** in optimal atom efficiency (Scheme 3 **B**).[3] Since both, the formation of the intermediate metal-π complexes **IV** and the subsequent introduction of the nucleophile take place under stereochemical inversion, overall retention of the configuration occurs.

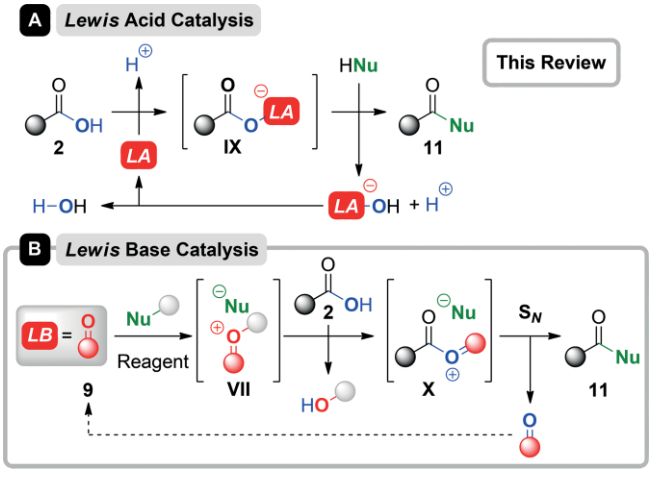
In the last years, transition metal-catalyzed transformations of alkanols into type **6** alkylamines and α-alkylated carbonyl compounds have grown into a prospering research area (Scheme 3 **C**).[4] These S_N-like reactions are commenced by dehydrogenation of **1** yielding carbonyl compounds **V**, in which hydrogen is "borrowed". Next, unsaturated intermediates of type **VI** arise either from an imine or aldol condensation. Eventually, hydrogen is returned by means of reduction of **V** to **6**. Since the stereochemical information is lost inevitably in the conversion of **1** to **V**, racemic products are isolated in the instance of non-chiral catalysts. S_N-reactions of this class are also distinguished by an optimal atom economy because H_2O is generated as sole by-product.

Inspired predominantly by the Appel and Mitsunobu reaction (see Scheme 2), Lewis base catalysis has emerged as a powerful tool for S_N-type bond formation (Scheme 3 **D** + **E**).[5,6,15] Thereby, two different approaches can be differentiated based on the oxidation state of the reactive center of the catalyst, which either remains unaltered or changes throughout the process. Catalysts for the redox-neutral version have a Lewis basic double-bonded oxygen atom as key structural motif in common (Scheme 3 **D**, for examples see Scheme 5 **B**). Activation of the HO moiety is attained in the presence of non-oxidative acid halide or anhydride reagents, which are also the source of the nucleophile. In terms of reaction mechanism, the Lewis base catalyst **9** is first acylated by means of the electrophilic reagent. Subsequently, the resulting electrophilic species **VII** undergoes a condensation with the starting material **1** to afford intermediate **I**, which bears a neutral leaving group and the nucleophile as counterion. Finally, nucleophilic displacement under stereochemical Walden-inversion in accordance with an S_N2-mechanism furnishes enantioenriched products **6** and completes the catalytic cycle.

In contrast, phosphane **5** catalyzed S_N-transformations are driven by an oxidation of the P atom in **5** (Scheme 3 **E**). Initially, **5** (oxidation state *+III*) is transformed by means of an oxidative halogenation reagent into tetravalent phosphonium intermediate **VIII** (*+V*). Reaction with the alcohol **1** then furnishes intermediate **Ia**, which shows resemblance with the redox-neutral approach. Afterwards S_N2-type substitution delivers product **6** under inversion of the configuration and phosphane oxide **10**. Ultimately, **10** is reduced to phosphine **5** using a silane, which concludes the catalytic process. Worthy of notice, the sequence **5** → **6** is identical with the Appel reaction (Scheme 2 **A**).

Since Lewis base-catalyzed S_N-reactions in the majority need a stoichiometric reagent, the atom efficiency is lower than in the aforementioned strategies. Beneficially, they are very variable in terms of substrate scope, since electron-rich and electron-poor, primary secondary or even tertiary alcohols are suitable as substrates. Due to the Walden inversion, the stereochemical integrity of enantioenriched alcohols **1** is largely preserved. As the reaction conditions are on average less acidic in comparison to Lewis and Brønsted acid-catalyzed protocols, levels of functional group compatibility are higher. Besides, several intriguing protocols for the Mitsunobu reaction, which are catalytic regarding the Lewis acidic diazo component, have been implemented lately and are summarized in an up-to-date review.[6b]

In the case of carboxylic acids **2**, in particular two catalytic concepts have been established in the past years (Scheme 4).[16] Boron, zirconium and hafnium Lewis acids, for instance, have facilitated a significant step forward towards the atom-efficient production of amides **11** (Scheme 4 **A**).[2,7] In addition, designated Lewis bases are capable to activate acids **2** in a catalytic manner, which enabled the straightforward synthesis of esters and amides of type **11** (Scheme 4 **B**).

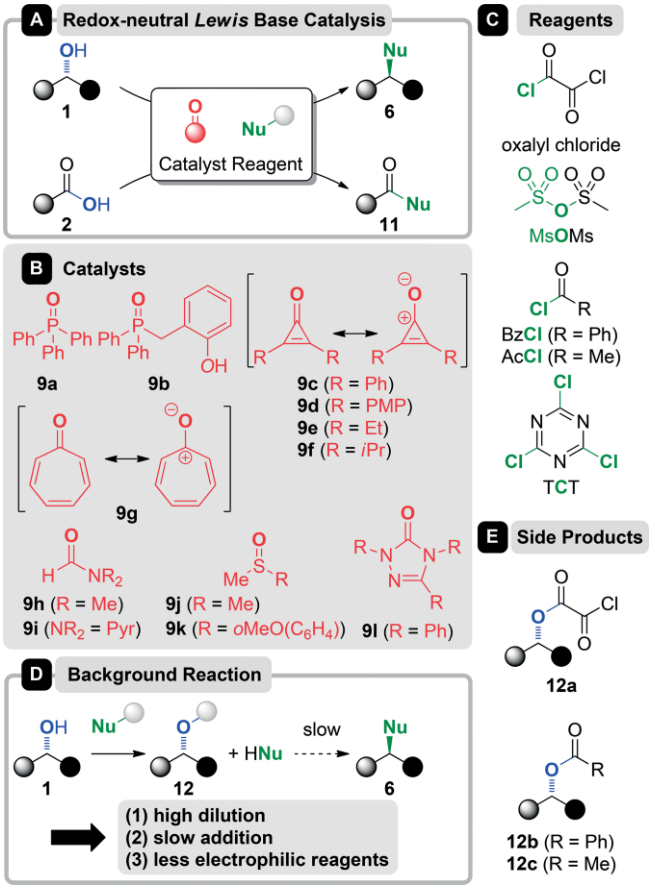


Scheme 4. Present concepts for catalytic nucleophilic substitutions involving carboxylic acids.

The current review focuses on the progress concerning Lewis base-catalyzed S_N-reactions according to the strategies delineated in Scheme 3 **D** and Scheme 3 **E** and Scheme 4 **B** since 2009. In addition, related non-catalytic Lewis base promoted transformations are discussed. In chapter 2 to 4, the methodological approaches are divided into the substrate categories alcohols, carboxylic acids, and aldehydes and epoxides. Each substrate class is partitioned in catalyst types in chronological order with respect to the year of the first literature precedent. In section 2 about alcohols initially redox-neutral approaches are introduced, which is succeeded by redox driven and non-catalytic protocols. In chapter 5 other important contributions concerning S_N-reactions are highlighted.

1.2. Lewis Base Catalyzed Nucleophilic Substitutions

Redox-neutral Lewis base promoted S_N-approaches enable the transformation of alcohols **1** and acids **2** into adducts **6** and **11**, for example (Scheme 5 **A**). A range of O-centered Lewis bases has been discovered as proficient catalysts for these processes (Scheme 5 **B**). Amongst them are phosphine oxides **9a** and **9b**, aromatic cyclopropenones **9c–f** and tropone **9g**, formamides **9h** (DMF) and **9i** (FPyr), sulfoxides **9j** (DMSO) and **9k** and triazolinone **9l**. In order to outcompete background esterification (vide infra), catalyst loadings of 5–20 mol-% are quite common. Nevertheless, this disadvantage is counterbalanced by the inexpensive nature and low molecular weight (down to <100 g/mol) of most organic Lewis bases employed, some of which are routine solvents (e.g. DMF and DMSO).



Scheme 5. Redox-neutral Lewis base-catalyzed *SN*-methodologies.

Thermodynamic driving force is guaranteed by acid chloride and anhydride reagents such as oxalyl chloride, methane sulfonic acid anhydride (Ms_2O), benzoyl and acetyl chloride (BzCl/AcCl) and trichlorotriazine (TCT), which is also known as cyanuric chloride (Scheme 5 **C**). The diminished atom economy in comparison to other catalytic methods (see section 1.1), is partially compensated by the low costs and molecular weights of these commodity chemicals. Since the reagent also delivers the nucleophile, Lewis base-catalyzed S_N-methods in the majority afford alkyl and acid halides as products. Notable, halo alkenes and acid halides allow for the introduction of virtually any nucleophile and hence are synthetically very useful and valuable intermediates. In addition, a plethora of chlorinated and brominated natural products have been described,[17] which are amenable by means of the reviewed methodologies.

In fact, the major challenge for Lewis base-catalyzed S_N-processes is an undesired background reaction (Scheme 5 **D**). In the absence of a viable catalytic species, nucleophilic alcohols **1** react with acid chlorides to afford esters of type **12** (Scheme 5 **E**). The nucleophilic alcohol **1** and the Lewis base catalyst **9** are both competing for the electrophilic reagent. The pivotal role of the catalyst **9** is to switch chemoselectivity in favor of the S_N2-substitution product **6**. The unwanted condensation yielding **12** has been mitigated by (1) diluted reaction media through the usage of large solvent amounts and (2) a very slow addition of a solution of the reagent to the reaction mixture with the aid of a syringe pump. Alternatively, (3) application of reagents that are less electrophilic than oxalyl chloride (e.g. BzCl and TCT), respectively, also allow decreasing esterification producing **12**.

1.3. Stereochemical Inversion and Green Metrics

Before the discussion of specific literature examples, some general aspects are taken into account. Due to the Walden inversion, the enantiomer of the opposite configuration of the starting alcohol **1** is formed preferentially, which renders S_N2-type reactions enantioselective. As coined by Lambert and Denton, "substitutions under inversion" are also termed as "invertive substitutions".[5a] S_N2-like displacements are also designated as stereospecific (or enantiospecific), because they "[•••] *produce different stereoisomers from stereoisomeric starting materials under identical conditions*".[18b] The preservation of enantiomeric purity is displayed by comparison of the enantiomeric excesses (*ee*) or enantiomeric ratios (*er*) of the product and starting compound. This is easiest accomplished through the chirality transfer (*c.t.*) as suggested by Samec,[19] which is determined as follows:

$$c.t. = \frac{ee\ (product)}{ee\ (starting\ material)} 100\%$$

If the starting material contains other stereogenic elements, two diastereomeric (and not enantiomeric) products potentially arise. In this instance, the *c.t.* is calculated based on the diastereomeric excesses (*de*) instead of the *ee*s. The exact definition of the chirality transfer (or transfer of chirality) is strictly speaking referring to reactions "[•••] *in which at least one element of chirality is translocated from one site to another*".[18b] In an S_N2 substitution no translocation of a stereocenter takes place, instead it remains on the very same carbon atom. Nevertheless, we are convinced (also to the lack of viable alternatives) that the chirality transfer is the best means to describe the conservation of stereoisomeric purity.

To compare a set of methods in terms of sustainability,[9] different green metrics have been engaged in the references included herein. All of them are calculated based on a specific chemical transformation. Therefore, an accurate comparative analysis requires data for the conversion of a selected starting material to a specific product. The simplest tool to assess the

ecological foot-print is the atom economy (AE), which is synonymous with atom efficiency.[20a] It is based on the molecular weights M of the starting materials, which appear in the balanced reaction equation, and of the desired product and their stoichiometric co-factors ν:

$$AE = \frac{\nu \cdot M(product)}{\sum_i \nu_i \cdot M_i(starting\ materials)} 100\%$$

A more detailed comparison is achieved by the reaction mass efficiency (RME), which relies on masses m:[20b]

$$RME = \frac{m(product)}{\Sigma m(starting\ materials)} 100\%$$

Therefore, the yield, which impacts the mass of the product, and the stoichiometry, in which the starting materials have actually been utilized, are accounted for. The E-factor facilitates an even more precise assessment:[20c]

$$E-factor = \frac{m(product)}{m(waste)} = \frac{m(product)}{\Sigma m(starting\ materials) - m(product)}$$

The E-factor is typically calculated using the masses of starting materials rather than of waste because the latter one is more difficult to specify. In contrast to the RME, masses of all starting materials are considered, which also includes solvents in the reaction, work up and purification (with the exception of water) and auxiliary chemicals for the work-up and purification (e.g. silica gel).

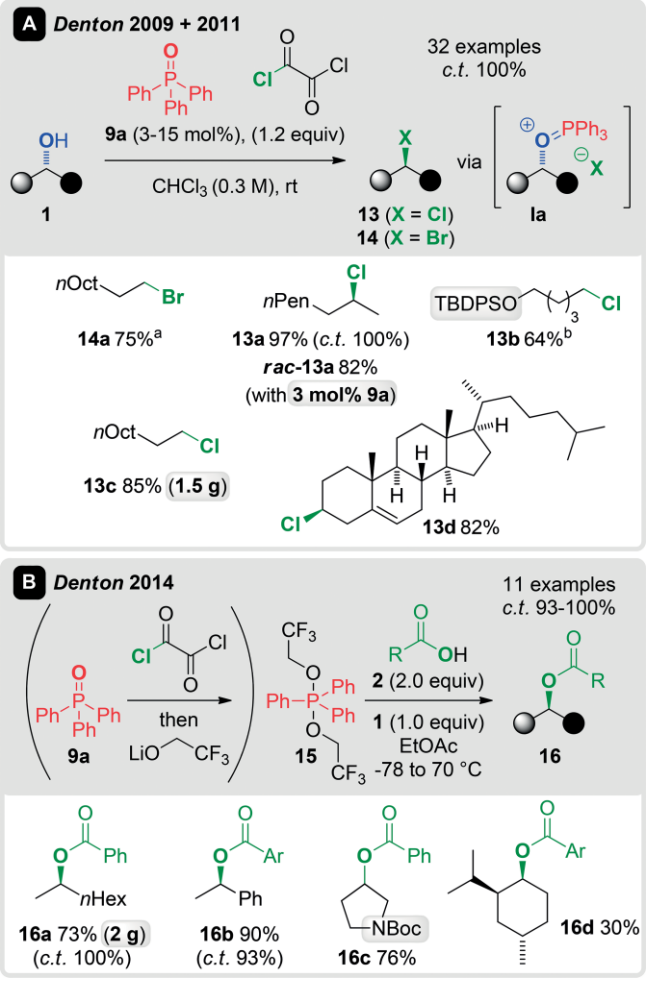
An essential aspect that coins the synthetic utility of any method is scalability. In this context, the largest scale example (≥1 g scale) is highlighted for each method in chapters 2 to 4. In terms of volume, the solvent is usually the main component of a reaction mixture. Thus, the concentration of the starting material with respect to the reaction solvent allows to roughly estimate the scalability. High substrate concentrations entail low solvent amounts, which in turn predicts reasonable scalability. Therefore, the molar concentrations of starting materials like **1** or **2** are noted for each protocol in "M" (= mol/L) below the reaction arrow right after the solvent in round brackets.

2. Substrate Class Alcohols

Most methods in this section have been demonstrated to be applicable towards primary and secondary alcohols, which typically encloses aliphatic, benzylic, allylic and propargylic examples. For the reason of clarity, only deviations from these basic sets of compatible carbon scaffolds such as tertiary alcohols are mentioned in the following. As a matter of fact, tertiary alcohols, which are likely to undergo substitution according to an S_N1-mechanism, are rarely represented in the substrate scopes discussed herein. Most of the methods tolerate (halo)arenes, alkenes, alkynes, alkylaryl ethers, methyl and ethyl esters, and nitroarenes. Therefore, only functional groups apart from these examples are explicitly noted in the following.

2.1. Phosphane Oxide Catalysis

The group of Denton discovered triphenylphosphane oxide **9a** as one of the first examples for Lewis base catalysts that promoted transformations of alcohols **1** into alkyl halides **13** and **14** (Scheme 6 **A**).[21] While alkyl chlorides were produced by means of oxalyl chloride, additional engagement of LiBr afforded the corresponding bromides (e.g. **14a**). This approach is referred to as a redox-neutral catalytic Appel reaction because the oxidation state of phosphorus remains *+V* throughout the catalytic cycle (compare with Scheme 2 **A**). Since only oxalyl chloride is required as reagent, overall a much better atom economy has been reached (e.g. in comparison to CCl_4/PPh_3). Just 3 mol-% of **9a** were sufficient for the production of ***rac*-13a**, which is one of the lowest catalyst loadings described to date for S_N-reactions. S_N2-type stereochemical inversion was substantiated through the synthesis of aliphatic chloride **13a** in high enantioselectivity. Concerning functional group compatibility, a secondary amide, and TBDPS ether **13b**, in the preparation of which 2,6-di-*tert*-butylpyridine was employed as base,



Scheme 6. Triphenylphosphine oxide enabled synthesis of alkyl halides and esters (Ar = 4-$O_2N(C_6H_4)$, TBDPS = *tert*-butyldiphenylsilyl). a. With 3 equiv. LiBr. b. Reaction performed in the presence of 1.8 equiv. 2,6-di-*tert*-butylpyridine.

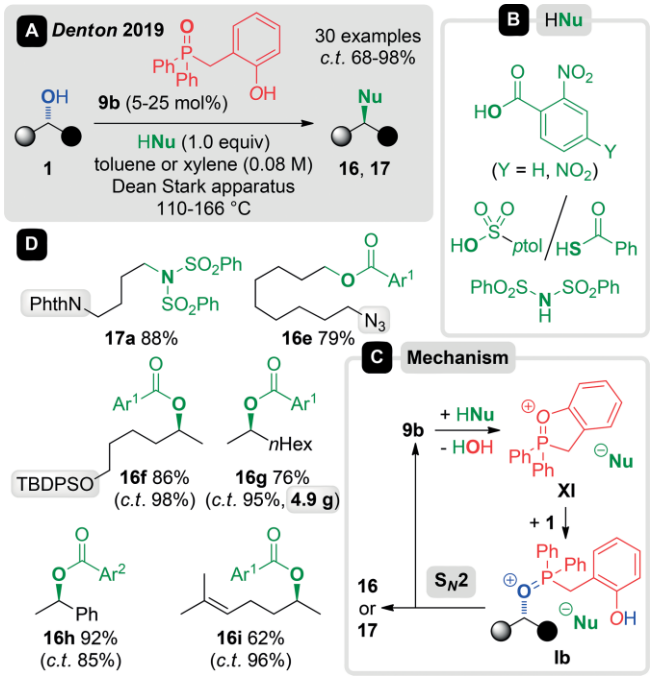
stand out. More acid-labile TES ethers were cleaved under the optimized conditions.

Worthy of note, cyclohexanol derivatives such as menthol are challenging substrates for S_N-reactions. An S_N2-type backside attack is restricted by the cyclohexyl backbone in the thermodynamically preferred chair conformer with the OH group in equatorial position. Since the positive charge of the secondary cyclohexyl carbeniumion is not well stabilized, an S_N1-mechanism is also not favorable. Against this background, sterically demanding substrates such as cyclohexanol, menthol, *tert*-butanol, and neopentyl alcohol turned out to be non-viable starting materials, a limitation whom many other catalytic protocols share.

Key alkoxyphosphonium intermediate **Ia** was evidenced profoundly by NMR spectroscopy and X-ray crystal structure analysis. Interestingly, alkyl and arylphosphine oxides, which contain electron-rich aryl portions, did not foster halide **13** formation.

On the other hand tris-(4-fluorophenyl)phosphane oxide appeared as a slightly more competent catalyst. Next, Denton and co-workers disclosed an elegant redox-neutral Mitsunobu-type process for the synthesis of esters under inversion (see examples **16a**+**b** in Scheme 6 **B**).[22a] Ishikawa phosphorane **15**,[22b] which is received upon successive reaction of phosphane oxide **9a** with oxalyl chloride and trifluoroethanolate, served as reagent. With regard to functional group tolerance, even a Boc-carbamate resisted the reaction conditions (example **16c**). The sterically challenging menthol derived ester **16d** was isolated in a moderate yield. NMR studies corroborated phosphonium species **Ia** as pivotal intermediate.

Recently, the group of Denton succeeded in developing a redox-neutral fully catalytic version of the Mitsunobu reaction (Scheme 7, compare with Scheme 2 **B**).[22c] Water released as the only by-product was removed from the reaction mixture by means of a Dean–Stark apparatus at high temperatures. This ground-breaking work has been enabled by phosphane oxide catalyst **9b**, which is equipped with a 2-hydroxybenzyl moiety. Indeed, the phenolic OH group allows for the generation of crucial phosphonium intermediate **XI** upon reaction of catalyst **9b** with the acidic nucleophile under liberation of water (Scheme 7 **C**). Nucleophiles of high acidity such as nitrobenzoic and sulfonic acids and imides are required for the formation of **XI** (Scheme 7 **B**). Subsequently, condensation of **XI** with starting alcohol **1** delivers phosphonium species **Ib**, in which the OH group of **1** is activated as a neutral phosphane oxide leaving group. Eventually, nucleophilic substitution under inversion facilitates formation of esters, and imides. Evidence for intermediates **XI** and **Ib** was gathered by NMR.



Scheme 7. Fully catalytic Mitsunobu reaction (Ar^1 = 2,4-$(O_2N)_2(C_6H_3)$, Ar^2 = 2-$(O_2N)(C_6H_4)$, Phth = Phthaloyl, *p*Tol = *para*-tolyl).

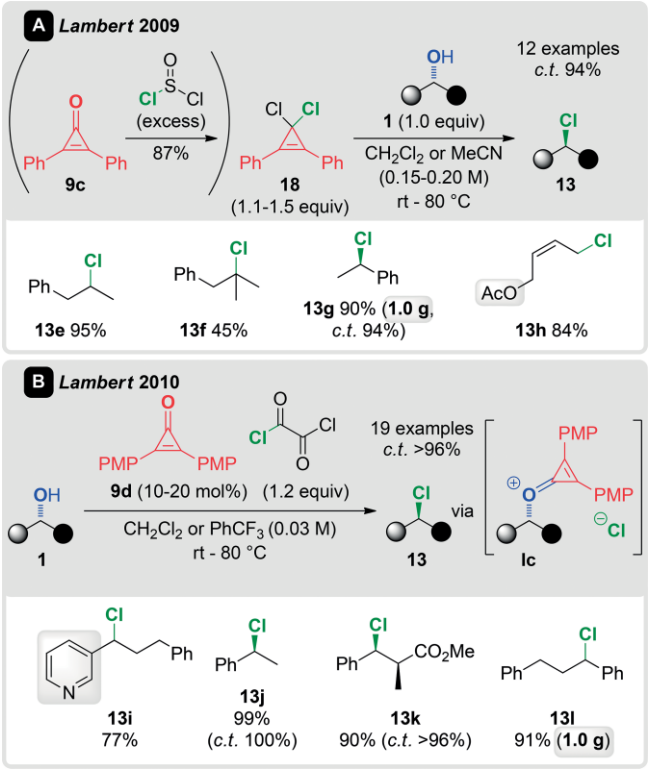
Interestingly, a derivative of phosphane oxide **9b**, in which the OH group had been methylated, effected ester formation in low yield and under retention of the configuration. This experimental observation emphasizes the essential role of the hydroxyl moiety in catalyst **9b**. Denton's intriguing method combines the advantages of Lewis acid (compare Scheme 3 **A**) and base-catalyzed S_N-strategies, which are no need for stoichiometric reagents and conservation of stereochemical purity, respectively. Tertiary amides, imides (example **17a**), sulfones, alkyl bromides, and nitriles are amongst the compatible functional groups (Scheme 7 **D**). Notable, ester **16e** contains an azido group, which would most likely not be tolerated under classical Mitsunobu conditions due to Staudinger reaction with PPh_3. Despite the acidic reaction conditions, TBDPS ether **16f** was produced in excellent yield.

Interestingly, the nucleophile had a main impact on the chirality transfer. Whilst 2,4-nitrobenzoic acid was recognized as optimal in the case of aliphatic substrates (e.g. **16g**), the highest level of inversion in the instance of benzylic product **16h** was accomplished using 2-nitrobenzoic acid. In addition, scalability has been approved by the multigram preparation of two examples including **16g**. Practical relevance has also been illustrated through the rapid synthesis of the antituberculosis drug thiocarlide. While the conventional Mitsunobu protocols display a reaction mass efficiency (RME) of 21 %, catalytic variants show deteriorated to moderately improved RMEs of 13–27 % (mean values of several examples).[6b] The fully catalytic Mitsunobu procedure, however, exhibits a significantly improved average RME of 65 %.[22c]

2.2 Cyclopropenone and Tropone Catalysis

In the aromatic cyclopropenyl and cylcoheptatrienyl resonance structures of cyclopropenones and tropone, respectively, the carbonyl O-atom carries a negative formal charge (see Scheme 5 **B**). Indeed, the aromatic character of these compounds results in a highly polarized carbonyl group, which makes cyclopropenones **9c–f** and tropone **9g** excellent Lewis bases. Cyclopropenone catalysis has been pioneered by the group of Lambert (Scheme 8 + Scheme 9). At the outset, the ability of dichlorocyclopropene **18**, which is obtained from diphenylcyclopropenone (**9c**) by means of thionyl chloride

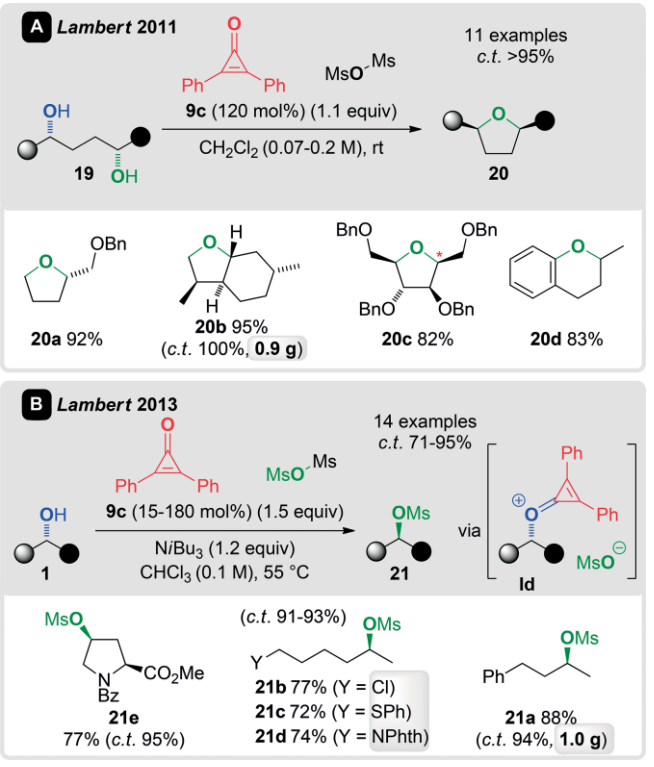
($SOCl_2$), to transform alcohols **1** into chloro alkanes was discovered (Scheme 8 **A**).[23a] Conversion of secondary aliphatic starting materials requested heating to 80 °C (see **13e**), whereas in all other cases room temperature was sufficient. Reagent **18** even allowed the preparation of tertiary chloride **13f** in a moderate yield. Remarkably, chiral benzylic chloride **13g**, which is prone to racemization due to competing S_N1-displacement, was synthesized under inversion on a gram scale in high levels of chirality transfer. Cyclopropenone activation gives rise of type **Ic** intermediates (here with Ph instead of PMP), which has been corroborated by means of ^{1}H-NMR.



Scheme 8. Cylcopropenone-promoted synthesis of chloro alkanes (PMP = *para*-methoxyphenyl).

Shortly after, the Lambert group implemented an S_N-method for the conversion of alcohols to alkyl chlorides that is catalytic in cyclopropenone (Scheme 8 **B**).[23b] Alkyl and arylcyclopropenones are both capable to catalyze the transformation **1** → **13**. Nevertheless, Lewis base **9d**, which incorporated two electron-rich *para*-methoxyphenyl substituents (PMP), came forward as privileged catalyst. Since reaction of thionyl chloride with alcohols readily affords chloro alkanes in the absence of catalysts, oxalyl chloride was selected as reagent. While transformations of more reactive benzylic, propargylic and allylic substrates **1** were carried out at room temperature, secondary aliphatic chlorides **13** had to be synthesized under heating to 80 °C in $PhCF_3$. Remarkable is the production of chloride **13i**, which contains a pyridyl heterocycle. To the best of our knowledge, this is the sole example in the field of Lewis-base catalyzed S_N-type reactions of alcohols that bears a Brønsted basic function.

Secondary non-racemic chlorides were formed under clean inversion, which was demonstrated in the instance of several



Scheme 9. Cylcopropenone facilitated nucleophilic substitutions using methylsulfonic acid anhydride (Ms = methylsulfonyl).

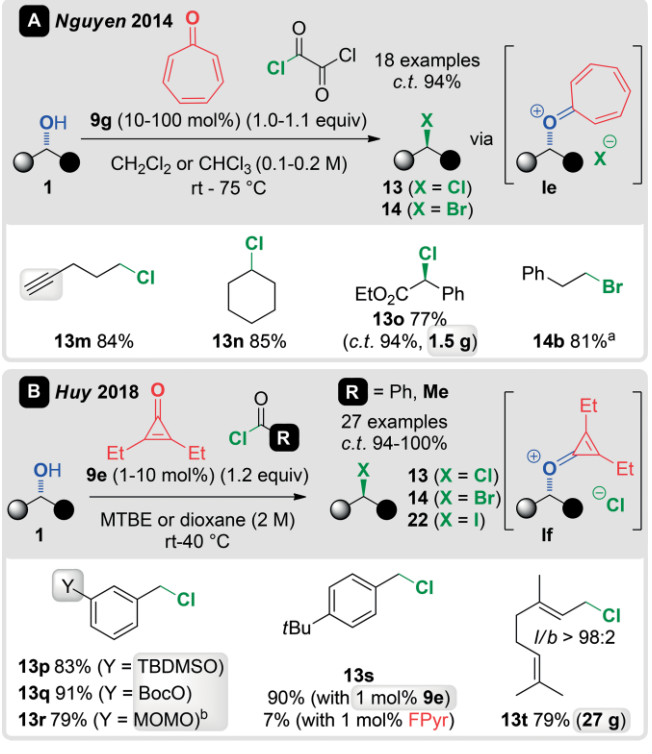
benzylic substrates and an α-hydroxy ester (e.g. **13j**+**k**). Comparison experiments with $SOCl_2$ showed significantly enhanced stereoselectivities.

In the following, the team of Lambert established a method for the invertive cyclodehydration of diols of type **19**, in which methyl sulfonic acid anhydride (Ms_2O) was applied as reagent (Scheme 9 **A**).[23c] Other reagents such as oxalyl chloride and trifluoroacetic anhydride did not cause furan **20** formation. This dehydrative cyclization has been facilitated by stoichiometric amounts of commercial diphenylcyclopropenone (**9c**), which could also be replaced by the diisopropyl congener **9f** (see Scheme 5 **B**). Thereby, not only saturated furans such as **20a–c** but also six-membered pyrans like **20d** were amenable.

The synthesis of **20a** and **20b** proceeded under retention of the configuration, which is explained by site-selective activation of the sterically less encumbered primary OH function in **19**. In contrast, inversion of one stereocenter was observed in the preparation of THF derivative **20c** from a C_2-symmetrical diol. Moreover, mesylates of type **21** have been synthesized from alcohols **1** under stereochemical inversion using Ms_2O and cyclopropenone **9c** as catalyst (Scheme 9 **B**).[23d] Worthy of note, in the absence of aromatic compound **9c** products of type **21** were generated under retention. The formation of **21** from intermediate **Id**, which resulted according to ^{1}H-NMR from reaction of **1** with Ms_2O in the presence of **9c**, was triggered by bases. A screening revealed sterically shielded tri-*iso*-butylamine as optimal candidate. In terms of molecular functionality, amides (example **21a**), imides (**21b**), chloro alkanes (**21c**) and sulfides (**21d**), for example, were found to be compatible. Additionally, levels of chirality transfer were in a range of 71–95 %.

While catalytic amounts of **9c** entailed the highest stereoselectivities, stoichiometric quantities affected enhanced chemical yields. The method allows for an alternative to the Mitsunobu reaction for the inversion of alcohols, which advantageously avoids the use of hazardous diazo compounds. Furthermore, a protocol was developed to ease up separation of cyclopropenones from the crude material. The addition of commercial tetraethylene pentamine at the end of the reaction imparted conversion of cyclopropenone to an amide with a residual amine moiety, which is readily removed by means of washing with dilute aqueous HCl solution. Noteworthy, in the approaches in Scheme 8 and Scheme 9, scalability has been verified by experiments on a gram scale. In addition, cyclopropenones can be recycled through chromatography.

In the following, the group of Nguyen discovered tropone (**9g**) as an efficient promoter for the transformation of alcohols into chloro and bromoalkanes **13** and **14**, respectively (Scheme 10 **A**).[24a] In the majority of the examples, reaction of commercially available tropone with oxalyl chloride engendered 1,1-dichloro-cycloheptatriene, which had been evidenced by NMR and HR-MS. Noteworthy, tropone can be reisolated by means of chromatography. In selected cases was demonstrated that catalytic quantities of tropone (10 mol-%) were appropriate to impart generation of **13**. Whereas preparation of aliphatic chlorides like **13m** and **13n** required heating to 75 °C, all other halogenated products were amenable at ambient conditions.



Scheme 10. Tropone and cylcopropenone catalyzed preparations of alkyl halides (TBDMS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, l = linear, b = branched). a. With 2.5 equiv. N*n*Bu$_4$Br. b. With 1.3 equiv. N*i*Bu$_3$ and 30 mol-% **9e**.

Although sterically encumbered cyclohexanol was converted successfully into cyclohexyl chloride (**13n**), a tertiary starting material was not suitable. To access bromo alkanes as **14b** either LiBr or N*n*Bu$_4$Br was used in addition. Stereochemical inversion has been certified through the production of α-chloroester **13o**. Prove for key intermediate **Ie** was collected by ^{1}H-NMR.

Eventually, the group of Huy exploited cyclopropenone catalysis for benzyl and acetyl chloride driven invertive halogenations of alcohols **1** (Scheme 10 **B**).[24b] Diethylcyclopropenone (**9e**), the preparation of which requires only one step and is high yielding,[25] was applied as catalytic component. Finkelstein-type reaction conditions using NaBr or NaI in acetone gave rise of bromo and iodo alkanes **14** and **22**, respectively.

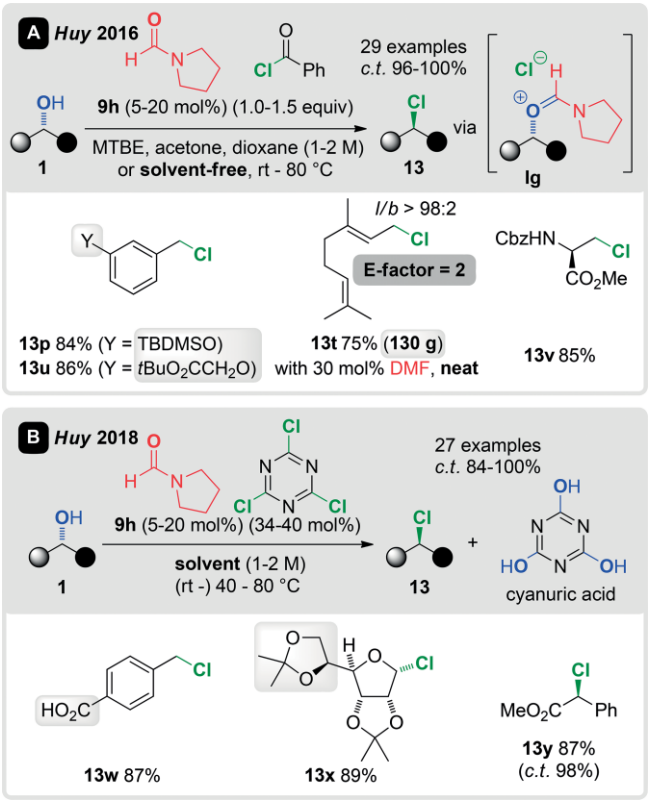
A particular advantage of the combination of cyclopropenone **9e** and BzCl is the tolerance of acid-labile functionalities such as silyl ethers (example **13p**), Boc carbonates (**13q**), acetals and *tert*-butyl esters. Moreover, even highly acid-susceptible MOM acetals (as in product **13r**) and aliphatic TBDMS ethers were not harmed when N*i*Bu$_3$ was utilized as base. To this end, such high levels of compatibility with functions sensitive to acidic reaction conditions have not met by other Lewis base-catalyzed S_N-approaches. This special feature is anchored in the milder reaction conditions as detailed in section 2.3.[26] High levels of chirality transfer have been substantiated with enantioenriched secondary aliphatic and benzylic alcohols and an α-hydroxy ester. As pivotal intermediate, **If** was corroborate by NMR spectroscopy.

Moreover, benzylic chloride **13s** was synthesized in 90 % isolated yield using just 1 mol-% of catalyst **9e**. This is the lowest catalyst loading reported in the area of Lewis base-catalyzed S_N-reactions to date. In comparison with 1 mol-% of 1-formylpyrrolidine (FPyr) **13s** was obtained in only 7 % yield under otherwise identical conditions. The beneficial catalytic activity of cyclopropenones also allowed to decrease the reaction temperatures in the case of aliphatic alcohols drastically (40 instead of 80 °C). For the first time, simple acetyl chloride (AcCl) was engaged as reagent in an S_N2-type substitution reaction under inversion. However, the use of AcCl is restricted to reactive benzylic and allylic substrates. Certain levels of preparative robustness have been witnessed by the synthesis of geranyl chloride (**13t**) on a >20 g scale.

2.3 Formamide Catalysis

Already around 1960 the organic solvent dimethylformamide (DMF) has been identified as a competent catalyst for the transformations of carboxylic acids into carboxylic acid chlorides.[28] Recently, the Huy group disclosed a formamide catalyzed method for the transformation of alcohols **1** into alkyl chlorides **13** that is promoted by benzoyl chloride (BzCl, Scheme 11 **A**).[26a,c] 1-Formylpyrrolidine (FPyr, **9h**) emerged as optimal Lewis base out of a catalyst screening with BzCl as the agent. Albeit more powerful, FPyr can be replaced by DMF or even methylformamide.

Incapable of production of alkyl chlorides are amides, which are not derived from formic acid, ureas, phosphine oxides, phosphorus triamides and tropone (**9g**). In contrast, cycloprop-

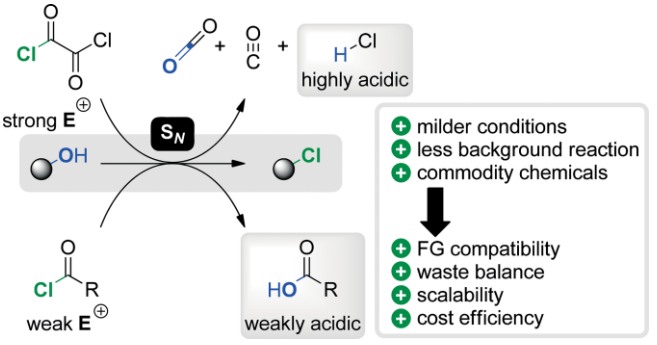


Scheme 11. Formamide catalyzed production of alkyl chlorides (solvent = dioxane, acetone, EtOAc or MeCN).

enones and sulfoxides also enabled the synthesis of haloalkanes, which lead to the development of distinctive methods (see Scheme 10 **B** and Scheme 14). Interestingly, in the absence of an appropriate catalyst reaction of BzCl with alcohols almost exclusively entails benzoate ester formation. Indeed, testing of a plethora of carboxylic acid chlorides confirmed BzCl as optimal reagent. Actually, application of AcCl mainly afforded alkyl acetates and is hence inappropriate for the synthesis of **13** under formamide catalysis. However, AcCl is feasible as reagent under cyclopronenone catalysis (see Scheme 10 **B**).

This can be explained by the higher electrophilicity of AcCl in comparison to BzCl. Reactive benzylic, allylic and propargylic alcohols were efficiently transformed into the respective halides **13** at room temperature (examples **13p**+**t**+**u**). Less reactive aliphatic substrates had to be heated to 80 °C in order to furnish chloro alkanes like **13v** in good yields. Worthy of note, a sterically demanding tertiary alcohol was converted in the corresponding chloride in good yield. In contrast, cyclohexanols are not suitable, because the cyclohexyl backbone impedes S_N2-displacement (see chp. 2.1). A variety of functionalities are compatible, to which sulfides, sulfones, aldehydes, secondary amides (tosyl and benzoyl), various carbamates (example **13v**) and heterocycles such as indole account. Of fundamental significance is the compatibility with acid labile functionalities including TBDMS ethers (example **13p**), *tert*-butyl esters (**13u**) and cyclic acetals, for instance. In fact, acid susceptible functional groups are largely missing in the substrate scopes of other catalytic S_N-protocols using oxalyl chloride or Ms_2O as reagent.

Indeed, in S_N-reactions of alcohols and carboxylic acids with oxalyl chloride, HCl is formed as by-product (Scheme 12). Therefore, the reaction medium is acidic, which can limit levels of functional group compatibility (especially with respect to acid-labile functions). Application of carboxylic acid chlorides as reagents instead produces carboxylic acids as by-products, which are weak Brønsted acids.



Scheme 12. Oxalyl and carboxylic acid chlorides as reagents in S_N-reactions (FG = functional group).

As a consequence, the reaction conditions are less acidic, which allows for the above-described improved functional group tolerance. The highly electrophilic nature of oxalyl chloride (and Ms_2O) leads to esterification of hydroxyl group bearing starting materials as an unwanted side-reaction (see Scheme 5 **D**). This has been mitigated by highly diluted reaction conditions and slow addition of an oxalyl chloride solution with the aid of syringe pumps. Low concentrations result in high solvent amounts (= waste) and hence moderate sustainability and scalability.

As carboxylic acid chlorides are much less electrophilic than oxalyl chloride, background esterification is automatically reduced. This facilitates high substrate concentrations and allows operatively simple protocols since an accentuated slow addition of the reagent is not mandatory.

As a matter of fact, scalability in the case of formamide catalysis has been demonstrated by the preparation of geranyl chloride (**13t**) on a >100 g scale. Notable, the underlying experiment was carried out in standard laboratory glassware ≤1 L. Indeed, the synthesis of **13t** only afforded the starting alcohol, 30 mol-% of DMF as inexpensive catalyst and stoichiometric amounts of BzCl, which were added by means of a standard dropping funnel without exclusion of water and air. Since, both, reaction and work-up were performed without the use of solvents, the preparation of **13t** is distinguished by an excellent E-factor of 2. This is in the range typical for the production of commodity chemicals.[9] In comparison to conventional procedures for the synthesis of geranyl chloride the waste amount was reduced by 89–94 %.[27]

Worthy of note are also the high levels of regioselectivity since the linear regioisomer was formed almost exclusively. The reaction of the parent alcohol (geraniol) with reagents such as thionyl chloride and phosgene provides mixtures containing also significant amounts of the branched regiosiomer (obtained via an S_N2'-displacement).[26a] Since geranyl chloride or related allylic chlorides have not been included in the substrate scopes

of other catalytic S_N-approaches relying on oxalyl chloride, a direct comparison with regard to regioselectivity is not possible. An assessment of different syntheses of 1-phenylethanol based on E-factors proved that the conjunction of FPyr and BzCl decreased the waste amount down to ≤4 % relative to other Lewis base catalyzed S_N-methods.[27] Stereochemical inversion with a chirality transfer of 96–100 % has been attested thoroughly by means of secondary benzylic and aliphatic alcohols and a α-hydroxy ester. Comparison experiments underlined the synthetic value because $SOCl_2$ and Appel conditions both gave rise to a chiral chloride with clearly depleted enantioselectivity. In addition, several alkoxyiminium chloride intermediates of type **Ig** were verified by NMR.

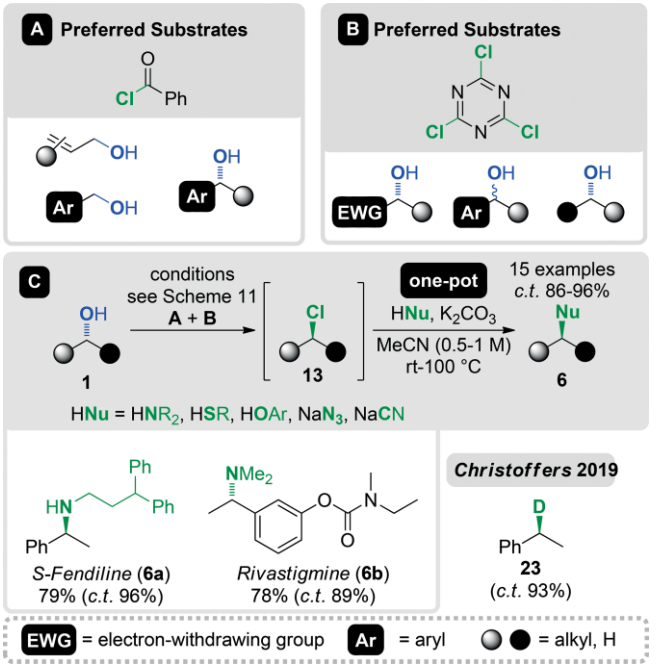
With regard to functional group compatibility, Brønsted bases represent a limitation, since they foster esterification of the starting material with BzCl. However, this might be a drawback of most catalytic S_N-methods, since only one example containing a basic moiety has been reported to date (chloride **13i** in Scheme 8 **B**).[23a]

In the following, an essential improvement concerning the atom economy has been accomplished by the team of Huy through application of cyanuric chloride (TCT) as reagent (Scheme 11 **B**). The TCT quantity could be reduced down to 34 mol-% with respect to substrate **1** (100 mol-%). The formation of cyanuric acid as weakly Brønsted acidic by-product unambiguously verified that all three Cl atoms of TCT had been transferred onto substrate **1**. Actually, cyanuric chloride is of exceptional cost-efficiency and even cheaper than oxalyl and thionyl chloride.

The substrate scope of the TCT mediated chlorination is of similar versatility than the BzCl promoted method (vide supra). Noteworthy is the chemoselective preparation of benzylic acid chloride **13w** besides an unprotected carboxylic acid function and of the sugar derivative **13x** under retention, which is rationalized by an S_N1-pathway. With TCT lower levels of inversion in the instance of benzylic alcohols and diminished regioselectivities with allylic alcohols were noted in comparison to BzCl. Advantageous, the application of TCT resulted in up to 31 % improved yields in the event of aliphatic chlorides. Furthermore, in the case of α-hydroxy esters the reaction temperature could be lowered from 80 (BzCl) to 40 °C (example **13y**). Privileged substrate categories for BzCl- and TCT-driven chlorinations, respectively, are compiled in Scheme 13 **A** and Scheme 13 **B**. Finally, scalability has also been illustrated by the synthesis of a chloro alkane on >60 g scale.

Since the type of solvent has a major impact on the ecological footprint some additional comments are required. In general, utilization of 1,4-dioxane allows for high yields for all types of alcohols, regardless if BzCl or TCT is employed as a stoichiometric component. However, dioxane is undesirable in terms of sustainability due to its toxicity and ranked similarly unfavorable like chlorinated solvents (CH_2Cl_2, $CHCl_3$, DCE, etc.).[9] Appreciably, dioxane could be replaced depending on the starting material applied by much more environmental-friendly solvents like EtOAc, acetone or MTBE (methyl-*tert*-butyl ether).

For both formamide catalyzed methods, a practical one-pot protocol for the S_N-transformation of alcohols with nucleophiles



Scheme 13. **A** + **B** Preferred substrate scopes and **C** catalytic chlorination and subsequent nucleophilic substitution.

has been devised (Scheme 13 **C**). Accordingly, the pharmaceuticals fendiline, clopidogrel, and rivastigmine were synthesized, which confirmed high levels of applicability. Recently, Christoffers and co-workers exploited the catalytic chlorination with FPyr and BzCl for the synthesis of enantioenriched 1-deutereo-1-phenylethane **23**, an agent for the elucidation of the stereochemistry of CH-activating enzymes.[29] Deuterodechlorination of the respective alkyl chloride with $LiAlD_4$ provided target compound **23** in 92 % *ee* under overall retention.

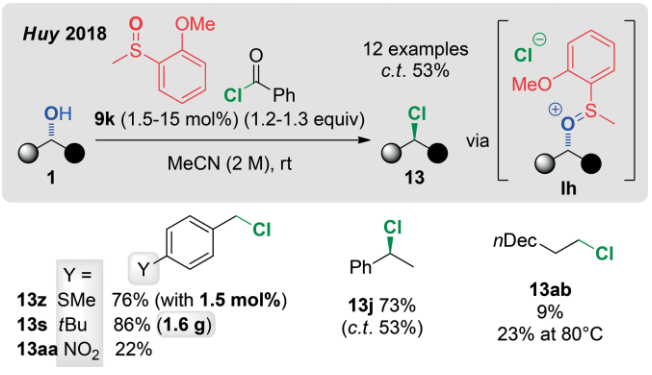
In fact, the determination of the enantiopurity of **23** was challenging. Reasoned by a low $[\alpha]_D$ value, the optical rotation is not feasible for this endeavor. Since deuterium and hydrogen atoms are of a similar steric demand, separation of the enantiomers by chiral chromatography is not possible. The authors accomplished determination of the enantiopurity of **23** by facile derivatization through chlorosulfonylation and subsequent amidation with a chiral amine. The diastereomers obtained were readily distinguished by means of ^{1}H-NMR.

2.4 Sulfoxide Catalysis

Dimethyl sulfoxide (DMSO **9a**)[30b,c] and also SeO_2[30a] have been described previously as Lewis base catalysts for the conversion of alcohols to chloro alkanes. With regard to DMSO as catalyst, a TMSCl promoted approach was exclusively applicable to primary and tertiary alcohols,[30b] whereas the use of TCT (120 mol-%) as agent facilitated the synthesis of benzylic chlorides only (2 examples).[30c]

In order to gain a better understanding of sulfoxide catalysis in S_N-reactions, the Huy group systematically evaluated a broad range of sulfonyl group containing Lewis bases in the transformation of alcohols **1** into chloro alkanes **13** (Scheme 14).[30d] In

fact, arylmethyl sulfoxide **9k** emerged as an optimal catalyst out of a screening of 31 Lewis bases, which either exhibited a S=O or Se=O motif. Especially electron-rich benzylic chlorides were prepared in good yields using low amounts of catalyst **9k** (≤5 mol-%) and BzCl (example **13z** and **13s**). However, electron-poor substrates are not feasible (example **13aa**).



Scheme 14. Sulfoxide catalyzed synthesis of chloro alkanes **13**.

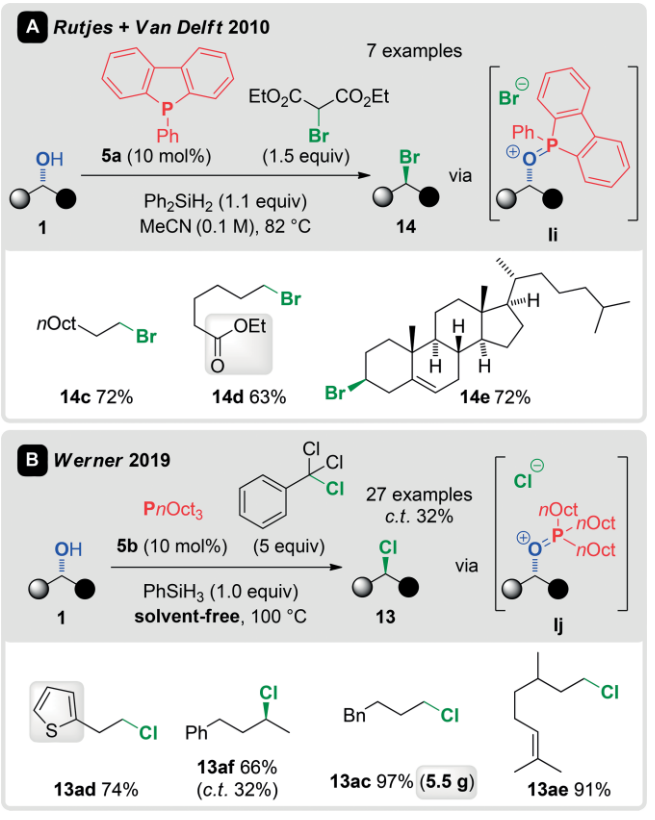
A secondary alcohol was inverted in moderate levels of chirality transfer (example **13j**). Besides electron-poor alcohols also aliphatic substrates constitute a limitation of sulfoxide catalysis (**13ab**). The restriction to reactive benzylic (and allylic) starting materials **1** has been traced back to competing Pummerer rearrangement of sulfoxide **9k** yielding (chloromethyl)(2-methoxyphenyl) sulfide. Eventually, sulfoxonium species **Ih** was proposed as a key intermediate.

2.5 Phosphane Catalysis

The compatibility of oxidative halogenation agent and silane reductant is the main challenge in redox promoted Lewis base catalyzed nucleophilic substitutions (Scheme 3 **E**). Rutjes and van Delft realized the first catalytic protocol of the Appel reaction for the synthesis of alkyl bromides **14** based on phosphane catalysis (Scheme 15 **A**).[31a] A rational catalyst design afforded cyclic phosphane **5a** as the most efficient Lewis base. Fine-tuning of the stoichiometric reaction components furnished diethyl bromomalonate and diphenylsilane as compatible oxidation and reducing agent, respectively. As delineated in Scheme 3 **E**, the silane had the function to reduce the in situ generated phosphine oxide of **5a** and therefore created a catalytic process.

The scope in terms of substrates focuses on aliphatic alcohols. Bromide **14e** was accessed under stereochemical retention, which was assigned to a neighboring group effect of the proximal C=C double bond. In analogy to the Appel reaction, phosphonium salt **Ii** was proposed as putative intermediate. In attempts to establish an analogous chlorination process yielding alkyl chlorides difficulties were encountered. For example, CCl_4 as oxidant and an electron-rich derivative of catalyst **5a** gave rise of an alkyl chloride in a moderate yield of 40 %.

In the following, the group of Werner investigated into the phosphane catalyzed Appel chlorination (Scheme 15 **B**).[31b] A careful optimization of phosphane catalyst, chloride source, and silane reducing agent finally yielded reaction conditions that



Scheme 15. Catalytic Appel type reactions.

allowed for the synthesis of chloro alkanes **13** in good to excellent yields. In fact, trioctylphosphine (**5b**) turned out to be a more effective catalyst than PPh_3 and other trialkylphosphines.

While $PhSiH_3$ in stoichiometric quantities was identified as optimal reductant, trichloromethylbenzene was exploited as a mild oxidant for the first time. Remarkably, the production of **13** did not require a reaction solvent. Under optimized conditions even two tertiary chlorides **13** were synthesized in 37–41 % yield. With regard to functional group tolerance, thiophene **13ac** and a sugar-derived chlorinated acetal are highlights.

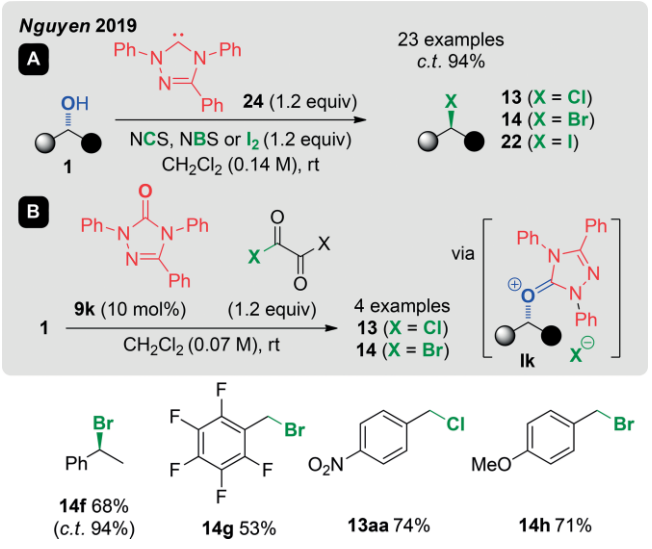
In the case of chloride **13ad**, preservation of stereochemical purity was found to be moderate. Nevertheless, a sugar derived chloro alkane was synthesized in 31 % yield under complete inversion of the configuration. Reasonable scalability has been proven by the preparation of chloride **13ae**, which emphasizes the high practical value of this S_N-approach. In addition, dichloromethylbenzene was identified as by-product, which originated from trichloromethylbenzene. Finally, the phosphonium salt **Ij** was suggested as a plausible reaction intermediate.

Notable are also phosphane catalyzed variants of the Mitsunobu reaction, which had been developed by O'Brien and Aldrich.[32] In this context, a recent review of Denton and coworkers addressing catalytic Mitsunobu reactions is pointed out.[6b]

2.6 *Lewis* Base Promoted Nucleophilic Substitutions

Lately, the team of Nguyen reported on a novel variant of the Appel reaction, in which PPh_3 was replaced by a Lewis basic

N-heterocyclic carbene (NHC, Scheme 16 **A**).[33] Indeed, NHC **24** was found to be a superior promoter in comparison to a range of structurally diverse N-heterocyclic carbenes. Controlled by the halogenation reagent (NCS, NBS or I_2), either chlorides **13**, bromides **14** or alkyl iodides **22** were formed as products. Thereby, **24** was accessed by deprotonation of the parent azolium salt with potassium hexamethyldisilylamide (KHMDS) prior to addition of the starting alcohol **1**. As an important aspect, benzylic bromide **14f** was generated under inversion in high levels of chirality transfer. The reaction of a tertiary starting material under the optimized conditions did not afford the respective halogenated product.



Scheme 16. NHC promoted synthesis of haloalkanes.

Moreover, triazolinone **9k**, which is generated as by-product in the above-mentioned protocol, was able to catalyze the conversion of alcohols to halides (Scheme 16 **B**). Oxalyl chloride and bromide, respectively, allowed to transform **9k** into chloro/bromotriazolium salts, which are crucial for the activation of the starting alcohol yielding proposed intermediate **Ik**. Comparison experiments revealed that **9k** is of similar catalytic efficiency than triphenylphosphine oxide, diphenylcyclopropenone, and tropone.

As discussed in the introduction, amines are not suitable as nucleophiles under the classical Mitsunobu reaction conditions, because their pK_a-value is significantly higher than 11 (Scheme 2 **B**). Against this background, the group of Kang developed an enhanced protocol that allows for the application of amines as the nucleophilic component for the first time (46 examples).[34a] As key finding, an N-heterocyclic phosphine instead of PPh_3 enabled this significant extension in terms of nucleophile scope. Aside from secondary amines also carboxylic acids were engaged as nucleophiles. Lower yields were attained with primary amines due to two-fold N-alkylation. High levels of chirality transfer of 95 % were illustrated by the production of an ester under inversion. A synthetic value was certified by the straightforward preparation of the pharmaceuticals piribedil and cinnarizine.

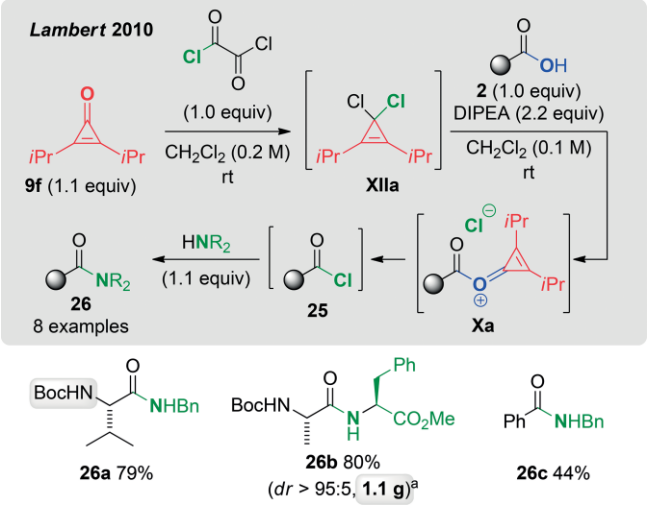
Furthermore, Xiao and co-workers reported syntheses of alkyl chlorides, bromides, and iodides from alcohols by means of PPh_3, N*n*Bu_4I and 1,2-dihaloethane as halide source (31 examples).[34b,c] In the presence of CsF, 1,2-diiodoethane and PPh_3 in DMF alkyl fluorides were formed (12 examples). An aliphatic secondary alkyl chloride was obtained under stereochemical inversion with 66 % chirality transfer. These reactions are suggested to be induced by oxidation of PPh_3 with the aid of the respective dihaloethane, which gives rise of halophosphonium salts known as intermediates of the Appel reaction.

Next, the team of Xiao expanded their methodology towards C–O, C–S and C–N bond formation (41 examples).[34c] 1,2-Diiodoethane in concert with PPh_3 and a nucleophile in DMF mediated the preparation of amines, azides, sulfides, ethers, and esters from alcohols at room temperature. These transformations were proposed to pass through alkoxyiminium intermediates of type **Ig** (see Scheme 11 **A**), which involves the solvent DMF.

3. Substrate Class Carboxylic Acids

3.1 Cyclopropenone and Tropone Catalysis

The group of Lambert exploited cyclopropenone **9f** for the facile synthesis of amides of type **26** (Scheme 17).[35a] Thereby, the reaction of **9f** with oxalyl chloride afforded 1,1-dichlorocyclopropene **XIIa**. This reagent allowed for activation of carboxylic acids **2** as acid chlorides of type **25** passing plausible intermediate **Xa**. The conversion **2** → **25** was accelerated significantly by di-*iso*-propylethylamine (DIPEA). Next, addition of an amine to the reaction mixture containing **25** yielded amides of type **26**. Amides that are derived from aliphatic acids were isolated in high yields (e.g. **26a**+**b**), whereas aromatic acids **2** delivered condensation products such as **26c** in deteriorated yields. Remarkable is the compatibility with acid-labile Boc carbamates (**26a**+**b**), cyclic acetals and TBDMS ethers.

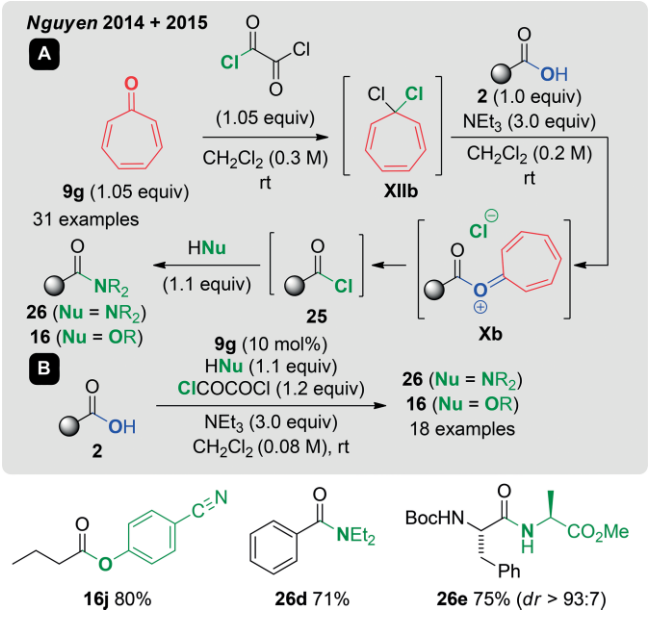


Scheme 17. Cyclopropenone facilitated activation of carboxylic acids (DIPEA = diisopropylethylamine). a. With dimesitylcyclopropenone.

Reagents of type **XIIa** are even able to impart the formation of peptidic C–N bonds without erosion of stereochemical integ-

rity such as in **26b**. Actually, epimerization is a serious issue in the synthesis of peptides via acid chloride intermediates, since α-chiral acid chlorides are labile towards racemization.[7]

The team of Nguyen recently published an ingenious tropone promoted method for the coupling carboxylic acids **2** with amines and alcohols (Scheme 18 **A**).[24a,35b] Reaction of tropone with oxalyl chloride initially led to 1,1-dichlorocycloheptatriene (**XIIb**). Subsequent condensation with acids of type **2** gave rise of acid chloride **25**, for which tropylium salt **Xb** was suggested as probable intermediate. Ultimately, addition of amines and alcohols, respectively, lead to products **26** and **16**.

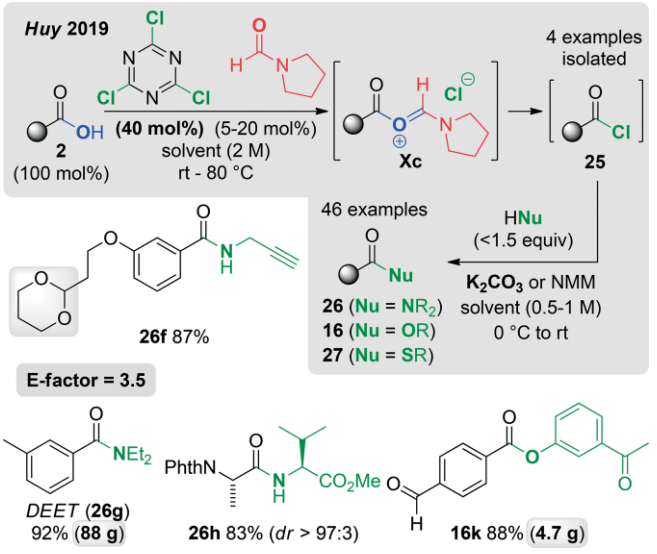


Scheme 18. Tropone promoted activation of carboxylic acids.

Furthermore, the authors succeeded in implementing a protocol that is catalytic in tropone (Scheme 18 **B**). Therein, oxalyl chloride was added slowly to a mixture of acid **2**, the desired nucleophile and NEt_3, which directly induced ester and amide formation. Both, aliphatic and aromatic acids **2** are well-suitable for this protocol (e.g. **16j** + **26d**). Aromatic or aliphatic alcohols were engaged as the nucleophilic coupling partner, while application of *tert*-butanol provided a corresponding ester in trace amounts. Primary and secondary amines and even aqueous ammonia solution are feasible for the production of amides. In the case of some esters, utilization of *N*,*N*-dimethylaminopyridine (DMAP) improved yields essentially. Of particular significance is the compatibility with Boc-carbamates and the proficiency to form peptide bonds in high levels of stereochemical preservation (see **26e**).

3.2 Formamide Catalysis

Lately, the Huy group introduced a formamide catalyzed method for the synthesis of amides **26**, esters **16** and thioesters **27** (Scheme 19).[35c] This process was initiated by the transformation of carboxylic acids **2** into type **25** acid chlorides using TCT in low amounts (40 mol-% with respect to **2**). Indeed, for chlorination formamide **9h** is absolutely pivotal as catalyst, since without **9h** mostly no reaction was observed. Activation of **2** is achievable at room temperature, but heating to 40–80 °C permits lower catalyst loadings and conveniently short reaction times.



Scheme 19. Formamide catalyzed activation of carboxylic acids (solvent = MeCN or EtOAc, NMM = *N*-methylmorpholine).

Subsequently, the addition of a nucleophile and either simple K_2CO_3 or an amine base (NMM or NEt_3) caused amide C–N and ester C–O bond formation, respectively. A diverse range of aliphatic and aromatic acids was tackled successfully as starting materials. As nucleophile primary and secondary aliphatic and aromatic amines are appropriate. Primary amides are amenable by usage of aqueous ammonia solution. Primary and secondary alcohols were coupled in high yields, whereby occasionally DMAP accounted for enhanced yields. In the case of tertiary alcohols yields of esterification were slightly deteriorated, which is most probably attributed to the increased steric shielding of these nucleophiles.

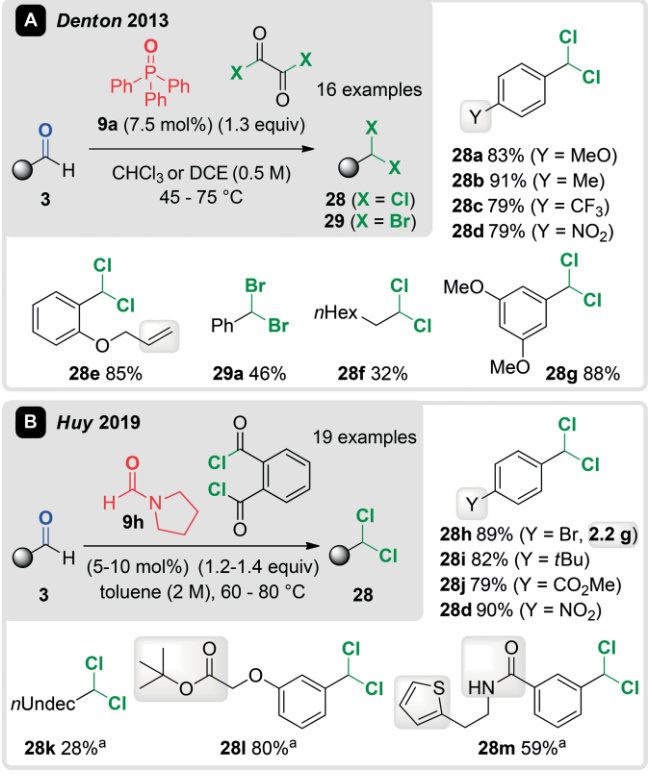
Even acid-labile TBDMS ethers and cyclic acetals in the carboxylic acid portion (example **26f**) are compatible functional groups. In addition, selected condensation products contained aldehydes (see **16k**), ketones, carbamates and heterocycles such as thiophene and pyridine in the molecule fragment that is derived from acids **2**. While a protected β-amino acid was transformed into an ester in a good yield, reaction of carbamate protected α-amino acids afforded cyclic carboxamides. However, peptide bond formation was accomplished applying phthaloyl protected amino acids with surprisingly little epimerization (example **26h**). Carboxyiminium salt of type **Xc** was suggested as logical intermediate. The practical value was underlined by the synthesis of the pharmaceuticals moclobemide and modafinil and the insecticide DEET (**26h**). Actually, the latter one was produced on an 88 g scale, which required only standard laboratory equipment (≤1 L). For this experiment an E-factor of 3.5 (including isolated cyanuric acid and reisolated solvents) witnessed a reasonable waste-balance. A high cost-efficiency is granted by application of TCT, which is cheaper

than all other activation reagents for carboxylic acids (with the exception of phosgene).[35c]

As an important aspect, the optimal solvent MeCN could also be replaced in most cases by environmental-benign EtOAc. A thorough assessment evidenced up to 78 % enhanced yields in comparison to a common literature protocol, which harnesses TCT and NMM for the activation of acids **2**. This tremendous difference was rationalized by the formation of acid chlorides **25** as intermediates instead of weaker electrophilic mixed anhydrides of **2** and cyanuric acid. Exemplary isolation of type **25** acid chlorides on a multigram scale unambiguously underpinned their existence as central intermediate.

4. Substrate Class Aldehydes and Epoxides

In addition, Lewis base catalysis is an effective means to access 1,1-dihaloalkanes of type **28** and **29**, which are also referred to as geminal dihalides, from carbonyl compounds **3** (Scheme 20). The first example stems from the group of Denton, in which triphenylphosphine oxide and oxalyl halides were exploited as catalyst and reagents, respectively (Scheme 20 **A**).[36a,b] Owing to the lower nucleophilicity of aldehydes in comparison to alcohols, higher reaction temperatures of 45–75 °C were required.



Scheme 20. *Lewis* base catalyzed synthesis of geminal dichlorides. a. Performed in DMF as solvent. DCE = 1,2-dichloroethane.

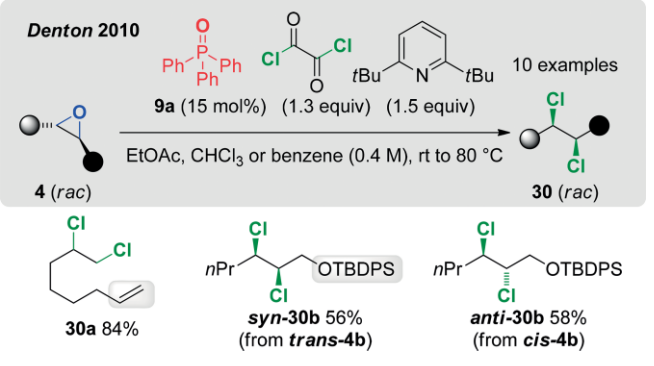
Feasible substrates are aromatic aldehydes regardless if they are electron-rich or poor (examples **28a-d**). Alkenes are compatible (product **28e**) and geminal dibromides were produced by means of oxalyl bromide (see **29a**). The reaction of an α,β-unsaturated aldehyde under optimized conditions afforded two regioisomeric dichlorides in a ratio of 54:46. The aliphatic dichloride **28f** was isolated in a moderate yield of 32 %. Ultimately, a short synthesis of resveratrol was realized through reductive coupling of two dichlorides and subsequent deprotection, which approved the applicability of the protocol.

In the following, the Huy group examined various carboxylic acid chlorides as reagents for the synthesis of 1,1-dichlorides (Scheme 20 **B**).[36c] Indeed, phthaloyl chloride ($PhthCl_2$) promotes the transformation of aldehydes into geminal dichlorides, whilst other acid chlorides such as AcCl and BzCl are ineffective. Although FPyr (**9h**) and DMF are potent catalysts for the preparation of dichlorides **28**, other Lewis bases like amides, which are not deduced from formic acid, ureas, cyclopropenone, tropone, and sulfoxides did not impart the transformation **3** → **28**. Again, higher reaction temperatures as in the case of alcohols of 60–80 °C were mandatory.

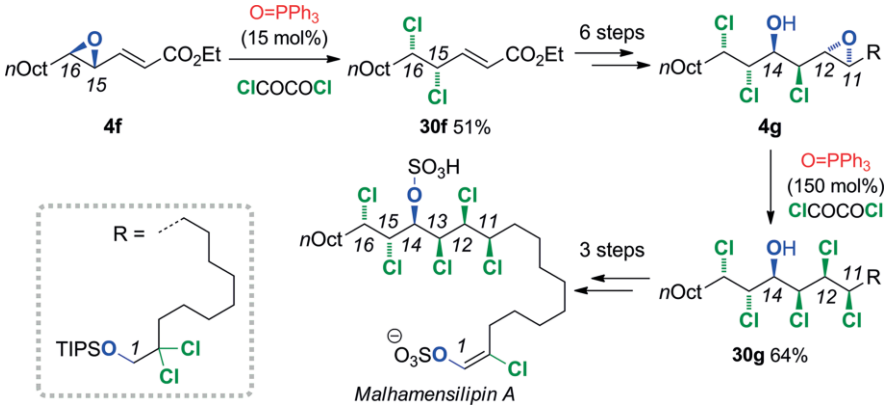
Both electron-rich and electron-poor aromatic aldehydes were converted to the respective geminal dichlorides in good to excellent yields (examples **28d** and **28h–j**). An α,β-unsaturated and an aliphatic aldehyde furnished the corresponding dihalides in low yields (28–45 %, see **28k**). Dichlorides derived from ketones (e.g. benzophenone, 4-bromoacetophenone) were not amenable.

Against this background, Lewis base catalysis seems to be largely limited to aromatic aldehydes, whilst aliphatic aldehydes and ketones are non-viable. Worthwhile, acid-susceptible *tert*-butyl esters (product **28l**) and cyclic acetals were not affected, when the reactions were carried out in DMF as solvent (and catalyst). In addition, the dichloride **28k**, which possesses both, an electron-rich thiophene moiety and a polar secondary amide function, was isolated in 59 % yield. Beyond these examples, Xiao and co-worker prepared geminal dihalides through reaction with PPh_3 and $NnBu_4I$ in 1,2-dichloro- and dibromoethane, respectively, as solvent at 60–80 °C.[34b]

Phosphane oxide catalysis (with **9a**) also allowed for the transformation of epoxides into vicinal dichlorides of type **30** (Scheme 21 **A**).[37a] Whereas oxalyl chloride was utilized as reagent, 2,6-*tert*-butylpyridine was applied as base to quench HCl formed as a side-product. Products **30** were derived from aliphatic mono and 1,2-disubstituted epoxides of type **4**. Of importance is the compatibility with distal alkenes (example **30a**), esters and TBDPS silyl ethers like in **30b**. The production of the diastereomeric 1,2-dichlorides ***syn-*** and ***anti*-30b** verified that the approach is completely stereospecific. In the Lewis base



Scheme 21. Phosphine oxide catalyzed synthesis of vicinal dichlorides.

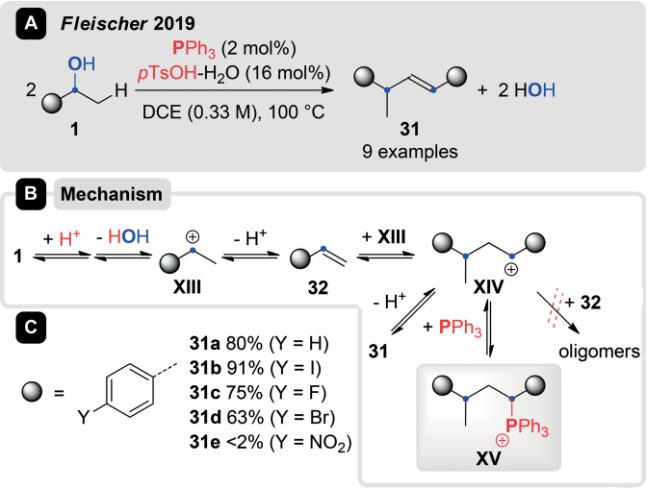


Scheme 22. Application towards the synthesis of *Malhamensilipin A* by Denton.

catalyzed synthesis of 1,1- and 1,2-dihaloalkanes no reaction intermediates have been proven to this end.

Indeed, Dentoń's group realized the total synthesis of the complex natural product Malhamensilipin A relying on Lewis base catalysis in two key steps (Scheme 22).[37b] Triphenylphosphine oxide mediated, stereospecific transformation of epoxides into dichlorides facilitated the introduction of four out of six chlorine atoms of this sulfolipid natural product.

Tanaka's protocol for the conversion of oxiranes in vicinal dichlorides, which uses PPh_3 and NCS as agents,[38a] is most frequently encountered in the total synthesis of sulfolipids. In addition, the catalytic Appel process of Werner created a synthetic entry towards 1,2-dichlorides **30** from aromatic epoxides **4**, too.[31b] Moreover, Xiao prepared 1,2-dihalides via reaction of epoxides with PPh_3, N*n*Bu_4I, and either 1,2-dichloro or dibromoethane.[38b]



Scheme 23. Impact of the *Lewis* base PPh_3 on the Brønsted acid catalyzed synthesis of alkenes **31**.

5. Additional Important Contributions

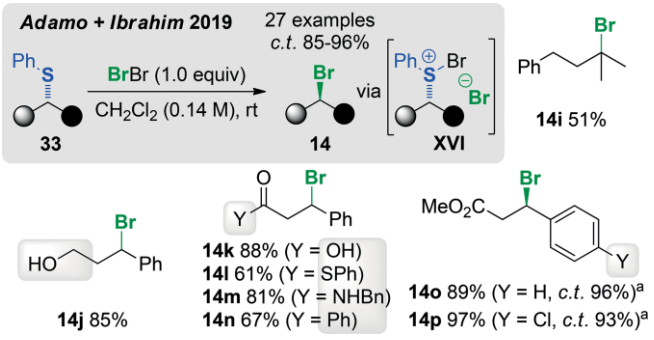
The following section contains a collection of S_N-methods that are not necessarily directly related to Lewis base catalysis. These contributions reveal, in the personal opinion of the author, important directions to the field of nucleophilic substitutions.

Most recently, a remarkable effect of the Lewis base PPh_3 on the Brønsted acid catalyzed condensation of alcohols **1** to alkenes of type **31** has been reported by Fleischer and co-worker (Scheme 23 **A**).[39a] According to the mechanistic rationale in Scheme 23 **B**, these transformations are induced by protonation of the starting alcohol **1** through *p*TsOH (*para* toluensulfonic acid) and subsequent water elimination yielding carbenium ion **XIII**. Next, elimination of a proton furnishes styrene **32**, which is attacked by an electrophilic addition of carbenium intermediate **XIII**. Eventually, deprotontation leads to the terminal product **31**. A tremendous improvement with respect to yield of **31** was achieved when a specific substoichiometric amount of PPh_3 was used.

The low yields in the absence of this Lewis base were reasoned by consumption of carbenium ion **XIV** through reaction with alkene intermediate **32**, which irreversibly provided complex oligomers. The impact of PPh_3 was explained through the addition of PPh_3 to cation **XIV**. The resulting phosphonium ion **XV** is not susceptible towards oligomerization anymore. Therefore, the concentration of carbenium ion **XIV** is lowered, which grants generation of the product **31** in enhanced chemoselectivity. Secondary benzylic alcohols were most suitable, whereas electron-poor substrates turned out to be rather unreactive (Scheme 23 **C**). This is plausible considering cationic intermediates **XIII** and **XIV**.

Recently, Adamo and Ibrahim and co-workers discovered a new synthetic access to bromo alkanes **14**.[39b] Under intriguingly simple reaction conditions with elemental bromine as the sole reagent, phenyl sulfides of type **33** underwent conversion to **14**. These nucleophilic substitutions are triggered by a bromination of the Lewis basic starting material **33**. The forming sulfonium ion **XVI** reacts further with the bromide counterion in an S_N2-fashion to give **14**. The substrate scope comprehends a number of secondary benzylic and tertiary bromides **14**, the latter of which were isolated in somewhat lower yields (e.g. **14i**) (Scheme 24).

Remarkable, even nucleophilic primary hydroxyl groups and carboxylic acids are tolerated (examples **14j**+**k**), which is virtually impossible for S_N-reactions using alcohols as starting materials. In addition, functional groups such as thioesters (**14l**), sec-



Scheme 24. Facile preparation of non-racemic alkyl bromides from alkyl-phenyl sulfides. a. Reaction performed at –40 °C.

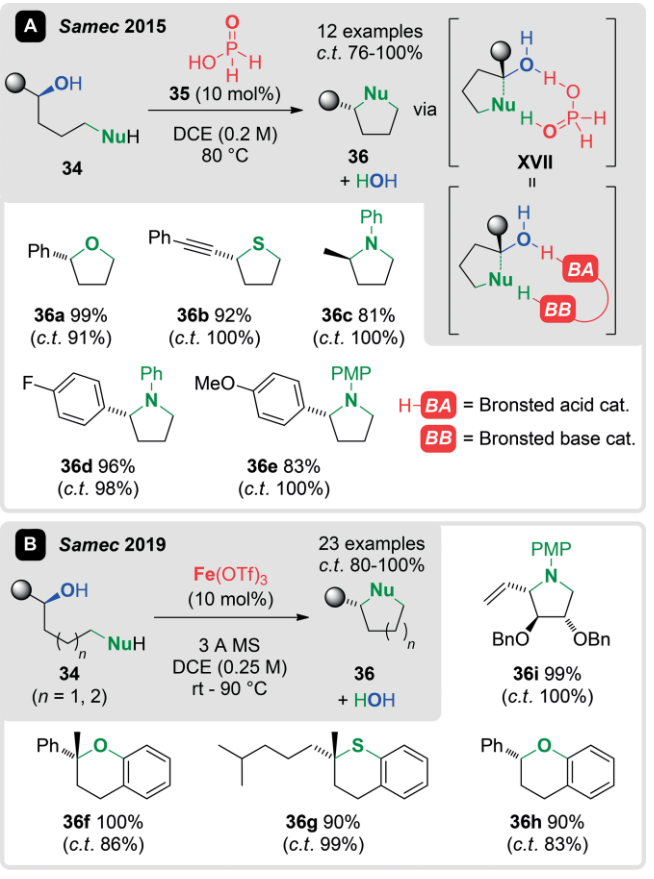
ondary amides (**14m**), ketones (**14n**), aldehydes and heterocycles like thiophene are compatible. High levels of chirality transfer were attested by means of the preparation of several non-racemic bromides under stereochemical inversion (e.g. **14o**+**p**).

As valuable background information, chiral sulfides of type **33** are easily accessible by asymmetric Michael addition of thiophenol to electron-poor arylalkenes. Chiral secondary bromides of type **14** easily racemize upon storage at room temperature. Nevertheless, storage at –20 °C allows for conservation of stereochemical purity on a time scale of weeks. With the formal synthesis of the drug dapoxetine, the authors demonstrated that alkyl bromides are viable intermediates for the production of enantioenriched bioactive compounds.

Samec and colleagues realized a Brønsted acid catalyzed cyclodehydration of diols, amino alcohols, and thioalcohols of type **34** that proceeds under inversion in optimal atom economy (water as exclusive by-product, see Scheme 25 **A**).[19a] Thus, the benefits of Lewis base and Brønsted acid catalysis are joined. For these intramolecular process phosphinic acid (**35**) was pivotal as catalysts. Other Brønsted and Lewis acids like phosphonic and phosphoric acid and $FeCl_3$ did not promote cyclodehydration or resulted in low levels of chirality transfer (e.g. with *p*TsOH, TfOH). In the crucial transition state **XVII** phosphinic acid acts simultaneously as Brønsted acid and base.

Even in the event of diols of type **34** the sterically more hindered secondary OH group was substituted, which was proven by inversion of the configuration at the respective C-atom. The approach created an access to several five-membered heterocyclic core units such as tetrahydrofurans (example **36a**) and –thiophenes (**36b**) and pyrrolidines (**36c–e**). Type **36** products contained aliphatic (**36c**), aromatic (**36a**+**d**+**e**), alkenylic and alkynylic (**36b**) side chains. The S_N2-mechanism was supported by DFT (density functional theory) calculations.

In the following, Samec and co-workers reported on a significantly improved method for cyclodehydration using $Fe(OTf)_3$ as Lewis acid catalyst in the presence of molecular sieves (Scheme 25 **B**).[19b] The utilization of other iron salts resulted in lower conversions and poorer chirality transfer. This approach allowed to extend the substrate scope towards six-membered heterocycles like dihydropyrans and benzopiperidines (examples **36f–h**). Outstandingly, several six-membered cycles were formed under stereochemical inversion at quaternary carbon centers (**36f**+**g**). In the instance of secondary substrates of type



Scheme 25. *Brønsted* and *Lewis* acid catalyzed cyclodehydration under S_N2-type inversion. MS = molecular sieves.

34, both, control experiments and DFT calculations supported an S_N2-mechanism. However, an S_N1 mechanism passing a tight ion pair was found to be more probable in the case of tertiary starting materials. High synthetic utility was shown by a concise total synthesis of the alkaloid lentiginosine via pyrrolidine **36i**, which was synthesized by the novel dehydrative cyclization.

6. Conclusion and Future Directions

In the past decade, substantial progress has been accomplished with respect to catalysis in S_N-type transformations. The present review gives a brief overview of contemporary strategies for catalytic nucleophilic substitutions (S_N) and details recent Lewis base promoted S_N-methods. As demonstrated visibly by the examples in this article, Lewis bases catalysis (1) allows for high levels of chirality transfer, (2) renders hazardous reagents obsolete, (3) reduces the waste-amount drastically and (4) results in decreased cost levels. Indeed, catalysis with respect to S_N-reactions has reached a new level, which is also witnessed by robust, scalable and very versatile approaches. Recent elegant achievements even enable S_N2-type substitutions under stereochemical inversion without the need for stoichiometric reagents.

However, several issues would be attractive to address in the future: (1) Despite a few exceptional cases, high catalyst loadings between 5–20 mol-% are still quite common. We are con-

vinced that kinetic studies in combination with DFT modeling, which are thus far unprecedented, could guide the rational design of more active catalysts.[40] (2) With the fully catalytic Mitsunobu reaction of Denton being the only positive exception, nucleophiles are limited to chloride, bromide and mesylate. This drawback could potentially also be overcome by an enhanced mechanistic understanding. In this respect also the concept of latent nucleophiles, in which a nucleophile is created in situ from a non-nucleophilic precursor, might play a key role.[41] (3) To this end, novel substrate classes such as acids of sulfur and phosphorus remain unexplored territory with regard to Lewis base catalysis. (4) Albeit many different types of Lewis bases have been applied, no asymmetric version utilizing enantioenriched chiral catalysts has been disclosed to date. In light of these significant open challenges there is much to accomplish in the field of S_N-type Lewis base catalysis.

Acknowledgments

We would like to thank the Fonds of the Chemical Industry (Liebig fellowship) and the German Research Foundation (DFG) for generous funding.

Keywords: Lewis base catalysis · Nucleophilic substitution · Stereochemical inversion · Organocatalysis · Green chemistry

[1] For selected reviews concerning S_N1-type Lewis and Brønsted acid catalyzed substitutions of alcohols see: a) M. Bandini, M. Tragni, *Org. Biomol. Chem.* **2009**, *7*, 1501–1507; b) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzziello, F. D. Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* **2011**, *2011*, 647–666; c) R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905–6948; d) R. Kumar, E. V. Van der Eycken, *Chem. Soc. Rev.* **2013**, *42*, 1121–1146; e) A. Baeza, C. Nájera, *Synthesis* **2014**, *46*, 25–34; f) M. Dryzhakov, E. Richmond, J. Moran, *Synthesis* **2016**, *48*, 935–959; g) X. Zhang, C. Lü, P. Li, B. Fu, W. Yao, *Chin. J. Org. Chem.* **2016**, *36*, 1287–1298; h) R. Ortiz, R. P. Herrera, *Molecules* **2017**, *22*, 574–585; i) N. Ajvazi, S. Stavber, *ARKIVOC* **2018**, *2*, 288–329; j) X. Dai, F. Shi, *Org. Biomol. Chem.* **2019**, *17*, 2044–2054; k) H. Qian, D. Huang, Y. Bi, G. Yan, *Adv. Synth. Catal.* **2019**, *361*, 3240–3280.

[2] Reviews on boronic acid catalysis in S_N-reactions: a) H. Zheng, D. G. Hall, *Aldrichim. Acta* **2014**, *47*, 41–51; b) D. G. Hall, *Chem. Soc. Rev.* **2019**, *48*, 3475–3496.

[3] For selected reviews on catalytic S_N-reactions of allylic, propargylic and benzylic alcohols proceeding through metal-π complexes see: a) J. Muzart, *Eur. J. Org. Chem.* **2007**, *2007*, 3077–3089; b) B. Sundararaju, M. Achard, C. Bruneau, *Chem. Soc. Rev.* **2012**, *41*, 4467–4483; c) N. A. Butta, W. Zhang, *Chem. Soc. Rev.* **2015**, *44*, 7929–7967; d) J. L. Bras, J. Muzart, *Eur. J. Org. Chem.* **2016**, *2016*, 2565–2593; e) S. L. Rössler, D. A. Petrone, E. M. Carreira, *Acc. Chem. Res.* **2019**, *52*, 2657–2672; f) see ref. [1a+d+f+i].

[4] Selected reviews on H_2 borrowing catalysis: a) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555–1575; b) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681–703; c) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641; d) A. J. A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635–636; e) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* **2011**, *3*, 1853–1864; f) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712; g) Q. Yang, Q. Wanga, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305–2329; h) F. Huang, Z. Liu, Z. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 862–875; *Angew. Chem.* **2016**, *128*, 872; i) A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410–1459; j) B. G. Reed-Berendt, K. Polidano, L. C. Morrill, *Org. Biomol. Chem.* **2019**, *17*, 1595–1607; k) see ref.[1h].

[5] Reviews on Lewis base catalysis in nucleophilic substitutions: a) J. An, R. M. Denton, T. H. Lambert, E. D. Nacsa, *Org. Biomol. Chem.* **2014**, *12*, 2993–3003; b) P. H. Huy, T. Hauch, I. Filbrich, *Synlett* **2016**, *27*, 2631–2636; c) see ref.[1i].

[6] Review on catalytic Mitsunobu reactions: a) S. Fletcher, *Org. Chem. Front.* **2015**, *2*, 739–752; b) R. H. Beddoe, H. F. Sneddon, R. M. Denton, *Org. Biomol. Chem.* **2018**, *16*, 7774–7781; c) L. Longwitz, T. Werner, *Science* **2019**, *365*, 866–867.

[7] Reviews on catalytic amidations: a) K. Ishihara, *Tetrahedron* **2009**, *65*, 1085–1109; b) H. Charville, D. Jackson, G. Hodgesc, A. Whiting, *Chem. Commun.* **2010**, *46*, 1813–1823; V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; c) R. M. Lanigan, T. D. Sheppard, *Eur. J. Org. Chem.* **2013**, *2013*, 7453; d) H. Lundberg, F. Tinnis, N. Selander, H. Adolfsson, *Chem. Soc. Rev.* **2014**, *43*, 2714–2742; e) R. M. de Figueiredo, J.-S. Suppo, J. M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122; f) A. Ojeda-Porras, D. Gamba-Sanchez, *J. Org. Chem.* **2016**, *81*, 11548–11555; g) J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*, 140–177; h) M. T. Sabatini, L. T. Boulton, H. F. Sneddon, T. D. Sheppard, *Nature Catal.* **2019**, *2*, 10–17; i) P. Huy, B. Zoller, *Nachr. Chem.* **2019**, *67*, 51–54.

[8] Selected reviews on renewable resources: a) P. N. R. Vennestrøm, C. M. Osmundsen, C. H. Christensen, E. Taarning, *Angew. Chem. Int. Ed.* **2011**, *50*, 10502–10509; *Angew. Chem.* **2011**, *123*, 10686; b) R.-F. van Putten, J. C. van der Waal, E. de Jong, C. B. Rasrendra, H. J. Heeres, *Chem. Rev.* **2013**, *113*, 1499–1597; c) J. G. de Vries, L. Wu, T. Moteki, A. A. Gokhale, D. W. Flaherty, F. D. Toste, *Chem* **2016**, *1*, 32–58; d) Y. Zhu, C. Romain, C. K. Williams, *Nature* **2016**, *540*, 354–362; e) A. Gandini, T. M. Lacerda, A. J. F. Carvalho, E. Trovatti, *Chem. Rev.* **2016**, *116*, 1637–1669; f) H. T. Luk, C. Mondelli, D. Curulla Ferré, J. A. Stewart, J. Pérez-Ramírez, *Chem. Soc. Rev.* **2017**, *46*, 1358–1426.

[9] Selected reviews regarding sustainability: a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273–1283; b) C. J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202; c) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021; d) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; e) R. A. Sheldon, *Chem. Soc. Rev.* **2012**, *41*, 1437–1451; f) P. J. Dunn, *Chem. Soc. Rev.* **2012**, *41*, 1452–1461; g) R. A. Sheldon, *Green Chem.* **2017**, *19*, 18–43.

[10] Reviews on the Appel reaction: a) R. Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811; *Angew. Chem.* **1975**, *87*, 863–874; b) D. L. Hughes in *Organic Reactions, Vol. 42* (Ed.: L. A. Paquette), Wiley: New York, **1992**, pp. 335–656; c) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551–2651.

[11] Recent reviews about the Mitsunobu reaction: a) Castro, B. R. in Organic Reactions, Vol. *29* (Ed.: W. G Dauben), Wiley: New York, **1983**, p. 1–162; b) T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340–1355; c) see ref.[6,10].

[12] P. Walden, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 133–138.

[13] A round-table of representatives of several pharmaceuticals companies repeatedly requested more efficient methods for amidations and activations of alcohols as primary targets: a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420; b) M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weibert, *Green Chem.* **2018**, *20*, 5082–5103.

[14] For stereoselective *Lewis*-acid catalyzed substitutions with tertiary trifluoroacetates and propargylic acetates, respectively, see: a) S. V. Pronin, C. A. Reiher, R. A. Shenvi, *Nature* **2013**, *501*, 195–199; b) A. Wendlandt, P. Vangal, E. N. Jacobsen, *Nature* **2018**, *556*, 447–451.

[15] The current manuscript refers to the term "Lewis base catalysis" as defined by Denmark: "*Lewis base catalysis is the process by which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom in one of the reagents or substrates. The binding event may enhance either the electrophilic or nucleophilic character of the bound species. Furthermore, the Lewis base should not be consumed or altered during the course of the reaction – a hallmark of any catalytic process.*" (see page 1563 in S. E. Denmark, G. L. Beutner, *Angew. Chem. Int. Ed.* **2008**, *47*, 1560–1638; *Angew. Chem.* **2008**, *120*, 1584). Although not determined so far, it is clear that the addition of the discussed Lewis bases causes increased reaction rates. As verified by means of many examples, in the absence of the respective Lewis bases the amount of the original main product is drastically diminished (often ≤2 % in comparison to ≥80 %, see for instance ref.[21,23b,24,26]).

[16] Lewis bases such as 4-(dimethylamino)pyridine (DMAP) are well-known as powerful catalysts for amidations of esterifications of carboxylic acids. For selected reviews see: a) B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–583; *Angew. Chem.* **1978**, *90*, 556; b) A. C. Spivey, S. Arseniyadis, *Angew. Chem. Int. Ed.* **2004**, *43*, 5436–5441; *Angew. Chem.* **2004**, *116*, 5552; c) R. P. Wurz, *Chem. Rev.* **2007**, *107*, 5570–5595; d) C. R. Müller, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042; *Angew. Chem.* **2011**, *123*, 6136.

[17] Selected reviews on halogenated natural products: a) G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141–152; b) D. K. Bedke, C. D. Vanderwal, *Nat. Prod. Rep.* **2011**, *28*, 15–25; c) C. Nilewski, E. M. Carreira, *Eur. J. Org. Chem.* **2012**, *2012*, 1685–1698; d) T. Umezawa, F. Matsuda, *Tetrahedron Lett.* **2014**, *55*, 3003–3012; e) W.-J. Chung, C. D. Vanderwal, *Acc. Chem. Res.* **2014**, *47*, 718–728; f) W.-J. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 4396–4434; *Angew. Chem.* **2016**, *128*, 4470–4510; g) P. H. Huy, P. Grewelinger, *Nachr. Chem.* **2019**, *67*, 63–67.

[18] a) G. Helmchen, H. Albrecht, M. Arend, in *Stereoselective Synthesis part 1*, Houben-Weyl, G. Helmchen, in Vocabulary and Nomenclature of Organic Stereochemistry, in Houben-Weyl Vol. E21a, Stereoselective Synthesis (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Georg Thieme, Stuttgart, **1995**, p. 1–74; b) C. Wolf, in *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, Royal Society of Chemistry, Cambridge, **2007**. The citations are located on page 182 and 234 in ref.[17b].

[19] a) A. Bunrit, C. Dahlstrand, S. K. Olsson, P. Srifa, G. Huang, A. Orthaber, P. J. R. Sjöberg, S. Biswas, F. Himo, J. S. M. Samec, *J. Am. Chem. Soc.* **2015**, *137*, 4646–4649; b) R. A. Watile, A. Bunrit, J. Margalef, S. Akkarasamiyo, R. Ayub, E. Lagerspets, S. Biswas, T. Repo, J. S. M. Samec, *Nat. Commun.* **2019**, *10*, 3826.

[20] a) B. Trost, *Science* **1991**, *254*, 1471–1477; b) A. D. Curzons, N. D. Mortimer, D. J. C. Constable, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1–6; c) R. A. Sheldon, *Chem. Ind.* **1992**, 903–906.

[21] a) R. M. Denton, J. An, B. Adeniran, *Chem. Commun.* **2010**, *46*, 3025–3027; b) R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749–6767.

[22] a) X. Tang, C. Chapman, M. Whiting, R. Denton, *Chem. Commun.* **2014**, *50*, 7340–7343; b) T. Kubota, S. Miyashita, T. Kitazume, N. Ishikawa, *J. Org. Chem.* **1980**, *45*, 5052–5057; c) R. H. Beddoe, K. G. Andrews, V. Magné, J. D. Cuthbertson, J. Saska, A. L. Shannon-Little, S. E. Shanahan, H. F. Sneddon, R. M. Denton, *Science* **2019**, *365*, 910–914.

[23] a) B. D. Kelly, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 13930–13931; b) C. M. Vanos, T. H. Lambert, *Angew. Chem. Int. Ed.* **2011**, *50*, 12222–12226; *Angew. Chem.* **2011**, *123*, 12430–12434; c) B. D. Kelly, T. H. Lambert, *Org. Lett.* **2011**, *13*, 740–743; d) E. D. Nacsa, T. H. Lambert, *Org. Lett.* **2013**, *15*, 38–41.

[24] a) T. V. Nguyen, A. Bekensir, *Org. Lett.* **2014**, *16*, 1720–1723; b) T. Stach, J. Dräger, P. H. Huy, *Org. Lett.* **2018**, *20*, 2980–2983.

[25] K. A. Netland, L.-L. Gundersen, F. Rise, *Synth. Commun.* **2000**, *30*, 1767–1777.

[26] a) P. H. Huy, S. Motsch, S. M. Kappler, *Angew. Chem. Int. Ed.* **2016**, *55*, 10145–10149; *Angew. Chem.* **2016**, *128*, 10300–10304; b) P. H. Huy, I. Filbrich, *Chem. Eur. J.* **2018**, *24*, 7410–7416; for further examples see:; c) P. H. Huy (Saarland University), WO patent **2016**/202894 A1; d) P. H. Huy, I. Filbrich (Saarland University), LU patent **2017**/93108.

[27] Most work up protocols in publications from academia have not been optimized towards sustainability (e.g. minimal amounts of chemicals). For a fair comparative assessment, we recommend to calculate E-factors only based on materials used in the reaction and not in the work-up and purification.

[28] a) R. Richter, B. Tucker, *Helv. Chim. Acta* **1959**, *42*, 1653–1658; b) H. Eilingsfeld, M. Seefelder, H. Weidinger, *Angew. Chem.* **1960**, *72*, 836.

[29] J. Küppers, R. Rabus, H. Wilkes, J. Christoffers, *Eur. J. Org. Chem.* **2019**, *2019*, 2629–2634.

[30] a) J. G. Lee, K. K. Kang, *J. Org. Chem.* **1988**, *53*, 3634–3637; b) D. C. Snyder, *J. Org. Chem.* **1995**, *60*, 2638–2639; c) L. Sun, G. Peng, H. Niu, Q. Wang, C. Li, *Synthesis* **2008**, *24*, 3919–3924; d) S. Motsch, C. Schütz, P. H. Huy, *Eur. J. Org. Chem.* **2018**, *2018*, 4541–4547.

[31] a) H. A. van Kalkeren, S. H. A. M. Leenders, C. Rianne, A. Hommersom, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Eur. J.* **2011**, *17*, 11290–1295; b) L. Longwitz, S. Jopp, T. Werner, *J. Org. Chem.* **2019**, *84*, 7863–7870.

[32] a) C. O'Brien, *WO patent* 2010118042 (**2010**); b) J. A. Buonomo, C. C. Aldrich, *Angew. Chem. Int. Ed.* **2015**, *54*, 13041–13044; *Angew. Chem.* **2015**, *127*, 13233–13236.

[33] M. A. Hussein, Thanh, V. Nguyen, *Chem. Commun.* **2019**, *55*, 7962–7965.

[34] a) H. Huang, J. Y. Kang, *J. Org. Chem.* **2017**, *82*, 6604–6614; b) J. Chen, J.-H. Lin, J.-C. Xiao, *Org. Lett.* **2018**, *20*, 3061–3064; c) J. Chen, J.-H. Lin, J.-C. Xiao, *Chem. Commun.* **2018**, *54*, 7034–7037.

[35] a) D. J. Hardee, L. Kovalchuke, T. H. Lambert, *J. Am. Chem. Soc.* **2010**, *132*, 5002–5003; b) T. V. Nguyen, D. J. M. Lyons, *Chem. Commun.* **2015**, *51*, 3131–3134; c) P. H. Huy, C. Mbouhom, *Chem. Sci.* **2019**, *10*, 7399–7406.

[36] a) J. An, X. Tang, J. Moore, W. Lewis, R. M. Denton, *Tetrahedron* **2013**, *69*, 8769–8776; b) X. Tang, J. An, R. M. Denton, *Tetrahedron Lett.* **2014**, *55*, 799–802; c) P. H. Huy, *Synthesis* **2019**, *51*, 2474–2483.

[37] a) R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* **2010**, *10*, 4678–4681; b) J. Saska, W. Lewis, R. S. Paton, R. M. Denton, *Chem. Sci.* **2016**, *7*, 7040–7049.

[38] a) T. Yoshimitsu, N. Fukumoto, T. Tanaka, *J. Org. Chem.* **2009**, *74*, 696–702; b) J. Long, J. Chen, R. Li, Z. Liu, X. Xiao, J.-H. Lin, X. Zheng, J.-C. Xiao, *Synlett* **2019**, *30*, 181–184.

[39] a) M. Böldl, I. Fleischer, *Eur. J. Org. Chem.* **2019**, *2019*, 5856–5861; b) D. Canestrari, C. Cioffi, I. Biancofiore, S. Lancianesi, L. Ghisu, M. Ruether, J. O'Brien, M. F. A. Adamo, H. Ibrahim, *Chem. Sci.* **2019**, *10*, 9042–9050.

[40] The contributions of Samec and colleagues about Brønsted and Lewis acid, respectively, catalyzed cyclodehydration are a positive exception thereof.

[41] a) M. H. Shaw, V. W. Shurtleff, J. A. Terrett, J. D. Cuthbertson, D. W. C. MacMillan, *Science* **2016**, *352*, 1304–1308; b) Y. Zi, M. Lange, C. Schultz, I. Vilotijevic, *Angew. Chem. Int. Ed.* **2019**, *58*, 10727–10731; *Angew. Chem.* **2019**, *131*, 10837–10841.

Received: October 10, 2019