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Formamide Catalyzed Nucleophilic Substitutions: Mechanistic Insight and Rationalization of Catalytic Activity

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ABSTRACT: Herein, detailed mechanistic investigation into formamide catalyzed nucleophilic substitution (S_N) of alcohols is reported. Alkoxyiminium chlorides and hexafluorophosphates were synthesized and characterized as key intermediate of the catalytic cycle. The determination of reaction orders and control experiments indicated that the nucleophilic attack of the formamide catalyst onto the reagent BzCl is the rate determining step. Linear Free Energy Relationship revealed a correlation between the quantified Lewis basicity strength of formamides by means of ^{11}B NMR spectroscopy and their catalytic activity in S_N-transformations. The observed difference in catalytic ability was attributed to NBO charge, dipole moment and Sterimol parameter B_5. Importantly, this rationalization enables the prediction of the capacity of formamides to promote S_N-type transformations in general.

Introduction

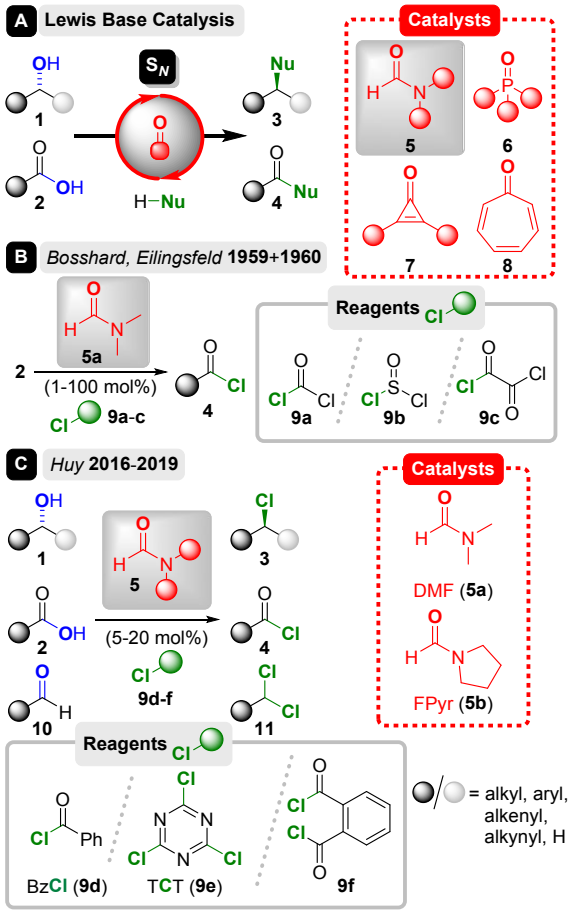
Nucleophilic substitutions (S_N) are amongst the most important and widespread chemical transformations.[1-3] Presently, Lewis base catalysis has turned into a powerful platform for S_N-type bond formations (Scheme 1 **A**).[2,3] Organocatalysts like formamides **5**,[4-6] triphenylphophane oxides **6**,[7] cyclopropenones **7**[8] and tropone (**8**)[9] enable substitutions with alcohols **1** and carboxylic acids **2**, for instance, in significantly enhanced atom- and cost-efficiency and sustainability. The products of these reactions, which are alkyl halides **3** and acid chlorides, esters and amides of type **4**, are essential for syntheses of peptides, pharmaceuticals, plant protection agents and polymers.[1-3]

Already in 1959 and 1960 Bosshard, Eilingsfeld and colleagues discovered that certain amides catalyze the conversion of carboxylic acids **2** to chlorides **4** with phosgene (**9a**), thionyl chloride (**9b**) and oxalyl chloride (**9c**), respectively (Scheme 1 **B**).[4] Notably, these are amongst the first examples of Lewis base catalyzed S_N-reactions.[10] Thereby, dimethylformamide (**5a**, DMF) was identified as paramount catalyst. The catalytic effect was rationalized by *in situ* formation of Vilsmeier Haack[11] type chloroiminium chlorides (e.g., **9g**, see Scheme 2 **B**). This mechanistic proposal was supported by the observations that (1) the reaction of DMF with the highly reactive acid chlorides **9a-c** furnishes **9g**; and (2) the reagent **9g** allows the synthesis of acid chlorides **4** from **2**.[4,11f] Meanwhile, the catalytic property of DMF to access acid chlorides may be considered as "common knowledge", testified by numerous examples.[12] Despite the original reports[4] there are no further systematic investigations regarding scope and mechanism.[10c,d]

Recently, the Huy group implemented formamide catalyzed S_N-approaches engaging alcohols **3**, carboxylic acids **2** and aldehydes **10** as substrates (Scheme 1 **C**).[5] The application of the moderately electrophilic reagents **9d-f** and phenyl chloroformate enables exceptionally mild reaction conditions. This is reasoned by the formation of weakly acidic by-products like benzoic acid in the case of benzoyl chloride (BzCl, **9d**).[5a]

In contrast, the strongly electrophilic reagents **9a-c** give rise of highly acidic HCl as by-product. Overall, the milder reaction conditions result in high levels of functional group compatibility, stereoselectivity and an improved sustainability. Furthermore, a screening of diverse Lewis bases including DMF yielded 1-formylpyrrolidine (FPyr, **5b**) as superior catalyst. As an essential aspect, reaction of alcohols **1** with BzCl furnishes esters of type **12** as main (and often exclusive) products (Scheme 2 **A**).[5]

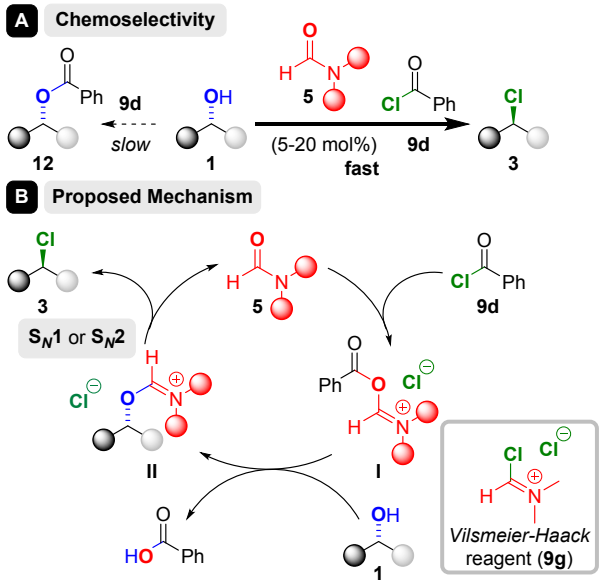
Scheme 1. Oxygen Lewis Base Catalysis in Nucleophilic Substitutions.



Solely in the presence of an appropriate formamide **5** alkyl chlorides **3** are obtained. Hence, the Lewis base catalyst **5** is crucial to shift chemoselectivity towards product **3**. Initial formation of intermediate **I**, which is structurally related to the Vilsmeier Haack reagent **9g**, has been proposed (Scheme 2 **B**).[5a,11] Since reaction of BzCl with DMF does not deliver reagent **9g**, the latter most likely does not occur as intermediate. Next, condensation with substrate **1** has been predicted to furnish alkoxyiminium intermediates of type **II** and benzoic acid. Eventually, S_N2 and S_N1 substitution in dependence on the starting material **1** should deliver **3** and catalyst **5**, which completes the catalytic cycle. This mechanistic rational is substantiated by the capability of the Vilsmeier Haack reagent to mediate transformations of alcohols into chloro alkanes.[13] Besides evidence for intermediate **II** no further mechanistic studies have been reported to this end. In fact, mechanistic elucidations in the field of oxygen Lewis base catalyzed S_N-transformations are so far limited to the proof of potential reaction intermediates derived from alcohols **1**.[2,4-9]

In general, over the last decades Lewis base catalysis has become a widely accepted concept enabling innovative and unique transformations in organic synthesis.[14] In this context, scales of Lewis basicity are a powerful tool to gauge the catalytic ability of Lewis bases,[15] and facilitate the development of novel reactions. Due to the necessity of a Lewis acid as reference to construct a basicity scale, a universal scale does not exist.

Scheme 2. BzCl Mediated Synthesis of Chloroalkanes.[5a]



Despite, various reference acids are known allowing the quantification for a wide range of different Lewis base classes.[15a] Previously, in the Hilt group the Lewis acidity of Lewis acid-oxazaborolidine complexes[16a] or of ferrocence-stabilized silicon cations[16b] were quantified by correlation of the activation strength and their catalytic activity in the Diels-Alder reaction. The major advantage of this alternative approach stems from the possibility to use correlation analysis for the disclosure of new reactions.

To the best of our knowledge, this approach of quantification has not been delineated for formamides in literature to date. This prompted us to quantify the Lewis basicity strength of formamides in respect to their catalytic activity with the aid of the Lewis base catalyzed nucleophilic substitution. We envisioned to explore the capability of activation by the chemical shift of a probe exerted by the coordination of the formamide. Kinetic studies were conducted to determine the catalytic activity. Moreover, we anticipated that multivariate linear regression analysis[17] reveals the relevant molecular descriptors which lead to different reactivity of the catalysts. In addition, we present detailed mechanistic investigations for formamide catalyzed substitution reactions promoted by BzCl. Levels of functional group compatibility[18] and the sensitivity of the reaction conditions towards deviations[19] were assessed thoroughly.

Results and Discussion

Reaction Intermediates. Since 1960 several protocols for the synthesis of chloro alkanes from alcohols by means of the Vilsmeier Haack reagent **9g** have been implemented.[13] They mainly differ in the production of the reagent **9g** itself. However, the putative intermediate **II** has not been verified. Indeed, reaction of equimolar amounts of aliphatic alcohols **1**, BzCl and formamides in $CDCl_3$ at room temperature affords alkoxyiminium chlorides **II** in 81-91% conversion (Scheme 3 **A**).[5a]

The connectivity between the alkoxy and formamide fragment was evidenced by (1) a strong nuclear Overhauser effect (NOE) between the formyl protons and the H atoms of the CH_2 and CH moiety next to the oxygen atom; (2) scalar $^3J_{C,H}$ coupling of the formyl proton with the carbon atom adjacent to oxygen as proven by HMBC-NMR. The electron-deficient nature of these species is demonstrated by a strongly deshielded singlets for the formyl proton.

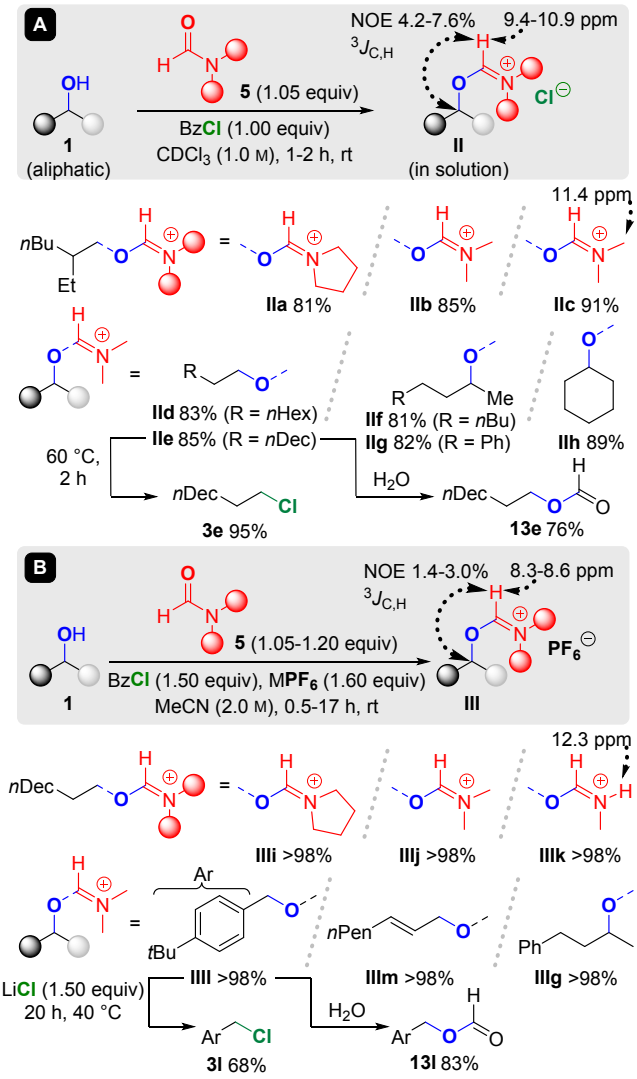
Remarkably, not only FPyr and DMF are feasible for the production of **II** but also *N*-methylformamide (MF, example **IIc**), which is also a good catalyst for the synthesis of alkyl chlorides.[5a] Reaction of several primary and secondary alcohols with DMF delivered the salts **IId-h**. Sterically encumbered cyclohexanol is a non-viable substrate for the catalytic chlorination. Nevertheless, alkoxyiminium chloride **IIh** was prepared with this alcohol. The sterically demanding cyclohexyl backbone impedes substitution of the formamide moiety in **IIh** via the chloride counter ion.[2c,20]

Alkoxyiminium chlorides of type **II** are productive intermediates: Heating of the reaction mixture containing **IIe** to 60 °C furnished chloro alkane **3e** in virtually quantitative yield. Addition of water on the other hand afforded formate **13e** in 76% yield as a likely result of hydrolysis of **IIe**. In fact, type **13** formyl esters are formed as side-products especially in the case of catalytic chlorination of aliphatic starting materials.

Treatment of activated benzylic and allylic alcohols with DMF under identical reaction conditions, did not lead to species **II**. Instead, the respective chloro alkanes were generated. While transformations of activated substrates into chlorides **3** were conducted at room temperature, the catalytic synthesis of aliphatic alcohols needed heating to 80 °C. This is explained by the higher reaction rate of activated alcohols with adjacent π-systems in S_N2-substitutions in comparison to aliphatic ones. Therefore, aliphatic alkoxyiminium salts **II** are more stable than those produced from activated alcohols.

However, type **II** intermediates derived from benzylic and allylic starting materials could be successfully verified by means of anion exchange (examples **IIIl** and **IIIm** in Scheme 3 **B**). Reaction of alcohols with BzCl and formamides in the presence of $NaPF_6$ or KPF_6 caused formation of the salts of type **III**, in which the nucleophilic chloride is substituted by a non-nucleophilic hexafluorophosphate anion. The increased stability of **III** in comparison to **II** enabled quantitative conversion of **1** and the aforementioned stabilization of benzyloxy and allyloxyiminium intermediates. Curiously, use of $NaPF_6$ results partially in the formation of iminium difluorophosphates (see chp. 2.3.2 in the Supporting Information = SI). The close proximity of catalyst and alkanol scaffold was again established on the basis of NOE and $^3J_{C,H}$ coupling. The formyl H atoms are slightly less deshielded than in the case of **II**. The productive nature of intermediates **III** was demonstrated by heating **IIIl** with LiCl to 40 °C, which furnished benzylic chloride **3l** in 68% yield.

Scheme 3. Alkoxyiminium Chlorides and Hexafluorophosphates.

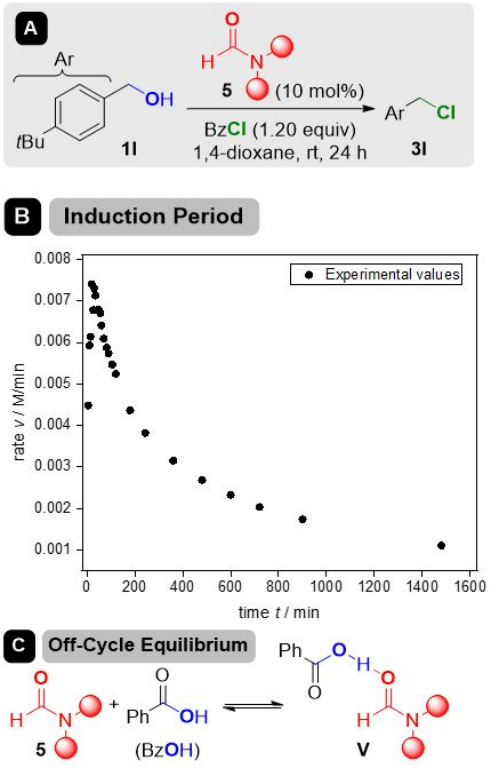


For detailed experimental conditions see SI. Conversion to species **II** and **III** as determined by ^{1}H NMR. Yields of **3e**, **13e**, **3l** and **13l** were determined by means of naphthalene as internal NMR standard.

Treatment of **IIIl** with water furnished formate **13l** as a probable result of hydrolysis. As in the case of **II**, iminium salts **III** could be synthesized using DMF, FPyr (**IIIi**) and methylformamide (**IIIk**), respectively. Low temperature NMR spectroscopy down to -40 °C using an equimolar solution of DMF and BzCl in $CDCl_3$ did not provide evidence for intermediate **I** (or **9g**). However, the synthesis of type **I** benzoyloxyiminium triflates with BzCl and DMF in the presence of silver triflate has been described,[21] which underpins the mechanistic proposal in Scheme 2 **B**.

Kinetic Studies. Kinetic studies were conducted in order to elucidate the mechanism of formamide catalyzed nucleophilic substitution, and to investigate the reactivity of different formamides as catalyst.

Figure 1. A. Reaction Conditions, B. Induction Period, and C. Off-Cycle Equilibrium.



Therefore, (4-(*tert*-butyl)phenyl)methanol (**1l**) was subjected to reaction conditions shown in Figure 1 **A**. The course of reaction was monitored by gas chromatography (GC). A typical phenomenon in catalysis is the presence of an induction period, whereby the rate raises at the beginning of the reaction and decreases exponentially as usual after reaching maximum. This circumstance can be explained by formation of the catalytic active species visualized by plotting the rate *v* against the time *t*. Accordingly, the appropriate graph displays a significant induction period for the formamide catalyzed nucleophilic substitution (Figure 1 **B**). Hence, we assume that this observation is consistent with the formation of intermediate **I** in Scheme 2 **B**.

Reaction Order. Subsequently, the reaction order was determined to gain further information about the effect of each component on the reaction rate. Therefore, we employed variable time normalization analysis (VTNA), which is a method reported by Burés obtaining the reaction order by visually comparing concentration profiles while using a normalized time scale.[22]

Regarding the substitution reaction, this technique permits to ignore the data of the induction period and enables an analysis during the entire course of reaction under synthetically relevant conditions. Consequently, only concentration data after the induction period were used to construct the normalized profiles. Since DMF catalyzes the reaction with similar yield and selectivity as FPyr,[5a] we performed the investigation of the reaction order using DMF as catalyst.

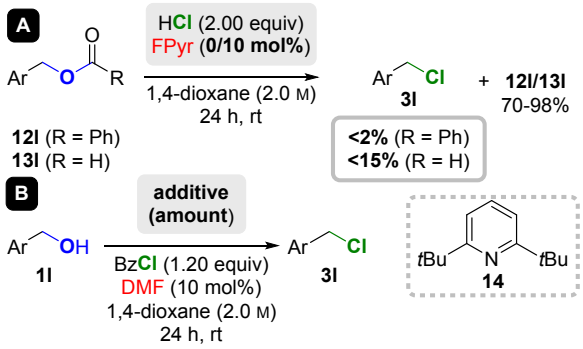
As shown in Figure 2 **A**, a zero-order dependence in benzyl alcohol **1l** was observed excluding the second step as rate determining. Considering the reaction order of the catalyst DMF, an appropriate overlay of the concentration profiles was attained with the normalization factor $\alpha = 1.1$ (Figure 2 **B**). Notably, deviation at higher conversion for both reaction profiles stems most likely from an off-cycle-equilibrium between the formamide and benzoic acid (**2a**), which is formed as stoichiometric side-product (Figure 1 **C**).

Since BzCl is not detectable by GC analysis, its concentration cannot be determined during the reaction, so VTNA is not applicable. Instead, an initial rate dependence was used to obtain the reaction order of BzCl. Therefore, five measurements with different initial concentration of BzCl, ranging from 2.0 M to 2.8 M, were performed at elevated temperature (40 °C) to suppress the induction period. Plotting the logarithm of initial rate v_o versus logarithm of concentration of BzCl revealed a reaction order of 0.9 (Figure 2 **C**).

Comparison Reactions. Benzoate **12l** and formate **13l**, which are both formed as side-products, provide only very small quantities of the product **3l** upon exposure to HCl (Scheme 4 **A**). Therefore, esters **12** and **13** can be ruled out as productive intermediates for the generation of chlorides **3**.

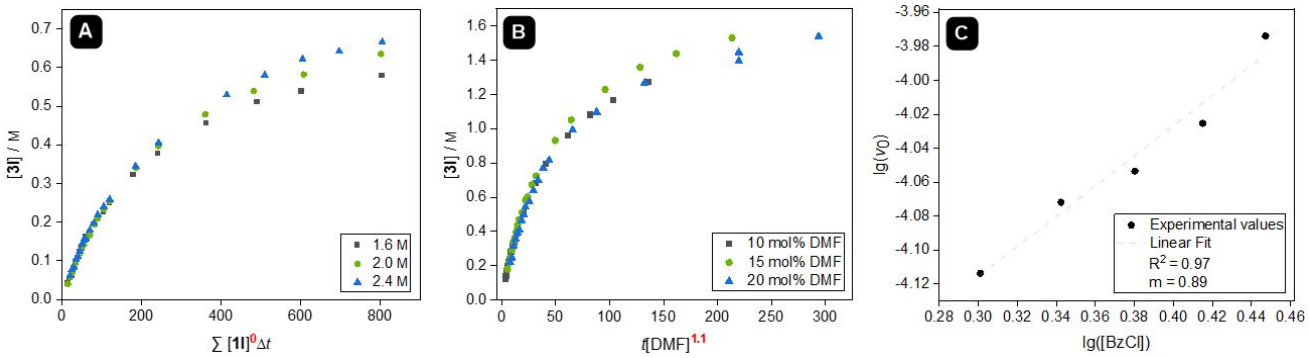
Figure 2. Determination of Reaction Order.

Scheme 4. Control Experiments.



Entry	Additive	Amount / equiv	k_{total} /·10^{-3} min^{-1}
1	–	–	3.02
2	**14**	1.00	2.92
3	Ph OH (**2a**)	1.00	2.84
4		2.00	2.09
5		3.00	2.29
6		5.00	1.92
7	LiCl	1.00	2.49
8	nBu$_4$NCl	1.00	2.84

For detailed experimental conditions see SI. Yields were determined by means of GC analysis using mesitylene as internal standard. Data after the induction period were collected to determine k_{total}



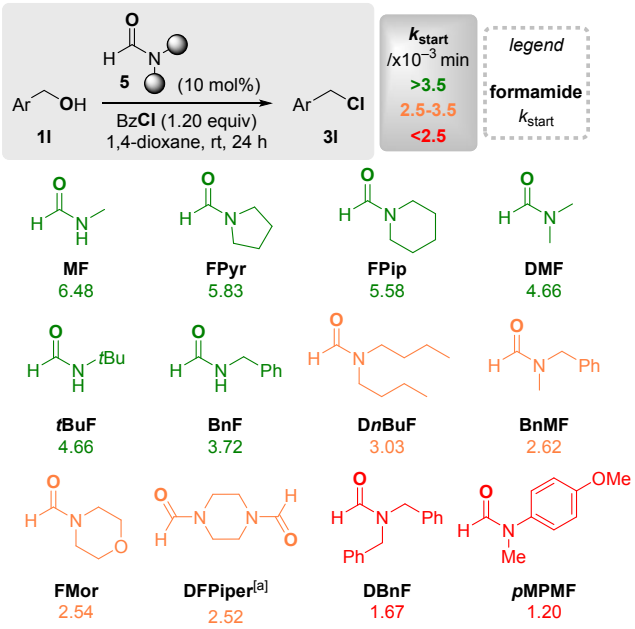
Moreover, addition of the sterically encumbered base 2,6-bis-*tert*-butylpyridine (**14**) exerted no effect on the initial rate (Scheme 4 **B**). Instead of an accelerating effect, addition of up to 5.00 equiv benzoic acid (**2a**) led to a decreased reaction rate (Scheme 4 **B**). This can be explained due to the off-cycle equilibrium between BzCl and the formamide (see Figure 1 **C**). Notably, addition of external chloride ions does not affect the reaction rate (Scheme 4 **B**). Based on this observation and on the results toward the reaction order, we hypothesize that the formation of acyloxyiminium ion **I** is the rate limiting step of the formamide catalyzed nucleophilic substitution.

Quantification of Catalytic Activity. With an efficient method for kinetic measurements in hand, we sought to quantify the catalytic activity of formamides reacting as Lewis base catalyst in the nucleophilic substitution. As shown in Scheme 5, different formamides were chosen to extend the catalyst scope. Due to a long reaction time, only the beginning of the reaction was considered and initial rate constant k_{start} served as parameter for the quantification study. In order to obtain the k_{start} value, data after the induction period, which were determined by plotting the rate *v* against the time *t* for each measurement, was used.

To ensure the accuracy of the obtained values for the initial rate constant k_{start}, all measurements were performed twice, whereby the mean value was employed for the following studies and is depicted in Scheme 5. Despite a similar order of magnitude, the k_{start} distinguish significantly, so that the kinetic study shows apparent trends. The formamides FPyr, FCy and MF are the most active catalyst. DMF, *t*BuF and BnF provided comparable activities. Thereby, MF is even superior to FPyr and DMF in terms of k_{start}. Nevertheless, the use of MF often results in lower yields and chemoselectivities in comparison to the latter two formamides.[5a] Since this is especially the case at low catalyst amounts, decomposition of MF is a likely explanation for this observation. While BnMF, FMor, DFPiper, and D*n*BuF exhibit a moderate catalytic activity, for DBnF and *p*MAMF a low activity was observed.

Quantification of Lewis Basicity. The quantification of Lewis basicity of formamides was illustrated by the capability of activation coordinating to a reference probe, especially a Lewis acid. The effect that the formamide exerted on the probe was recorded by NMR spectroscopy. Accordingly, we decided to use $B(C_6F_5)_3$ as probe because of its excellent properties as Lewis acid, which should ensure a complete coordination of the formamide. Since 1,4-dioxane could also act as a Lewis base, CH_2Cl_2 was selected as solvent for these measurements.

Scheme 5. Catalyst Scope for the Quantification of Lewis Basicity of Formamides.



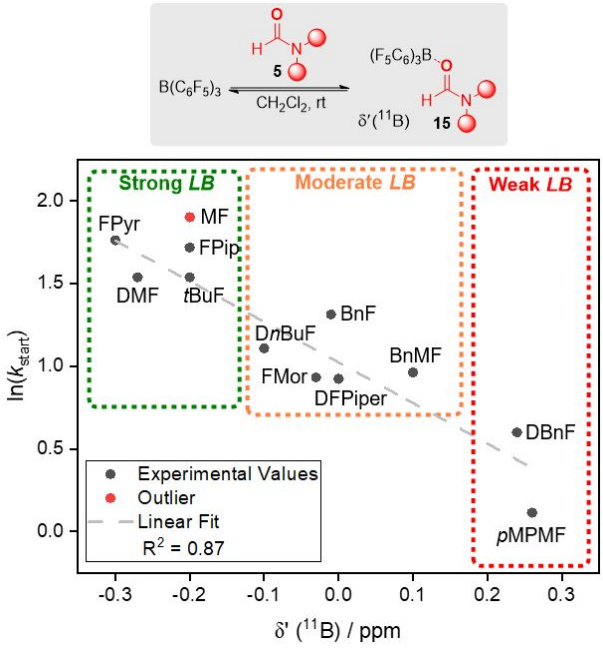
For detailed reaction conditions see SI. The yields were determined via GC with mesitylene as internal standard. Data after induction period were collected to determine k_{start}. The mean value of two measurements of k_{start} is depicted. MF = methylformamide, FPip = *N*-formylpiperidine, *t*BuF = *tert*-butylformamide, BnF = benzylformamide, D*n*BuF = di-*n*-butylformamide, BnMF = Benzylmethylformide, FMor = *N*-Formylmorpholine, DFPiper = 1,4-diformylpiperazine, DBnF = dibenzylformamide, *p*MPMF = (*para*-methoxyphenyl)methylformamide.

Remarkably, the ^{11}B chemical shift of the complex **15** formed between $B(C_6F_5)_3$ and the formamides vary significantly and served to gauge the Lewis basicity. (see chp. 2.6 in the SI). Considering the chemical shift of the formed complex **15**, which is displayed in x-axis in the graph shown in Figure 3, formamides could be categorized in three groups regarding their activation. The most noticeable effect on the probe was induced by FPyr, DMF, MF, FPip, and *t*BuF that is clarified by the obvious highfield

shift of the respective complexes. A moderate Lewis basicity was observed for D*n*BuF, BnF, FMor, DFPiper and BnMF. Compared to these formamides, DBnF and *p*MPMF showed a lower capability to activate $B(C_6F_5)_3$ that could be attributed to a lower Lewis basicity.

Linear Free Energy Relationship. Linear free energy relationship (LFER) is an established method to elucidate a correlation between two parameters.[23] In this context, we explored, if the quantified activation of $B(C_6F_5)_3$ by the formamides relates to the initial rate constant k_{start}. Accordingly, plotting the acquired chemical shift $\delta(^{11}B)$ of the complex **15** against the logarithm of the k_{start} values revealed an apparent correlation between the Lewis basicity of the formamides and their catalytic activity in the substitution reaction (Figure 3). Generally, the observed correlation demonstrates that a higher Lewis basicity leads to a higher catalytic activity of the formamide.

Figure 3. LFER between the Quantified Lewis Basicity and the Catalytic Activity of Formamides.



For reaction conditions see SI. The classification in terms of Lewis basicity relies on the change of the chemical shift in the ^{11}B NMR.

In particular, resulting from a higher Lewis basicity, the formamides transfer more electron density toward $B(C_6F_5)_3$ observed by a stronger highfield shift of the respective complex **15** and were found to be the most active catalysts. For instance, FPyr, DMF, MF, FPiper and *t*BuF are very reactive catalysts and exhibit a high Lewis basicity. In contrast, DBnF and *p*MPMF show a low reactivity according to their basicity strength. Apparently, the formamide MF differs from the correlation so that the chemical shift of the formed complex **15** with $B(C_6F_5)_3$ does not serve for estimation of its catalytic activity. Hence, MF was excluded from the LFER and marked as outlier. Overall, the observations concerning the reactivity of the formamides coincide well with the mechanistic proposal presented at the beginning (see Scheme 2 **B**). The formamide attacks nucleophilic BzCl to form the acyloxyiminium ion **I** which seems to be the rate determining step of the reaction.

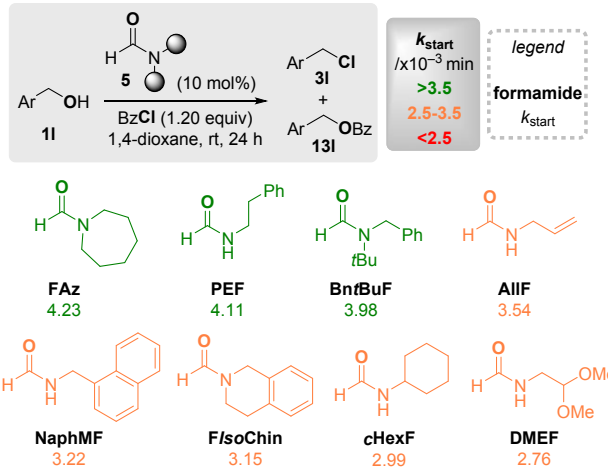
Multivariate Linear Regression Analysis. In general, the difference in reactivity of the formamides disclosed by the LFER shown in Figure 3 may be attributed to several molecular descriptors. In this context, Sigman has refined multivariate linear regression analysis (MLR), a pivotal method to predict any experimental reaction outcome, such as enantio- or regioselectivity, turnover number, turnover frequency or yield, combining mechanistic relevant molecular descriptors.[17a] Correlation between experimental and predicted values provides a model that can be used for mechanistic interpretation or for a virtual catalyst screening. The success of this approach stems from a low computational requirement because physically molecular descriptors can be calculated easily from the energy-minimized structures. This conjunction to mechanistically relevant parameters implicates a good predictive power of the constructed model and constitutes the second advantage of MLR.[17]

This encouraged us to apply MLR constructing an additional model to predict the initial rate constant k_{start} with the aim to find crucial molecular descriptors by which the different reactivity could be explained. Since the model reaction is a substitution, we anticipated that especially electronic parameters may affect the activity of the catalysts.

Accordingly, calculated NBO charges, dipole moment, and IR vibration (frequency and intensity) were employed as potential descriptors. Besides electronic also steric parameters are important and have become substantial for this prediction method.[17b] Consequently, various bond lengths, bond angles, dihedral angles, and Sterimol parameters were also utilized for this analysis. All examined parameters were calculated at the B3LYP-D3/def2-TZVP level of theory,[24] are tabulated in chp. 3.2 in the SI.

In order to generate a meaningful model, a broad variety of structural and electronic properties of the formamide is required, and therefore the catalyst scope was expanded. After the synthesis of several formamides, the new catalysts were subjected to the reaction conditions, shown in Figure 1 **A**, while the yield of **3l** and the selectivity between the chloride **3l** and the ester **13l** were determined by GC analysis. Detailed information about yield and ratio between **3l** and **13l** for all synthesized and tested formamides are summarized in the SI in Figure S52. Pleasingly, aliphatic and cyclic formamides catalyzed the substitution reaction very efficiently as well as benzyl derivatives and *N*-allylformamide (AllF) emphasized as competent catalysts (Scheme 6). As described before, the mean value of two measurements of k_{start} were utilized for the following investigation. Typically, due to high rotation barriers around the C-N amide bond unsymmetrical formamides exist as rotational isomers (Figure 4 **A**).

Scheme 6. Extended Catalyst Scope for MLR.

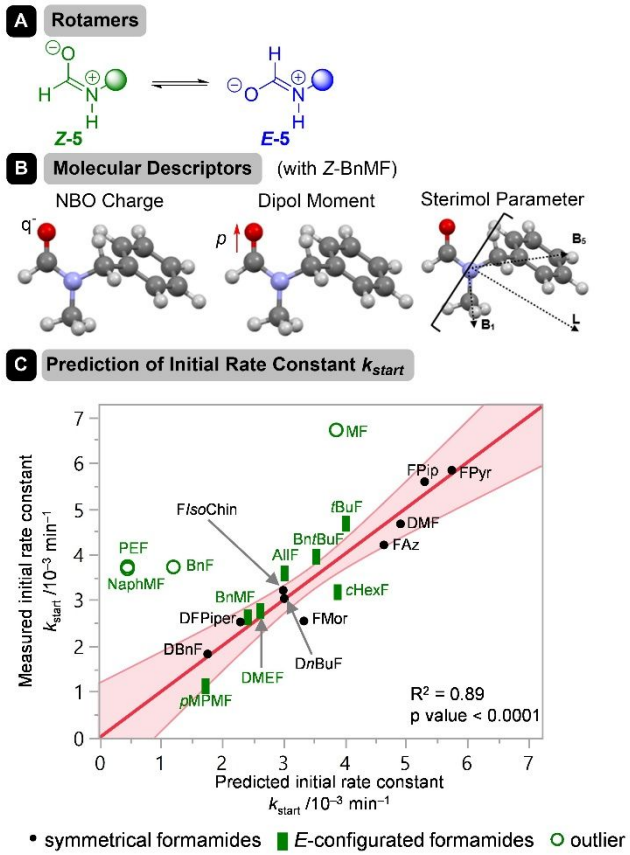


Yields of **3l** and selectivity between **3l** and **13l** were determined by means of GC analysis using mesitylene as internal standard. The mean value of k_{start} of two measurements is depicted. AllF = allylformamide, *c*HexF = *cyclo*-hexylformamide, DMEF = 2,2-diemethoxyethyl formamide, PEF = 2-phenylethylformamide, FAz = *N*-Formylazepane, Bn*t*BuF = benzyl-*tert*-butylformamide, BaphMF = (naphtha-1-ylmethyl)formamide.

Recently, Rebek impressively illustrated the significance of the configuration of formamides regarding their chemical properties by demonstrating that *E*-configured formamides possess a higher hydrophilicity compared to the *Z*-rotamer.[25] Based on this, we employed only symmetric formamides (Scheme 5 and Scheme 6) for model construction, and afterwards we added separately the unsymmetrical formamides in their *E*- and *Z*-configuration, respectively, to circumvent effects resulting from their configuration.

To our delight, we found three parameters (Figure 4 **B**), including NBO charge of the oxygen atom at the carbonyl group, dipole moment of the carbonyl group and the Sterimol parameter B_5, to predict the initial rate constant k_{start} for symmetric formamides adequately (for further information see chp. 3.3 in the SI). Having developed a first model for the symmetric formamides, the second step is the addition of *E*-configured unsymmetrical formamides. The resulting correlation is represented in Figure 4 **C**. Remarkably, the three identified descriptors are also effective to assess the catalytic activity for the additional *E*-configured formamides. For the formamides with *Z*-configuration a similar model with a comparable predictive power could be generated (see chp. 3.4 + 3.5 in the SI). The obtained correlation revealed general trends of the molecular descriptors for an effective catalyst. To afford a high catalytic activity, the formamide catalysts should exhibit a high dipole moment of the carbonyl group and a small NBO charge at the oxygen atom of the carbonyl group. Simultaneously, a high initial rate constant k_{start} could be accomplished with small values for the Sterimol parameter B5.

Figure 4. Multivariate Linear Regression Analysis.



It should be mentioned that both models, based either on the *E*- or on the *Z*-configured formamides, showed up some catalysts whose reactivity cannot be described by the correlation. These formamides were excluded from the model and marked as outliers. In particular, for aromatic monoalkylated derivatives the predicted value for k_{start} does not agree with the measured one and could not be adjusted after repeating the kinetic measurement. This divergence could be ascribed to further parameters that additionally affect their reactivity. Moreover, the constructed model does not provide a validated prediction of k_{start} for MF as well. The deviation for MF is in accordance with the result obtained in LFER studies since its catalytic activity also cannot be gauged using $B(C_6F_5)_3$ as NMR probe. This outcome could be reasoned by decomposition of MF during the reaction.

Nevertheless, NBO charge, dipole moment and Sterimol parameter B_5 are precious molecular descriptors to predict the initial rate constant k_{start} of a widespread variety of formamides except aromatic monoalkylated derivatives. This generated model allows the assessment of reactivity of so far unknown formamides by simple calculation of NBO charge, dipole moment and Sterimol parameter B_5 (see chp. 3.3, SI), as well may facilitate the establishment of enantioselectivity.

Robustness Screen. The group of Glorius designed an additive based screening that allows to quantify and compare the functional group compatibility of chemical methods.[18] In this as robustness screen formalized approach a model reaction is performed in the presence of equimolar amounts of selected compounds containing different functionalities. The deviation of the product yield

from the reaction without additive (standard yield) and the recovery yield of the additives **16** provide information on the tolerance of the involved functional moieties.

We applied the robustness screen to the formamide catalyzed transformation **1l** → **3l** with a truncated set of 15 additives[18c] (Scheme 7 **A**). In the original protocol yields were determined by means of GC analysis with a flame ionization detector (FID) and a feasible internal standard. In order to allow a one-point calibration through a single measurement containing all additives, the additives **16** were chosen based on their retention time. In the present study the yields were specified via ^{1}H NMR with an internal standard after work up and solvent evaporation. Advantageous over GC, NMR also allows to identify side-products.

To increase the boiling point and hence reduce volatility, some of the additives were altered without changing the crucial functional groups. Details on these differences and analytical data of all additives **16**, which are commercially available, are included in the SI for future applications (chp. 2.3.6).

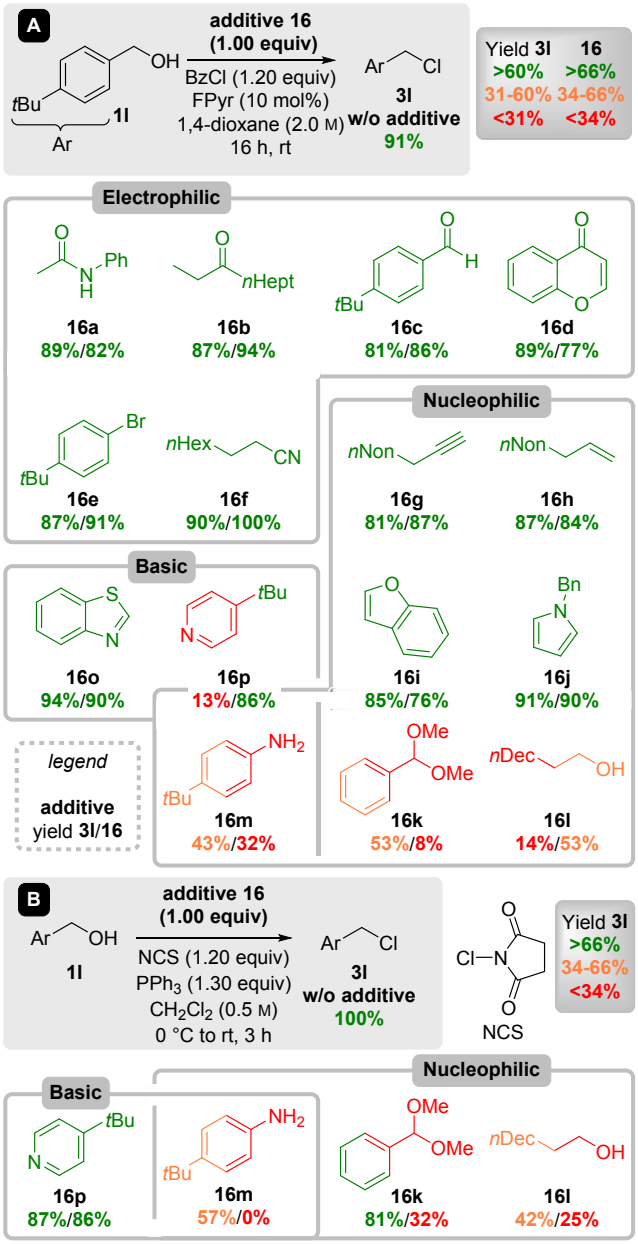
The additives are categorized into electrophilic, nucleophilic and basic according to their underlying features.[18c] Since compound **16m** is basic and nucleophilic, it is accounted to both categories. Three different ranges of yields are visualized by a traffic light color code. In general, electrophilic functional groups were tolerated well.

Additionally, nucleophilic compounds **16** were preserved except for alcohol **16l** and acetale **16k**. Alcohol **16l** acts as a concurrence nucleophile to substrate **1l** and acetale **16k** is partially hydrolyzed, which was verified by the formation of benzaldehyde. Since acid labile acyclic acetale **15k** is not compatible, we would like to highlight that other acid-prone moieties are tolerated (see Figure 5 **A**).[5a]

The released methanol again competes with the starting material. Remarkable is the preservation of the electron-rich heteroarenes **16i** and **16j**, which would undergo formylation with the Vilsmeier Haack reagent **9g**.[11] Brønsted basic functional groups constitute a limitation, which was witnessed by additives **16p** and **16m**. In the case of aniline **16m** a reaction with BzCl is very probable, whereas pyridine **16p** accelerates the benzoylation of the starting material **1l** with BzCl tremendously.

The four critical additives were reinvestigated under the conditions of the Appel reaction, which is known to be very functional group tolerant (Scheme 7 **B**).[26] While pyridine derivative **16p** had no impact, aniline **16m**, the highly acid-susceptible acetale **16k** and **16l** were incompatible, too. The full details on the robustness screen under Appel conditions are available Scheme S1 and Table S3 in the SI. Then, we set out to explore chlorination of alcohols promoted by thionyl chloride against the robustness screen (see SI, Table S4 and Scheme S2). Too our surprise, a similar average yield of **3l** and additive recovery were attained (see Figure S3 in the SI).

Scheme 7. Robustness Screen.

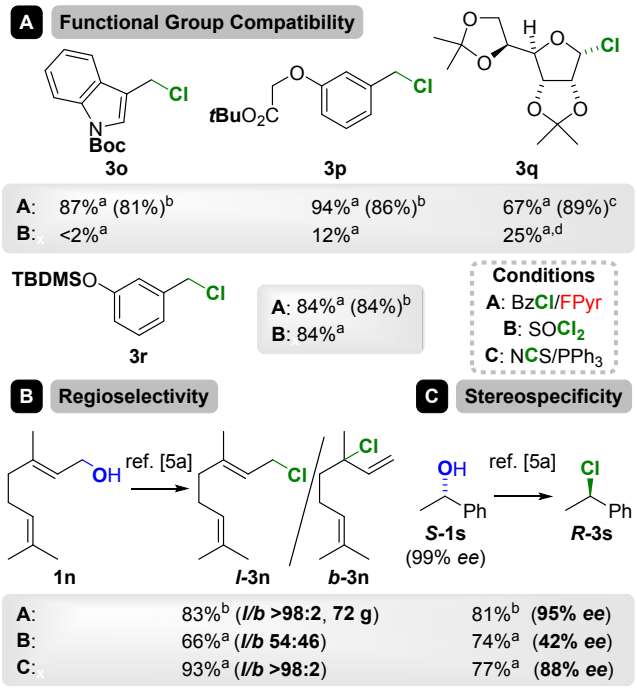


Yields were determined with the aid of mesitylene as internal NMR standard. Color coding for the yield of 3l are referenced to the standard yield of 91 and 100%, respectively.

Thus, for S_N-type methods the truncated set of additives[18c] may not fully display the level of functional group tolerance. However, the robustness screen provides a valuable insight into general trends in terms of the compatibility with diverse functions. Indeed, for all tested protocols the lowest yields for product **3l** were observed in the case of nucleophilic additives. This is explained by a competition of nucleophilic moieties with the nucleophilic starting alcohol for the electrophilic reagent. Indeed, the advantageous of formamide catalysis over both, thionyl chloride driven alcohol activation and the Appel reaction are best illustrated by the examples compiled in Figure 5. Except for an aromatic TBDMS ether (example **3r**), acid-labile functional groups are cleaved when $SOCl_2$ is used (Figure 5 **A**). In addition, levels of regioselectivity in the chlorination of allylic alcohols like geraniol are

significantly lower with thionyl chloride than BzCl/FPyr (and Appel conditions, Figure 5 **B**). Finally, application of FPyr in the synthesis of chiral benzylic chloride ***R*-3s** under stereochemical inversion enables by far the highest levels of stereospecificity (Figure 5 **C**).

Figure 5. Benefits of Formamide Catalysis.

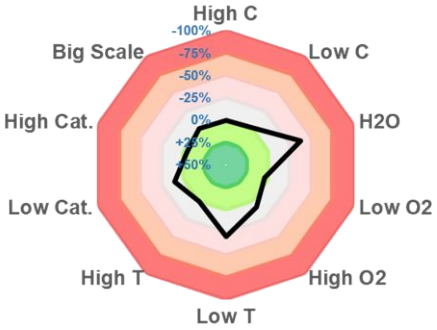


a. Yield determined by internal NMR standard. b. Isolated yield after chromatography or distillation. c. Isolated yield after chromatography, prepared with 40 mol% TCT instead of BzCl according to reference 5b. d. Mixture of diastereomers. TBDMS = *tert*-butyldimethylsilyl.

Sensitivity Assessment. To quickly assess the sensitivity of chemical methods towards changes of reaction parameters, an approach has been implemented by Glorius and co-workers recently.[19] For this so-called sensitivity assessment a set of experiments is performed, in which one reaction parameter is varied at the time. The difference in terms of product yield from the standard reaction conditions as starting point is visualized by means of a radar diagram (Figure 6).[19] This allows to identify critical reaction parameters with a large influence on the reaction outcome, which is pivotal to ensure high levels of reproducibility.

Parameters examined are substrate concentration (low and high C), levels of water (H_2O) and oxygen (low O_2 and high O_2), reaction temperature (low and high T) and scalability (big scale).

Figure 6. Sensitivity Assessment.



The light intensity in the original protocol was replaced by catalyst loading (high and low cat.). For the evaluation of our method we mostly choose more drastic deviations from the standard conditions as original proposed (see chp. 1.2 in the SI for details). The results of the sensitivity assessment in the case of model reaction **1l** → **3l** (see Scheme 7 **A**) indicated a low sensitivity towards changes of reaction parameters, since the standard yield of 91% was well reproducible (Figure 6). Only addition of water (1 vol%, entry H2O) and a lower reaction temperature T (10 instead of 25 °C) had a detrimental effect. Water likely engenders hydrolysis of BzCl and electrophilic intermediates like **I** and **II**. The lower temperature results in a decrease of the reaction rate and therefore mitigated conversion. The same effect was also observed to a weaker extent with a lower catalyst loading (Low Cat.). Scalability was evidence by a thousand-fold upscaling of the synthesis of geranyl chloride.[5a]

Conclusion

Herein, detailed mechanistic elucidations for formamide catalyzed nucleophilic substitutions of alcohols using BzCl as agent have been presented. Kinetic measurements revealed a zeroth-order dependence of the reaction rate in terms of starting alcohol **1** and a first-order dependence in both, BzCl and the formamide catalyst **5**. Control experiments verified that (1) Brønsted acid catalysis is not involved in product **3** formation; and (2) the chloride ion concentration has no effect on the reaction rate. In addition, a significant induction period was observed. These findings evidence that the rate determining step is the formation of benzoyloxyiminium salt **I** from BzCl and **5**.

In addition, alkoxyiminium chlorides of type **II**, derived from aliphatic substrates **1** have been witnessed by NMR spectroscopy. These labile salts could be stabilized by an anion exchange, which yielded hitherto unkown type **III** alkoxyiminium hexafluorophosphates. Remarkably, this allowed for the synthesis of highly reactive benzyl and allylic alkoxyiminium salts. Both, **II** and **III** could be transformed into alkyl chlorides **3**. Control experiments demonstrated that benzoate and formate esters, which are obtained as side-products, can be ruled out as productive intermediates. These observations testified that iminium species of type **II** are the second key intermediate in the production of chloro alkanes **3**. Furthermore, a clear correlation between the catalytic activity and the Lewis basicity of the applied formamides **5** was established. While the catalytic activity was displayed by the initial rate

constant k_{start} of the model reaction **1l** → **3l**, the Lewis basicity was quantified by ^{11}B NMR spectroscopy with $B(C_6F_5)_3$ as probe. This linear free energy relationship shows that high catalytic activity most likely is attained using a highly Lewis basic formamide. Additionally, the observed difference in catalytic activity of type **5** formamides was attributed to three molecular descriptors: The NBO charge, the dipole moment and the Sterimol parameter B_5. This was accomplished by constructing a model to predict k_{start} by means of a multivariate linear regression analysis. Importantly, this model enables the prediction of the catalytic activity of formamides.

A robustness screen according to Glorius and comparison with the well-known Appel reaction revealed a broad functional group tolerance. As particularly valuable for practitioners, a sensitivity assessment illustrated that only water and low reaction temperatures effect mitigated yields. We are convinced that the current investigations will guide the development of more active catalysts and may even facilitate the development of enantioselective substitutions using chiral formamides.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, NMR spectra and optimized structures.
This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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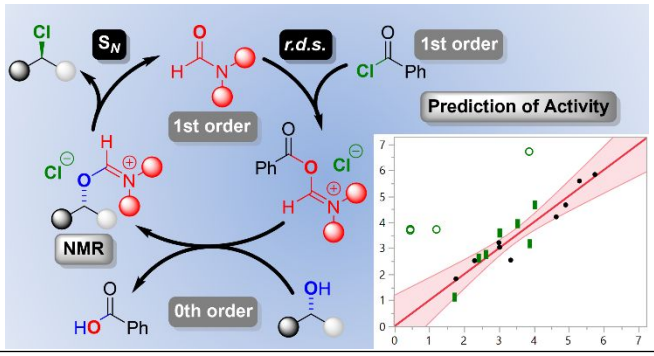
S_N
r.d.s.
1st order
1st order
Prediction of Activity
NMR
0th order