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INVESTIGATING THE UNIQUE REACTIVITY OF NOVEL HX (X=Cl,
Br) REAGENTS WITH ALKENES AND ALKYNES

By

Rene E. Ebule

A Dissertation
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University of Louisville
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Br) REAGENTS WITH ALKENES AND ALKYNES

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A Dissertation Approved on

November 16th, 2018

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ABSTRACT

INVESTIGATING THE UNIQUE REACTIVITY OF NOVEL HX (X=Cl, Br) REAGENTS WITH ALKENES AND ALKYNES

Rene E. Ebule

November 16th, 2018

The addition of hydrogen halides to carbon-carbon unsaturated systems is a classic synthetic transformation that gives rise to a variety of halogenated products as well as building blocks.¹ The different routes to achieve hydrohalogenation make use of the hydrogen halides either in the gaseous form² or in solution³, or their surrogates⁴. Only second to dihalogens, hydrogen halides are the most atom efficient source of halogenation. However, hydrogen halides are reactive gases at ambient temperature, posing a major challenge in their application. Handling gaseous hydrogen halide reagents requires expert knowledge and specialized equipment. We have investigated the formulation of environmentally benign organic aprotic hydrogen halide solutions to address this challenge. The properties of these formulations have been investigated in reactions with unsaturated systems.

Given that hydrogen bonding may play a role in the formation of stable HX solutions, we sought to screen and investigate various solvents with strong hydrogen bonding capabilities that do not adversely jeopardize the intrinsic properties the HX molecules. The few commercially available aprotic HX-solutions have low concentrations of HX and

therefore offer few synthetic advantages.⁵ The formulation of stable HX solutions with higher concentrations and better reactivity in hydrohalogenation was our goal.

Inspired by Laurence *et al*'s concept of hydrogen bond basicity⁶ and their classification of organic molecules based on their basicity (pK_{BHX} scale), we found that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) formed a stable complex with HF molecules. Our newly formulated solution of hydrogen fluoride in DMPU has exhibited higher reactivity than its predecessors in a wide scope of transformations.⁷ We are pleased to report novel DMPU solutions of HCl and HBr. The advantages of these solutions are their relatively higher HX concentrations (12.6 M HCl and 10 M HBr) and bench stable over long periods of time compared to the commercially available organic solutions. Another unique quality of these solutions is their compatibility with water and/or base-sensitive reactions. In addition, DMPU is non-nucleophilic, so it won't compete with halides in nucleophilic reactions. These new organic-based solutions of hydrogen halides have been applied in a metal-free hydrobromination of alkynes⁸ and a homogenous gold-catalyzed hydrochlorination of alkynes⁹. In addition, the combination of our new HCl reagent (HCl/DMPU) with sulfoxides forms a unique chlorothiolation system for alkenes with high regioselectivity.¹⁰ Under mild and transition-metal-free conditions, dimethylsulfoxide (DMSO) undergoes a one-carbon homologation to afford 4-chloropiperidines from homoallylic amines via a Pummerer fragmentation mechanism. The reactions are scalable and have broad substrate scope.

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1. INTRODUCTION

1.1. Literature background for halogenation

The elements of group VIIA of the periodic table are known as the halogens. They include fluorine (F), chlorine (Cl), bromine (Br), iodine (I) and astatine (At). The incorporation of these elements into compounds is also typically known as halogenation. Halogenation is a highly desirable process because it drastically modifies the physical and chemical properties of compounds and materials. Also, introducing halogens into molecules does not only provide functional handles due to the polar nature of the newly formed bonds, but also more avenues for molecular complexity via nucleophilic substitution¹¹, radical¹² or coupling¹³ reactions. For example, the electronic properties of materials have been tuned or drastically modified by halogen incorporation. The resulting electronic or semiconductor materials are high yielding and have more stable active layers¹⁴. In the energy sector where natural gas has become an important source of energy feedstock in the later part of the 20th century, the relative inertness of natural gas makes it challenging for converting it to valuable products. One solution to this challenge has been to incorporate halogens into natural gas. In the pharmaceutical industry, fluorinated compounds make up at least 25% of all pharmaceuticals¹⁵ while chlorinated compounds are estimated at over 50% of all industrial chemicals and polymers¹⁶. 20% of pharmaceuticals and about 30% of agrochemicals are chlorine containing compounds¹⁷. Key chlorinated building blocks have experienced growth from 18 Mtons in the mid-1960s to 75 Mtons in the recent years. The chlorine tree¹⁸ (Figure 1) exemplifies the use of chlorine in the manufacture of a vast range of products. Bromination on the other hand, is a very important transformation in a vast number of

organic syntheses¹⁹. This has led to constant innovation in brominating reagents²⁰. Compounds of bromine also have extensive applications as fire retardants and drilling fluids which constitute about 0.8 Mtons of brominated building blocks per year²¹.

As evidenced by the large number of halogenated pharmaceuticals, agrochemicals and functional materials, the syntheses of new halogenated materials with diverse applications has arisen. This prevalence has resulted to extensive reports of novel halogenation techniques with the past few decades^{17, 22}. Despite the extensive study of the chemistry of halogens and halogenated compounds, environmentally friendly technologies of incorporating halogens into daily consumer products are still sought.

Figure 1. Chlorine tree highlighting the range of chlorinated products

Chemists are therefore constantly challenged to provide novel reagents, processes and methodologies to incorporate halogens into diverse compounds in an efficient and

environmentally safe fashion. Despite their excellent atom economy, the use of molecular dihalogens is limited due to their extreme reactivities, toxicity and difficulties in handling the gases. Safer alternative reagents such as the N-halo reagents have been developed to replace elemental halogens in electrophilic halogenation processes. Their poor atom economy and production of stoichiometric amounts of amide by-products makes them unsuitable for large-scale processes. The halogenation reagents developed to date fall under three classes; electrophilic,²³ radical and nucleophilic halogenating reagents (Table 1). Of these, the electrophilic halogenating reagents are predominant.

Table 1. Various halogenating agents

	Reagent	Class	Advantage	Disadvantage
Fluorination	F ₂	Electrophilic, nucleophilic, radical	Excellent atom economy	Highly reactive, toxic
	HF (gas, Olah's reagent, Py.HF, etc.)	Nucleophilic	Excellent atom economy	Extremely corrosive, hazardous.
	Fluoride salts (KF, CsF, etc.)	Nucleophilic	Low atom economy, easy to handle	Highly moisture sensitive
	N-F reagents (NSFI, Selectfluor, etc.)	Electrophilic, radical	Easy to handle, low toxicity	Expensive, large amine waste
	Trifluoromethylating (Togni, Umemoto, Ruppert, etc.)	Electrophilic, nucleophilic, radical	Easy to handle	Expensive, large silicon and iodoarene wastes
	Cl ₂	Electrophilic, nucleophilic, radical	Excellent atom economy	Highly reactive, toxic
	HCl (aq., ether, AcOH solutions, etc.)	Nucleophilic	Low atom economy	Low concentrations, competing

				reactions
Chlorination	Chloride salts (NaCl, KCl, etc.)	Nucleophilic	Easy to handle. Low atom economy	Poor solubilities in organic solvents
	Covalent chloride (Si, P, Al, In, Sn, Ti)	Nucleophilic	Easy to handle	Highly toxic, moisture sensitive
	SO ₂ Cl ₂ , SOCl ₂ , COCl ₂ ,	Nucleophilic	Inexpensive	Highly toxic
	N-Cl reagents	Electrophilic, radical	Easy to handle and mostly stable	Expensive, large amine wastes
	TCICA, CBMG, CFBSA, ^t BuOCl,	Electrophilic and radical	Stable and easy to handle	Expensive and large wastes
Bromination	Br ₂	Nucleophilic, radical	Excellent atom economy	Highly toxic
	HBr	Nucleophilic	Low atom economy	Highly corrosive and toxic
	Bromide salts	Nucleophilic	Easy to handle, low atom economy	Poor solubility
	N-Br reagents	Electrophilic, radical	Easy to handle and mostly stable	Expensive, large amine wastes
	Covalent bromides (Si, P, Al, Zn, Ni)	Nucleophilic	Easy to handle	Hygroscopic and highly toxic

Another diatomic halogen source are the hydrogen halides. Of these, hydrogen fluoride is very dangerous to human tissue causing severe burns, while hydrogen chloride gas or acid solution is a strong corrosive acid, and hydrogen bromide is very pungent fuming gas. The interhalogens or organic halogenated compounds are another source. Simple halide salts will be ideal nucleophilic halogenating source due to their relatively mild and inert nature and ease of handling. However, solubility issues diminish their application in

organic syntheses. Widely applicable nucleophilic halogenating reagents are still rare. The covalent halides are extensively utilized for nucleophilic halogenation. They are however not easy to work with because they easily hydrolyze when exposed to moisture. This research specifically addresses some of the above challenges by developing of new atom economical, stable, practical and environmentally benign hydrogen halide (bromide and chloride) reagents. These novel nucleophilic halogenating reagents will be explored for their application in halogenation reactions.

1.2. Hydrohalogenation

1.2.1 General

The addition of hydrogen halides to alkenes and alkynes is the most common and atom economical method of preparing halogenated alkanes and alkenes respectively. The addition reactions may proceed *via* a couple of pathways; first is the initial formation of a carbocation by bonding of the proton of the hydrogen halide to one of the carbons of the unsaturated system followed by the halide nucleophilic attack onto the carbocation²⁴. A second and closely related pathway involves an initial proton bonding followed by a simultaneous anion addition. This precludes a distinct carbocation formation^{24a, b, 25}. A third involves a $2\pi + 2\sigma$ addition (syn- or cis-)²⁶ (Figure 2). However, hydrogen halides are gases at ambient temperature. This also presents a challenge in their utility. Nonetheless, given their acceptable solubilities in organic solvents²⁷, various concentrations of aqueous and organic solutions of HX are commercially available (0.01 M to 12 M)²⁸. The choice of the hydrogen halide source is important based on the nature of the reaction type. For example, reactions that are moisture sensitive will require a non-aqueous source while proton sensitive reactions will require non-protic solvents. Also, high temperature dependent reactions will require HX solutions that have a

relatively higher heat capacity (the ethereal sources are very volatile). A worthwhile endeavor will be that which will provide an organic hydrogen halide source that will be tolerant over a wider range of reaction conditions, inexpensive and easy to make. We considered hydrogen bonding as the basis of our research to seek strong hydrogen bond acceptor compounds which will form stable complexes with HX molecules.

Figure 2. Pathways for HX addition across π -bonds of alkenes or alkynes

Based on extensive work reported by Abraham²⁹ and Laurence⁶ whereby the hydrogen bond ability of H-bonded complexes between anionic H-bond acceptors (HBAs) and neutral H-bond donors (HBDs) in organic solvents were quantified, a comprehensive database of hydrogen-bond basicity (pK_{BHX}) was established. On this database, a larger pK_{BHX} value indicates higher hydrogen-bond basicity or a better hydrogen bond acceptor characteristic. (Figure 3) Caution must be taken to not assume there is a simple correlation between the relative hydrogen-bond strength or hydrogen-

bond basicity with their basicity (pK_{aH}). The correlation may only hold true for closely related compounds in a series.

Figure 3. pK_{BHx} and pK_a Scale

For example, pyridine ($pK_{aH} = 5.2$) is a much stronger base than pyridine N-oxide ($pK_{aH} = 0.79$), but pyridine ($pK_{BHx} = 1.86$) is a weaker hydrogen bond acceptor than pyridine N-oxide ($pK_{BHx} = 2.72$).

1.2.2 Hydrofluorination

Hydrogen fluoride (HF) solutions have been made and found to have great utility in installing fluorine in molecules, significantly transforming their properties. These fluorinated compounds are biologically active and find applications in pharmaceutical drugs^{15b} (Figure 4). In functional materials, they are applied in ionic liquids³⁰, fluorinated graphene or fluorine-containing polymers³¹, water-proofing and non-stick coatings, such

as Teflon. The commercially available sources of HF solutions such as pyridine·HF (Olah's reagent) and triethylamine·HF though widely used still have some limitations in scope due to incompatibility with base sensitive substrates and in transition metal-catalyzed reactions where coordination with the metal reduces their reactivity³². With the development of a non-protic, non-basic and highly concentrated source of HF by our group, we found a way of circumventing some of the mentioned drawbacks. 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) is a non-basic and weakly coordinating (towards cationic metal) hydrogen bond acceptor that can form stable complexes through hydrogen bonding⁷ with HX molecules.

Figure 4. Examples of fluorine containing drugs

1.2.3. Hydrochlorination

Hydrogen chloride is a very common laboratory acid. It is a gas at room temperature that readily dissolves in water to be used for many chemical applications. It is used on an industrial scale for the purification of table salt, leather processing, removal of sulfur from petrol, hydraulic fracturing, gelatin production, in sanitation and for the synthesis of vinyl chloride; a monomer of plastic PVC (polyvinyl chloride).

The commercially available non-aqueous hydrogen chloride (HCl) solutions include HCl-ether and HCl-alcohol formulations whose maximum acid concentrations are 6 M. Due to the vast application of HCl in industry as a chlorinating source, a more concentrated source will reduce solvent waste. HCl is used in the chemical industry to produce a large variety of organic chlorinated compounds including fertilizers, dyes and the hydrochloride salts commonly used for drugs (Figure 5). In the metal industry, hydrometallurgical processes use hydrogen chloride to enhance the separation coefficient of ores and in electroplating. In the electronics industry, hydrogen chloride is used in semiconductor fabrication for etching of native oxide, CVD reactor cleaning or moisture getter³³ and materials industry in photographic, textile, and rubber products.

Figure 5. Examples of chlorine-containing drugs

1.2.4 Hydrobromination

Hydrogen bromide (HBr) is an important bromine source for many organic and inorganic compounds³⁴. The commercially available solutions of HBr are aqueous HBr (48 % w/w) or HBr in acetic acid (33 % w/w). The use of these solutions for brominating or hydrobromination often result in competing reactions between the bromide nucleophiles and solvent anions. An HBr/DMPU complex will provide another anhydrous source for

hydrogen bromide whose reactivity has not been explored before. Some examples of brominated natural products and drug molecules are given in Figure 6.

Figure 6. Examples of bromine containing compounds

1.3. Research aims

1.3.1. Aim 1: The controlled hydrobromination of unactivated alkynes and alkenes.

Although several easy-to-handle HBr reagents are available commercially or have been recently made,^{4e} none of them are good choices for general hydrobromination reactions due to scope limitations and competing reactions. Thus, we investigated synthesizing vinyl bromides and bromoalkanes from unactivated alkynes and alkenes using HBr/DMPU under metal-free and solvent-free conditions. HBr and DMPU form the room temperature-stable complex HBr/DMPU, providing a mild, effective and selective hydrobrominating reagent toward alkynes, alkenes and allenes.

1.3.2. Aim 2: A hydrogen-bond donor assisted Au-catalyzed hydrochlorination of unactivated alkynes.

Synthesizing vinyl chlorides from unactivated alkenes using HCl/DMPU with homogenous gold (I) chloride in a hydrogen-bond donor solvent, hexafluoroisopropanol (HFIP) is a novel approach that we aimed to develop. This highly regioselective homogeneous gold(I)-catalyzed *anti*-hydrochlorination of unactivated alkynes was studied at ambient temperature. We sought to overcome the incompatibility between conventional cationic gold catalysts and chloride by using a hydrogen bonding activation of Au-Cl bond. This approach was evaluated for scalability, functional group tolerance, and air sensitivity.

1.3.3. Aim 3: A metal-free chlorothiolation of alkenes.

We used HCl/DMPU and mild and non-toxic DMSO as source of thiomethyl moiety and explored its utility for the synthesis of β -chloromethylsulfides from alkenes. A novel method for the chlorothiolation of alkenes using HCl and sulfoxides to achieve the 1,2-difunctionalization of unactivated alkenes was investigated. The combination of our new HCl reagent (HCl/DMPU) with sulfoxides affords a unique chlorothiolation system. Alkene scope, gram scale and product applications was investigated.

1.3.4. Aim 4: Synthesis of 4-chloropiperidines from homoallylic amines via an aza-Pummerer approach.

We studied a substrate dependent variation of aim 3. Here, HCl/DMPU induced the formation of (thiomethyl)methyl carbenium ion from DMSO. Homoallylic amines reacted with the generated electrophile to afford 4-chloropiperidines in good yields. The applicability of the method was studied for both aromatic and aliphatic amines. The use of HCl/DMPU as both non-nucleophilic base and chloride source constitutes an

environmentally benign alternative for piperidine formation. The reaction scope, functional group tolerance and scalability was also investigated.

2. HBr/DMPU: THE FIRST APROTIC ORGANIC SOLUTION OF HYDROGEN BROMIDE

2.1 Background

Alkyl and alkenyl bromides are common substrates in a wide scope of transformations, including nucleophilic substitution reactions,³⁵ metallation reactions³⁶ and transition metal-catalyzed cross-coupling reactions.³⁷ Highly efficient synthetic approaches toward organic halides are in high demand because of their crucial role in synthesis. Electrophilic addition of hydrogen halides to alkenes and alkynes provides a uniformed approach toward branched alkyl and alkenyl halides, and is a model reaction in most textbooks of organic chemistry.³⁸ Compared with other approaches, including deoxyhalogenation,³⁹ Hunsdiecker reaction,⁴⁰ hydrometallation-electrophilic halogenation,⁴¹ olefin metathesis⁴² and transition metal-catalyzed hydrohalogenation,⁴³ the electrophilic addition of hydrogen halides is atom economical. However, to succeed in such transformation, handling gaseous hydrogen halides⁴⁴ with special and expensive equipment⁴⁵ is almost always required. While there may be other methods to achieving hydrobromination of alkynes and alkenes, these usually involve the use of less environmentally benign precursors, conditions and low atom economy.⁴⁶ Moreover, HBr addition to alkynes and alkenes in solution also results in uncontrollable radical-chain additions that give the anti-Markovnikov products.^{5, 47} We herein report the first room temperature stable solution of HBr in a neutral aprotic organic solvent - DMPU that expands the utility of HBr. This complex yielded a mild, effective and selective hydrobrominating reagent toward alkynes, alkenes and allenes. HBr/DMPU could also

replace other less atom-economic halogenating reagents in the halo-Prins reaction and deoxy-bromination reactions.

Of the commercially available HBr reagents or those recently made,^{4e} none are a good choice for a more general hydrobromination reaction due to scope limitations. Acetic acid solution of HBr is capable of hydrobrominating unsaturated hydrocarbons, but selectivity between hydrohalogenation and undesired hydroacetoxylation is poor,^{24c, 48} because of the weak, but still nucleophilic, acetate anion and the reduced nucleophilicity of halide anions in protic medium.^{24b, 49} In addition, the rearrangement of the intermediate carbocation is not uncommon.⁵⁰ Triphenylphosphine hydrobromide is known as an alternative HBr source, but triphenylphosphine tends to further react with formed alkyl bromides to produce phosphonium salts.⁵¹ Kropp *et al*⁶² in a minireview, highlighted a few applications of HBr with the aforementioned challenges. In this regard, HBr solution in a neutral aprotic medium would be the optimal choice to prevent competitive solvolysis reaction and to achieve high reactivity. However, the excess reactivity of HBr toward ethers and esters excludes ethereal and ester solvents. Inspired by the concept of hydrogen bond basicity (pK_{BHX}) that was first systematically summarized by Laurence,⁵³ we previously succeeded in a new formulation of hydrogen fluoride, HF-DMPU,⁵⁴ which exhibits a higher reactivity than its predecessors⁵⁵ in a wide scope of transformations. We hypothesized that DMPU could effectively form hydrogen bond complexes with HBr. In addition, DMPU is inert toward alkylation reactions, thus it should not compete with HBr.

2.2 Results and discussion

We were pleased to find that, by passing HBr gas through DMPU, we obtained a solution of HBr/DMPU in the form of a room temperature-stable liquid (Table 2, entry 3) with a higher mass percentage compared to other HBr solutions.

Table 2. Comparison of Different Formulation of Hydrogen Halide Solutions

Entry	Formulation	Mole ratio (HX:solvent)	pK_{BHX} of stabilizer
1	HBr/water, 48% ^[a]	0.21	0.65
2	HBr/AcOH, 33% ^[a]	0.36	N/A
3	HBr/DMPU, 58%	2.2	2.79

^[a] Commercially available.

We tested the reactivity of HBr-DMPU in hydrohalogenation reactions. HBr-DMPU showed a high reactivity toward alkyne **2-1a**. Under neat conditions, it completely converted **2-1a** into the hydrobromination product **2-2a** in 83% yield, without the formation of the 6-*exo-trig* cyclization product (eq 1).⁵⁶ Gram-scale reaction gave the same product in 85% isolated yield (eq 1). A small amount of *gem*-dibromide, because of a two-fold hydrobromination, was observed after extended reaction times. HBr-DMPU eliminated the use of gaseous HBr,^{44b} the competitive hydroacetoxylation reaction using HBr-HOAc^{48c} and avoided using a catalyst.^{43a, 57}

A wide scope of alkynes could react smoothly with HBr/DMPU under ambient conditions (Table 3).

Table 3. Hydrobromination of Alkynes

^a Reaction conditions: **1** (0.3 mmol), 0.15 mL of HBr/DMPU (58% w/w), room temperature, yields are isolated. ^b Reaction run at 70 °C

Homopropargyl ester **2-1b**, amide **2-1c** and imide **2-1d** afforded the corresponding 3-bromo-but-3-enyl ester **2-2b**, amide **2-2c** and imide **2-2d** in 82%, 83 % and 80% yields respectively, without any ester cleavage. Hex-5-ynoic acid **2-1e** and its nitrile **2-1f** also

yielded products **2-2e** and **2-2f** in 78 % and 89% respectively. Phenylacetylene, **2-1h**, yielded (1-bromovinyl)benzene and (2-bromovinyl)benzene in a 97:3 ratio with a combined 92 % yield. With internal alkynes, 1-phenylpropyne **2-1i** yielded a 3:2 mixture of α - and β -bromides **2-2i** with exclusive *Z*-configuration. The exclusive formation of *Z*-isomers (*trans* addition) indicated to us that this transformation follows an $\text{Ad}_{\text{E}3}$ mechanism⁵⁸ and the bromide concentration in the reaction medium is not low.⁵⁰ Hydrobromination of decyne **2-1j** provided **2-2j** in a similar yield. **2-1k** and **2-1l** yielded the corresponding hydrobromination product **2-2k** and **2-2l** in regioselective manner, albeit a lower selectivity for **2-2k**. This probably due to the diminished steric difference between methyl and bromomethyl.^{58a, 59} The predominant *Z*-isomer is inferred from a *trans* addition of HBr. We however, do not have experimental evidence of that. Diphenylacetylene (**2-1m**) yielded the *Z*-product in a modest 68 %. The unsymmetrical diaryl acetylene (**2-1n**) gave a 4.6:1 mixture of regioisomers. The reaction with derivatized amino acid (**2-1o**) and estrone (**2-1p**) also proceeded in 71 % and 95 % yields respectively, showing the wide applicability of this method.

Alkenes are also suitable substrates for HBr/DMPU hydrobromination (Table 4). Allylbenzenes **2-3a** to **2-3c** and tridecene **2-3e** afforded the corresponding Markovnikov hydrobromination products **2-4a**, **2-4b**, **2-4c** and **2-4e** in excellent yields. The reaction time of **2-3b** should be limited to 1 hour, since prolonged reaction times caused the demethylation of **2-4b**. Styrene **2-3d** was completely hydrobrominated, without the formation of commonly observed polymers.⁶⁰ Homoallyl amide **2-3f**, imide **2-3g** and ester **2-3h** afforded the corresponding hydrobromination products in good yield and with functional group tolerance. **2-4f** could be directly converted into azetidine **2-5** upon a treatment with sodium hydride in DMF (eq. 2). The hydrobromination of internal alkenes were partially successful. β -Methyl styrene **2-3i** and cyclohexene could be

hydrobrominated in quantitative yield, but several substrates could not be effectively hydrobrominated. For example, hydrobromination of α -methyl styrene **2-3k** could be only partially achieved, even after an extended reaction time or after adding extra loading of HBr/DMPU. The relative reactivity could be attributed to the highly conjugated system for the benzylic carbocation.

Table 4. Hydrobromination of Alkenes

^a Reaction conditions: **3** (0.3 mmol), 0.15 mL of HBr/DMPU (58% w/w), room temperature, yields are isolated. Numbers in parenthesis are NMR yields using CH₂Br₂ as an internal standard.

Hydrobromination of methyl cinnamate **2-3l** and stilbene **2-3m** was not successful due to their slow conversion, competition with undesired demethylation or easy loss of HBr during purification.

Alkynes are known to be less reactive than alkenes in a wide scope of electrophilic addition reactions,⁶¹ because of the anticipated highly energetic vinyl cation intermediate.^{58a} However, using HBr/DMPU, alkyne **2-1b** showed a faster conversion than alkene **2-1m** in both, parallel and competition experiments (Scheme 1).

Scheme 1. Reactivity comparison

Parallel experiments

Competition experiment

This inversed reactivity could be attributed to the high concentration of HBr in the reaction medium, signaling a reaction profile that is different from that in diluted reaction medium.⁶²

Scheme 2. Other synthetic reactions using DMPU-HBr

a) Bromo-Prins reaction

literature methods

DMPU-HBr

b) Bromination of alkyl alcohol

literature methods

2-8a, 48%

2-8b, >95%

c) Hydrobromination of allene

HBr/DMPU was shown to be very useful in other bromination reactions. For example, typical halogenating reagents employed in organic synthesis are gaseous hydrogen halides, metal halides (e.g. AlX₃, InX₃, NbX₅, GaX₃, FeX₃, SnX₄), sulfonyl halides, boron

halides, phosphorus halides or silicon halides (Scheme 2),⁶³ which either require special handling or produce large amounts of side products after the reaction, and each transformation requires a different halogenating reagent. HBr/DMPU, on the other hand, provided a uniform solution to all these transformations. It could substitute niobium and gallium halides in the bromo-Prins reaction (Scheme 2a).

It can also convert alkyl alcohols **2-7** into alkyl bromides **2-8**, with comparable yields thus replacing the corrosive PBr₃ (Scheme 2b).⁶⁴

Hydrobromination of allenic ester **2-9a** occurred with the regioselective protonation of the *sp*²-hybridized α -carbon, producing a β -vinylic cation that was further trapped by bromide to provide a vinyl bromide **2-9b** in 54% yield (Scheme 2c).⁶⁵ The reduced yield was primarily caused by cleavage of the benzyl group, since formation of benzyl bromide was observed on GC-MS.

2.3 Conclusion

In conclusion, HBr-DMPU is a good alternative to existing of hydrogen bromide solutions. Its advantages lie in the ease of handling, high HBr concentration, high reactivity towards the hydrobromination of alkenes and alkynes without competition reactions caused by rearrangement or solvolysis.

2.4 Experimental

2.4 1. General

GC-MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column,

HP-5MS). NMR spectra were recorded on 400 MHz instrument. The chemical shifts are reported in δ (ppm) values relative to CHCl_3 (δ 7.26 ppm for ^1H NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, J , are reported in Hertz. All air and/or moisture sensitive reactions were carried out under argon atmosphere. DMPU was received from commercial supplier and dried over molecular sieves. All other commercially available reagents and solvents were used without further purification. The products were purified using a CombiFlash system or a regular glass column chromatography. TLC was developed on Merck silica gel 60 F254 aluminum sheets. All NMR solvents were purchased from Cambridge Isotope Laboratories, Inc. Most products formed in this reaction have been reported in literature (references are found in the manuscript), hence we only used NMR to confirm their identities by comparison with the published spectra.

2.4.2. Reagent preparation

A general assembly is indicated below (Figure 7). All operations were conducted in well ventilated fume hoods.

Figure 7. Set-up for the preparation of HBr/DMPU

An argon inlet, a pressure-equalizing dropping funnel and inlet of a P₂O₅ gas washing tower are attached onto a 500 mL of three-neck round-bottom flask. One joint of another two-neck round-bottom receiving flask is connected to the outlet of a gas-washing tower, another joint of the same flask is attached to a drying tube.

After flushing the whole system by argon for 10 minutes, phosphorus pentoxide (500 g, 1.8 mol) and a stirring bar are added to the three-neck flask, hydrobromic acid (100 mL, 0.89 mol) is charged into a dripping funnel, and DMPU (10 mL, 82.7 mmol) and a tiny stirring bar are placed in the receiving flask. Both two flasks are cooled in ice-water bathes. The argon flow rate is maintained at 1 mL/min.

Hydrobromic acid (48%, w/w) is gradually dropped onto phosphorus pentoxide at a rate of 1 drop per 10 second, and an extremely exothermic reaction ensues. During absorption of HBr, the colorless DMPU turns into a viscous yellowish liquid and the receiving flask weighed periodically until there is no further increase in weight. The final weight of the solution is measured, and concentration reported as % w/w (58 % w/w).

The resulting HBr-DMPU solution is then pipetted into an argon-flushed glass vessel with PTFE-lined cap. This solution is fumes slightly but is relatively bench-stable for several months.

2.4.3. General procedure for Hydrobromination of Alkenes and Alkynes

To an argon-flushed 2-dram vial loaded with 0.3 mmol of alkene or alkyne, 0.15 mL of HBr-DMPU was added under stirring at room temperature. GC-MS and TLC monitored reaction progress. Once complete, the reaction mixture was quenched by adding 2 mL of saturated sodium bicarbonate solution and extracted by 2 mL of ethyl acetate over a vortex mixer for 3 times. To the combined extract, 1 gram of silica gel was added, and

the solvent was removed under a reduced pressure. The final product was purified by flash column chromatography using ethyl acetate-hexane eluent.

2.4.4. General procedure for bromo-Prins cyclization reaction

Homoallylic alcohol (43 μ L, 0.5 mmol) and aldehyde (0.5 mmol) were dissolved in 0.5 mL dichloromethane, then HBr-DMPU was added to the mixture and was stirred at room temperature. Upon completion, the reaction the mixture was quenched with cold water and the organic phase was extracted with chloroform. The organic phase was washed with aqueous sodium bicarbonate, and brine, dried over sodium sulfate and was concentrated to dryness in vacuum. The crude product purified by column chromatography with a 10:1 mixture of hexanes and EtOAc to afford the desired product.

2.4.5. Product characterization

2-2a

^1H NMR (400 MHz, CDCl_3) δ 7.30 (t, J = 7.5 Hz, 2H), 7.19 (d, J = 7.4 Hz, 3H), 5.58 (s, 1H), 5.43 (s, 1H), 2.64 (t, J = 7.8 Hz, 2H), 2.46 (t, J = 7.4 Hz, 2H), 1.91 (p, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, CDCl_3)** δ 141.7, 134.3, 128.5, 128.4, 125.9, 116.8, 40.8, 34.5, 29.5.⁶⁶

2-2b

52.3 mg of Homopropargyl benzoate reacted with DMPU-HBr under standard conditions afforded 62.7 mg of **2c** in 82% yield.

¹H NMR (400 MHz, CDCl₃) δ 8.11 – 7.95 (m, 2H), 7.64 – 7.53 (m, 1H), 7.51 – 7.38 (m, 2H), 5.80 – 5.65 (m, 1H), 5.54 (d, *J* = 1.7 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.3 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 133.0, 133.1, 129.6, 129.4, 128.4, 119.1, 62.2, 40.7. **HR-MS (ESI):** Exact Mass Calcd for C₁₁H₁₁BrNaO₂ ([M+Na]⁺): 276.98401 Found: 276.98369.

2-2c

44.7 mg of *N*-Toluenesulfonyl homopropargyl amide reacted with HBr-DMPU under standard conditions afforded 50.6 mg of **2d** in 83% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.94 – 7.61 (m, 1H), 7.41 – 7.18 (m, 1H), 5.58 (s, 0H), 5.46 (s, 0H), 4.74 (s, 0H), 3.26 – 3.02 (m, 1H), 2.55 (t, *J* = 6.3 Hz, 1H), 2.42 (s, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 143.6, 136.9, 129.8, 129.6, 127.0, 120.0, 41.3, 40.9. **HR-MS (ESI):** Exact Mass Calcd for C₁₁H₁₄BrNNaO₂S ([M+Na]⁺): 325.98263 Found 325.89250.

2-2d

59.8 mg of Homopropargyl phthalimide reacted with HBr-DMPU under standard conditions yielded 67.5 mg of **2e** in 80% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.84 (dd, *J* =

5.4, 3.1 Hz, 2H), 7.71 (dd, $J = 5.5, 3.0$ Hz, 2H), 5.61 (d, $J = 1.6$ Hz, 1H), 5.44 (d, $J = 1.8$ Hz, 1H), 3.93 (t, $J = 6.9$ Hz, 2H), 2.84 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 134.0, 131.9, 129.7, 123.3, 119.2, 40.0, 36.5.

2-2e

56.1 mg of 5-hexynoic acid reacted with HBr-DMPU under standard conditions afforded 77.2 mg of **2f** in 80% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.26 (s, 1H), 5.66 – 5.56 (m, 1H), 5.48 – 5.33 (m, 1H), 2.50 (t, $J = 7.5$ Hz, 2H), 2.39 (t, $J = 7.4$ Hz, 2H), 1.91 (p, $J = 7.1$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 179.2, 133.1, 117.6, 40.3, 32.2, 22.7.

2-2f

46.6 mg of 5-cyanopentyne reacted with with HBr-DMPU under standard conditions afforded 67.8 mg of **2g** in 78% yield. ^1H NMR (400 MHz, CDCl_3) δ = 5.70 (d, $J=1.1$, 1H), 5.50 (s, 1H), 2.60 (t, $J=6.9$, 2H), 2.38 (ddd, $J=7.0, 4.2, 1.3$, 2H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 131.4, 118.9, 39.6, 23.3, 15.6.

2-2g

122 mg of non-8-yn-1-yl benzoate reacted with HBr-DMPU under standard conditions provided 144.7 mg of **2h** in 89% yield. **¹H NMR (400 MHz, CDCl₃)** δ = 8.03 (d, J =7.3, 2H), 7.54 (t, J =7.4, 1H), 7.43 (t, J =7.6, 2H), 5.53 (s, 1H), 5.36 (s, 1H), 4.30 (t, J =6.6, 2H), 2.39 (t, J =7.4, 2H), 1.81 – 1.69 (m, 2H), 1.60 – 1.18 (m, 14H). **¹³C NMR (100 MHz, CDCl₃)** δ 166.7, 134.9, 132.8, 130.5, 129.5, 128.3, 116.2, 65.1, 41.4, 29.3, 28.7, 28.3, 27.8, 26.0.

2-2h

32.9 μ L of phenylacetylene reacted with HBr-DMPU under standard conditions provided 168.4 mg of **2h** in 92% yield. **¹H NMR (400 MHz, CDCl₃)** δ = 7.58 (d, J =5.6, 2H), 7.33 (m, 3H), 6.11 (d, J =1.9, 1H), 5.77 (d, J =1.9, 1H). **¹³C NMR (100 MHz, cdcl₃)** δ 138.5, 133.8 129.1, 128.2, 127.3, 117.7.

2-2i- α and 2-2i- β

46.5 mg of 1-Phenyl prop-1-yne reacted with HBr-DMPU under standard conditions provided 72 mg of **2i** in 90% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.61 – 7.49 (m, 2H), 7.39 – 7.27 (m, 3H), 6.74 (s, 0.42H for **2i- β**), 6.29 (q, J = 6.6 Hz, 0.67H for **2i- α**), 2.50 (d, J = 1.4 Hz, 1.4H for **2i- β**), 1.96 (d, J = 6.6 Hz, 2.1H for **2i- α**). **¹³C NMR (100 MHz, CDC₃)**

δ 140.1, 128.7, 128.2, 128.1, 127.9, 127.5, 127.5, 126.6, 126.3, 126.2, 121.9, 30.7, 18.2.⁶⁷

2-2j

Reaction of 73.4 μ L of 4-octyne reacted with HBr-DMPU under standard conditions afforded 85 mg of **2j** in 89% yield. **¹H NMR (700 MHz, CDCl₃)** δ = 5.61 (t, J =6.8, 1H), 2.38 (t, J =7.2, 2H), 2.12 (q, J =7.1, 2H), 1.59 – 1.52 (m, 2H), 1.41 (dd, J =14.8, 7.4, 2H), 0.89 (dt, J =25.6, 7.4, 6H). **¹³C NMR (176 MHz, CDCl₃)** δ 128.5, 128.2, 43.5, 33.3, 21.8, 21.3, 13.7, 12.8.

2-2k

Reaction of 43.8 μ L mg of 1-bromo-2-butyne reacted with HBr-DMPU under standard conditions afforded 94.1 mg of **2k** in 88% yield. **¹H NMR (400 MHz, CDCl₃)** δ 5.97 (ddd, J =7.9, 4.6, 1.3, 1H), 4.04 (dd, J =7.8, 0.7, 2H), 2.39 – 2.30 (m, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 128.7, 124.9, 30.3, 28.9.

2-2l

Reaction of 82.6 μL of ethylphenylpropiolate reacted with HBr-DMPU under at 70 °C to afford 94.4 mg of **2l** in 74% yield. **^1H NMR (400 MHz, CDCl_3)** δ = 7.69 – 7.55 (m, 2H), 7.45 – 7.33 (m, 3H), 6.72 (s, 1H), 4.28 (q, J =7.1, 2H), 1.34 (t, J =7.2, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 164.4, 139.3, 130.4, 128.5, 128.1, 120.4, 60.7, 14.2.

2-2m

Reaction of 35.6 mg of diphenylacetylene reacted with HBr-DMPU at 70 °C to afford 35.2 mg of **2m** in 68% yield. **^1H NMR (400 MHz, CDCl_3)** δ 7.70 (d, J = 7.8 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H), 7.43 – 7.29 (m, 6H), 7.21 (s, 1H). **^{13}C NMR (100 MHz, CDCl_3)** δ 141.0, 136.3, 130.0, 129.9, 129.2, 128.7, 128.2, 127.8, 124.0.

2-2n

Reaction of 98.1 mg of 1-fluoro-4-(phenylethynyl) benzene reacted with HBr-DMPU at 70 °C to afford 103.9 mg of **2n** in 75% yield. **^1H NMR (400 MHz, CDCl_3)** δ 7.17 - 7.61 (m, 4H), 7.43 – 7.30 (m, 3H), 7.16 (s, 1H), 7.11 - 7.04 (m, 2H). **^{13}C NMR (100 MHz, CDCl_3)** δ 131.1, 129.9, 129.5, 129.1, 128.8, 128.4, 128.2, 127.7, 115.3, 115.1. **^{19}F NMR (376 MHz, CDCl_3)** δ -112.80.

2-2o

Reaction of 54.7 mg of (S)-methyl 2-(hex-5-ynamido)-3-phenylpropanoate reacted with HBr-DMPU under standard conditions afforded 50.3 mg of **2o** in 71% yield. **¹H NMR (400 MHz, DMSO-*d*6)** δ 12.63 (s, 1H), 8.18 (d, $J=8.2$, 1H), 7.36 – 6.96 (m, 5H), 5.60 (s, 1H), 5.38 (d, $J=1.7$, 1H), 4.40 (td, $J=10.0$, 4.5, 1H), 3.04 (dd, $J=13.8$, 4.6, 1H), 2.80 (dd, $J=13.8$, 10.2, 1H), 2.51 – 2.46 (m, 2H), 2.26 (t, $J=7.7$, 2H), 2.04 (dd, $J=11.6$, 7.6, 2H), 1.60 (dd, $J=13.7$, 6.4, 2H). **¹³C NMR (100 MHz, DMSO-*d*6)** δ 173.7, 172.0, 138.2, 134.1, 129.5, 128.6, 126.8, 118.1, 53.7, 40.6, 40.3, 39.9, 39.6, 39.3, 37.1, 33.8, 23.9.

2-2p

Reaction of 75.7 mg of (8R,9S,13S,14S)-3-(but-3-yn-1-yloxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one reacted with HBr-DMPU under standard conditions to afford 87.3 mg of **2p** in 95% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.19 (d, $J=8.6$, 1H), 6.70 (dd, $J=8.6$, 2.2, 1H), 6.64 (s, 1H), 5.55 (s, 1H), 5.38 (s, 1H), 3.93 (q, $J=6.1$, 2H), 2.89 (dd, $J=10.8$, 4.6, 2H), 2.54 – 1.91 (m, 10H), 1.81 – 1.24 (m, 14H), 0.90 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 221.0, 157.1, 137.7, 134.7, 131.8, 126.3, 116.4, 114.5, 112.1, 67.7, 52.8, 50.4, 48.0, 44.0, 41.3, 38.4, 35.9, 31.6, 29.7, 29.2, 28.4, 28.1, 26.6, 25.9, 21.6, 13.9.

2-4a

Reaction of 23.8 mg allylbenzene with HBr-DMPU under standard conditions yielded 32.6 mg of **4b** in 83% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.36 – 7.29 (m, 2H), 7.29 – 7.26 (m, 1H), 7.22 – 7.18 (m, 2H), 4.31 (m, 1H), 3.23 (dd, J = 14.0, 7.0 Hz, 1H), 3.07 (dd, J = 14.0, 7.3 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.5, 129.2, 128.4, 126.8, 50.5, 47.5, 25.7.⁶⁸

2-4b

Reaction of 29.6 mg 4-allyl anisole with HBr-DMPU under standard conditions after 1 hour afforded 40.2 mg of **4c** in 87% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.14 – 7.12 (m, 2H), 6.87-6.85 (m, 2H), 4.27 (m, 1H), 3.80 (s, 3H), 3.17 (dd, J = 14.1, 6.9 Hz, 1H), 3.01 (dd, J = 14.1, 7.3 Hz, 1H), 1.69 (d, J = 6.6 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 158.5, 130.6, 130.2, 113.8, 51.1, 46.6, 25.5.⁶⁹

2-4c

Reaction of 30.3 mg 3-(4-fluorophenyl) propene with HBr-DMPU under standard conditions yielded 39.8 mg of **4d** in 92% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.24 – 7.11 (m, 2H), 7.09 – 6.90 (m, 2H), 4.35 – 4.15 (m, 1H), 3.17 (dd, J = 14.2, 7.3 Hz, 1H), 3.06

(dd, $J = 14.2, 6.8$ Hz, 1H), 1.70 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 161.8, 134.1, 130.7, 115.2, 50.5, 46.5, 25.6.⁷⁰ ^{19}F NMR (376 MHz, CDCl_3) δ -116.03.

2-4d

Reaction of 20.8 mg styrene with HBr-DMPU under standard conditions yielded 30.7 mg of **4d** in 83% yield after chromatography purification. ^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.42 (m, 2H), 7.38 – 7.32 (m, 2H), 7.31 – 7.26 (m, 1H), 5.22 (q, $J = 6.9$ Hz, 1H), 2.06 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 128.7, 128.3, 126.8, 49.6, 26.8.⁷¹

2-4e

Reaction of 36.4 mg of tridecene with HBr-DMPU under standard conditions yielded 43.1 mg of **4f** in 82% yield. ^1H NMR (400 MHz, CDCl_3) δ 4.21 – 4.05 (m, 1H), 1.89 – 1.76 (m, 2H), 1.70 (d, $J = 6.6$ Hz, 3H), 1.26 (s, 20H), 0.88 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 52.0, 41.2, 31.9, 31.6, 29.6, 29.6, 29.5, 29.3, 29.1, 29.0, 22.7, 22.6, 14.1.

2-4f

Reaction of 45.1 mg *N*-homoallyl sulfonamide with HBr-DMPU under standard conditions yielded 53.2 mg of **4g** in 87% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.84 (t, *J* = 6.5 Hz, 1H), 4.13 (ddt, *J* = 9.7, 6.7, 3.8 Hz, 1H), 3.28 – 2.98 (m, 2H), 2.43 (s, 3H), 2.05 – 1.95 (m, 1H), 2.13 – 1.80 (m, 1H), 1.67 (d, *J* = 6.7 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 143.5, 136.7, 129.8, 127.1, 127.0, 47.8, 41.7, 40.6, 26.4, 21.5.

2-4g

Reaction of 40.2 mg homoallyl phthalimide and HBr-DMPU under standard conditions yielded 48.8 mg of **2-4h** in 86% yield. **¹H NMR (400 MHz, CDCl₃)** δ 7.89 – 7.77 (m, 2H), 7.74 – 7.66 (m, 2H), 4.20 – 4.00 (m, 1H), 3.88 (ddd, *J* = 14.0, 7.5, 6.6 Hz, 1H), 3.80 (ddd, *J* = 13.9, 7.6, 6.8 Hz, 1H), 2.30 – 2.07 (m, 2H), 1.75 (d, *J* = 6.6 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 168.2, 134.0, 132.0, 123.3, 47.3, 39.4, 36.6, 26.4.⁷²

2-4h

Reaction of 35.2 mg of homoallyl benzoate with HBr-DMPU under standard conditions yielded 47.2 mg of **2-4i** in 92% yield. **¹H NMR (400 MHz, CDCl₃)** δ 8.15 – 7.91 (m, 2H), 7.64 – 7.51 (m, 1H), 7.50 – 7.36 (m, 2H), 4.54 (dt, *J* = 11.2, 5.6 Hz, 1H), 4.44 (ddd, *J* = 11.3, 7.8, 5.7 Hz, 1H), 4.30 (td, *J* = 8.7, 6.8, 4.9 Hz, 1H), 2.38 – 2.11 (m, 2H), 1.79 (d, *J* = 6.7 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 166.3, 133.0, 130.0, 129.6, 128.4, 63.0,

46.9, 39.8, 26.6. **HR-MS (ESI):** Exact Mass Calcd for $C_{11}H_{13}BrNaO_2$ ($[M+Na]^+$): 278.99966 Found 278.99940.

Cyclization of 2-4f

30 mg of **2-4f** was dissolved in 1 mL of DMF and the solution was stirred in an ice bath for 10 minutes. 12 mg of sodium hydride was added in one portion. Reaction was continued for 1 hour and quenched by addition of 1 mL of brine. To reaction mixture, silica was added and dried over a rotary evaporator. Final product was obtained after a flash column chromatography.

2-5

1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 2H), 7.42 – 7.29 (m, 2H), 4.03 – 3.83 (m, 1H), 3.67 (dd, J = 8.0, 3.6 Hz, 1H), 3.48 (q, J = 8.7 Hz, 1H), 2.44 (s, 3H), 2.05 – 1.91 (m, 1H), 1.92 – 1.83 (m, 1H), 1.39 (d, J = 6.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 132.1, 129.7, 128.4, 125.4, 60.3, 60.2, 47.4, 24.06, 22.3. **HR-MS (ESI):** Exact Mass Calcd for $C_{11}H_{15}BrNaO_2$ ($[M+Na]^+$): 248.07212 Found 248.07240.

2-6a

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.32 (m, 5H), 4.33 (dd, *J* = 11.2, 2.1 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.16 (ddd, *J* = 12.0, 4.8, 1.7 Hz, 1H), 3.60 (td, *J* = 12.0, 2.4 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.30 – 2.18 (m, 2H), 2.11 – 2.05 (m, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 141.1, 128.5, 127.9, 125.8, 80.2, 68.2, 46.4, 45.5, 37.7.

2-6b

¹H NMR (400 MHz, CDCl₃) δ = 7.60 (d, *J*=8.0, 2H), 7.44 (d, *J*=8.0, 2H), 4.39 (d, *J*=11.0, 1H), 4.28 (dd, *J*=14.1, 9.8, 1H), 4.17 (dd, *J*=12.0, 3.0, 1H), 3.60 (t, *J*=12.1, 1H), 2.48 (d, *J*=12.9, 1H), 2.27 (d, *J*=13.2, 1H), 2.21 – 2.08 (m, 1H), 2.00 (dd, *J*=24.2, 12.0, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ = 145.1, 129.8, 125.9, 125.4, 122.7, 79.5, 68.2, 45.6, 37.5. **¹⁹F NMR (376 MHz, CDCl₃)** δ = -62.58.

2-6c

¹H NMR (400 MHz, CDCl₃) δ = 7.89 – 7.72 (m, 4H), 7.45 (t, *J*=7.2, 3H), 4.50 (d, *J*=11.4, 1H), 4.34 (t, *J*=12.1, 1H), 4.20 (d, *J*=11.9, 1H), 3.66 (t, *J*=12.0, 1H), 2.57 (d, *J*=12.3, 1H), 2.35 – 2.06 (m, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.5, 133.3, 133.0, 128.3, 128.2, 127.9, 127.6, 126.1, 125.9, 124.5, 123.8, 80.2, 68.3, 46.4, 45.5, 37.7.

2-9b

Reaction of 40.5 mg allene **3a** with HBr-DMPU under standard conditions afforded 30.5 mg of **4a** in 54% yield. ^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.29 (m, 5H), 5.17 (s, 2H), 3.63 (s, 2H), 1.92 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 135.7, 135.3, 128.5, 128.2, 128.1, 110.6, 66.7, 43.4, 20.7.

2.4.6. ^1H , ^{13}C and ^{19}F NMR Spectra

2-2a

2-2b

2-2i and 2-2i'

2-4a

2-4a

2-4b

2-4b

7.76
7.74
7.33
7.31
4.89
4.88
4.86
4.16
4.15
4.14
4.13
4.12
4.11
3.17
3.15
3.15
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3.09
3.08
3.07
2.43
2.01
2.00
1.99
1.98
1.97
1.96
1.92
1.92
1.91
1.91
1.90
1.89
1.88
1.88
1.87
1.68
1.66
1.66

3. CHLORIDE-TOLERANT GOLD(I) CATALYZED REGIOSELECTIVE HYDROCHLORINATION OF ALKYNES

3.1 Background

Chlorination is one of the most important transformations in organic synthesis because of the biological activities and synthetic value of the chlorinated products.¹ More specifically, vinylchloride is one of the most important group of chlorine-containing compounds. Vinylchlorides are widely found in natural products, pharmaceuticals and agrochemicals,^{1, 73} and also are valuable coupling partners in coupling reactions such as Buchwald-Hartwig amination⁷⁴ and Suzuki-Miyaura coupling.⁷⁵ Compared to the traditional syntheses of vinylchlorides, such as halogenations of carbonyl compounds^{67b, 76} and electrophilic chlorination of alkynes,⁷⁷ the direct hydrochlorination of alkynes from HCl is a straightforward and atom-economic method. However, given that HCl itself is a dangerous gas and handling is problematic, synthetic chemists have focused on indirect hydrochlorination strategies for activated alkynes,^{4a, b, 78} using RCOCl, TMSCl or metal chlorides as chlorine sources (Scheme 3a).^{4d, 79} One notable example is the recent work by Engle and coworkers on the palladium-catalyzed *anti*-hydrochlorination of alkynes using a directing group (Scheme 3b).⁸⁰ The direct hydrochlorination of unactivated alkynes using HCl has been rarely reported. Dai and coworkers found that gaseous HCl could hydrochlorinate electron-rich phenylacetylenes but the use of gaseous HCl, and hydration side products present major drawbacks.⁸¹ Derien and coworkers developed a ruthenium-catalyzed hydrochlorination of alkynes that gave good yields (Scheme 3c).^{43a} Although this method works well for terminal alkynes, higher temperature was needed

and low stereoselectivity was observed for internal alkynes. Moreover, a restrictive Schlenk environment was essential.

Scheme 3. Major synthetic methods for chlorination of alkynes to synthesize vinylchlorides

a) Indirect hydrochlorination of activated alkynes

b) Regioselective hydrochlorination of alkynes facilitated by directing groups

c) Ruthenium catalyzed hydrochlorination of unactivated alkynes

d) Heterogeneous gold catalyzed hydrochlorination of unactivated alkynes

e) This work: chloride-tolerant gold(I) catalyzed hydrochlorination of alkynes

The heterogeneous gold catalyzed hydrochlorination of acetylene for manufacture of vinyl chloride monomer (VCM) is a well-studied process,⁸² and has been industrialized recently (Scheme 3d).⁸³ Recently, and independently, Corma group⁸⁴ and our group⁸⁵ reported a heterogeneous gold (TiO₂/Au) catalyzed hydrochlorination reaction of alkynes. Although good *syn*-addition selectivity was observed, high temperatures were

needed (Scheme 3d). Though homogeneous cationic gold catalysts are considered as the most powerful catalysts for the electrophilic activation of alkynes,⁸⁶ the cationic gold-catalyzed hydrochlorination of alkynes has not been reported because of the high affinity between cationic gold and chloride.⁸⁷ Indeed, commonly used gold pre-catalysts, such as PPh_3AuCl , usually need silver salts to break the strong Au-Cl bond and release an active cationic gold species and chloride is known to easily poison cationic gold species (Scheme 4a).⁸⁸ We are now pleased to report a homogenous gold-catalyzed alkyne hydrochlorination with exclusive *anti*-selectivity that overcomes the incompatibility between cationic gold catalysts and chloride (Scheme 3e).

We proposed that a combination of strong hydrogen bond donor solvents such as hexafluoroisopropanol (HFIP), and HCl would generate a strong hydrogen bonding donor network **A**, and that the hydrogen bonding between chlorine in L-Au-Cl and **A** might weaken the Au-Cl bond (Scheme 4b). This would generate a partially cationic gold species **B** via hydrogen bonding interaction. This strategy would avoid the use of a silver salt to activate the gold pre-catalyst, a step that is known to exert negative effects in gold catalysis.⁸⁹

Scheme 4. Conventional cationic gold catalysis and chloride-tolerant homogenous gold catalysis

$$\text{L-Au-Cl} \xrightarrow{\text{AgX}} \text{L-Au}^{\oplus} \text{X}^{\ominus} \xrightarrow{\text{Cl}^-} \text{L-Au-Cl}$$

strong cationic character;
not tolerant towards chloride X = OTf⁻, SbF₆⁻ ... L = Ligand

$$m \text{ HCl} + n \text{ HFIP} \longrightarrow (\text{HCl})_m(\text{HFIP})_n \xrightarrow{\text{L-Au-Cl}} \text{L-Au}^{\delta+}\cdots\text{Cl}^{\delta-} \cdots (\text{HCl})_m(\text{HFIP})_n$$

$\text{HFIP} = \text{F}_3\text{C}-\text{CH}(\text{OH})-\text{CF}_3$

weaker cationic character;
 chloride tolerated gold specie

We used 4-phenylbutyne **3-1a** as the model substrate for reaction optimization. We screened various ligands, HCl sources and solvents (Table 5). Due to its high hydrogen bond basicity but low Brønsted basicity,^{90,6} DMPU is able to form a stable and highly concentrated complex with hydrogen chloride (HCl).¹⁵ Using 1.5 equiv of HCl/DMPU and 2 mol % of gold catalyst and various ligands (**3-L1** to **3-L6**) led to high yields of product (Table 5, entries 1-6). However, the *anti*-Markovnikov and dichlorinated products were also obtained in varying amounts. The use of **3-L5** improved the selectivity of the produced vinylchloride to 95 % yield, needing only 1.2 equiv of HCl/DMPU (Table 5, entry 7). Formation of the dichlorinated byproduct was avoided by running the reaction at ambient temperature (Table 5, entry 8-9), with both **3-L5** and **3-L6** working equally well. A poor yield was obtained in the absence of gold (Table 5, entry 10). Notably, lower selectivity and poor yields were observed when commercially available HCl sources (HCl/PrOH and HCl/ether) were used (Table 5, entries 11 and 12). We screened other solvents to further optimize the regioselectivity. We found that a 1:1 HFIP: CH₃NO₂ mixture provided optimal conditions. It is worth noting that *tert*-butanol and THF gave substantial amounts to the corresponding ketone.

Table 5. Screening of homogeneous gold catalyzed hydrochlorination of alkynes

Entry	L	m	HCl	Solvent	Yield (%) ^a	Ratio of 2a:2a':3a
1	L1	1.5	HCl/DMPU	HFIP	80	75:8:17
2	L2	1.5	HCl/DMPU	HFIP	55	76:9:15
3	L3	1.5	HCl/DMPU	HFIP	65	90:8:2
4	L4	1.5	HCl/DMPU	HFIP	38	82:9:9
5	L5	1.5	HCl/DMPU	HFIP	95	93:4:3
6	L6	1.5	HCl/DMPU	HFIP	96	90:7:3
7	L5	1.2	HCl/DMPU	HFIP	95	95:4:1
8 ^b	L5	1.2	HCl/DMPU	HFIP	98	97:3: -
9 ^b	L6	1.2	HCl/DMPU	HFIP	95	97:3: -
10	-	2.4	HCl/DMPU	HFIP	34	59:16:25
11 ^b	L5	1.2	HCl/ <i>i</i> PrOH	HFIP	72	88:12: -
12 ^b	L5	1.2	HCl/Et ₂ O	HFIP	<5	n. a.
13 ^{b, c}	L6	1.2	HCl/DMPU	<i>t</i> BuOH	85	51: -: -
14 ^{b, c}	L6	1.2	HCl/DMPU	THF	78	82:8: -
15 ^{b, d}	L6	1.2	HCl/DMPU	HFIP/MeNO ₂	97	99:1: -
16 ^{b, d}	L6	1.2	HCl/DMPU	HFIP/ DMF	93	98:2: -

^aYields were determined by GC-MS using dodecane as internal standard. ^bReaction run at rt for 24 h.

^cKetone product formed (accounts for the remaining ratio of product). ^dSolvent mixture is 1:1 by volume.

A 1:1 HFIP: DMF combination worked well also (Table 5, entry 16). With optimized conditions in hand, we investigated the substrate scope (Table 6). We first examined the scope of aliphatic alkynes. A wide variety of terminal alkynes reacted smoothly to give the corresponding vinylchlorides in good to excellent yields. Nitrile (**3-2b**), ester (**3-2d**), imide (**3-2e**), sulfide (**3-2f**), amide (**3-2u**), and ketone ether (**3-2v**) functional groups were well tolerated under the standard conditions. The reaction with derivatized amino acid (**3-2u**) and the natural product estrone (**3-2v**) led to the corresponding products in 69 % and 95 % yield, respectively. The internal alkyne 4-octyne (**3-2c**) also worked well, although higher temperature and longer reaction time were needed. When we explored the scope of arylacetylenes we found good to excellent yields using electron-rich and electron-deficient arylacetylenes. *Para* (**3-1h**), *meta* (**3-1i**) and *ortho* (**3-1j**) tolylacetylenes furnished the corresponding vinylchlorides in excellent yields. It is worth noting that electron deficient arylacetylenes gave increasing amounts of the anti-Markovnikov products (**3-2n**, **3-2o**, **3-2p**, and **3-2q**). A remarkable example was the heteroaromatic alkyne 2-ethynylpyridine (**3-1r**), which was expected to quench the reactivity of homogenous cationic gold due to its basic nature, but under our conditions, **3-1r** furnished the anti-Markovnikov vinylchloride (**3-2r**) in 70 % yield. The pyridinyl nitrogen acting as a directing group and coordinating with HCl or gold could have caused the change of regioselectivity in **3-2r**. 3-Ethynylthiophene (**3-1s**) gave an excellent yield of the corresponding chloro product. The electron deficient internal alkyne ethylphenylpropiolate (**3-1t**) also worked well, albeit a higher temperature (75°C) was needed, and the yield was modest (66%). In this case, a mixture of E/Z isomers was obtained, possibly due to the isomerization caused by the elevated temperature. It should be noted that our homogenous gold catalyzed reaction required milder conditions (room temperature) than the recently reported heterogeneous gold catalyzed process, and that the stereochemistry of the addition was different.⁸⁴

Table 6. Substrate scope of homogeneous gold catalyzed hydrochlorination of alkynes

^aReaction conditions: alkyne **1** (0.5 mmol), HCl/DMPU (1.2 equiv), **L6**AuCl (2 mol %), HFIP:CH₃NO₂ (0.125 mL) at rt for 16-36 h. Isolated yields. ^b75 °C was used.

Due to the milder conditions of our reaction, we expected better functional group tolerance. Indeed, the peptide (**3-2u**) and derivatized estrone (**3-2v**) were tolerated under our conditions. The homogenous gold process gave the *anti*-addition pattern (Table 6, **3-2c** and **3-2r**), which is consistent with typical homogeneous gold catalysis

where cationic gold activates alkyne substrates. On the other hand, the nanogold catalyzed process gave *syn*-addition products, which suggests that nano-gold initially activates HCl rather than the alkyne.⁸⁴

Scheme 5. Gram-scale synthesis and the synthetic utility of vinylchlorides

Our strategy for the hydrochlorination of unactivated alkynes was easily expanded to large-scale synthesis, without affecting yield and regioselectivity (Scheme 5a). To examine the synthetic value of the synthesized vinylchlorides, we conducted two classic reactions that use vinyl chlorides as building blocks, namely the Suzuki coupling and the Buchwald–Hartwig amination. In both cases, the desired products were isolated in good yields (Scheme 5b and Scheme 5c).

3.3. Conclusion

In conclusion, we have accomplished the first efficient regioselective homogeneous gold-catalyzed hydrochlorination of unactivated alkynes. We have overcome the

traditional incompatibility between conventional cationic gold catalysts and chloride. This method can be easily scaled up, and the reactions can be conducted in the open air.

3.4. Experimental

3.4.1. General

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz using CDCl_3 as a solvent. The chemical shifts are reported in δ (ppm) values (^1H and ^{13}C NMR relative to CHCl_3 , δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR and CFCl_3 (δ 0 ppm for ^{19}F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants (J), are reported in Hertz (Hz). All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was developed on silica gel 60 F254 aluminum sheets. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without any further purification.

3.4.2. Reagent preparation

A general assembly is indicated below. All operations were conducted in well ventilated fume hoods.

Figure 8. Set-up for the preparation of HCl/DMPU

A pressure-equalizing dropping funnel and inlet of a drying tube packed with CaCl_2 were attached onto a 500 mL of two-neck round-bottom flask. The outlet of the drying tube was attached to one joint of 100 mL two-neck round-bottom flask through tubing; a 5'' pipette was attached to the end of the tubing. The other joint of the same flask was attached to the second drying tube connected to a base bath (Figure 8). After flushing the whole system by argon for 10 minutes, sodium chloride and a stirring bar were placed in the 500 mL two-neck flask, the dropping funnel was charged with concentrated sulfuric acid, and DMPU and a small stirring bar were placed in a 100 mL receiving flask. Both flasks were cooled in ice-water baths. Concentrated sulfuric acid was then gradually dropped onto sodium chloride at a rate of one drop per second, and an extremely exothermic reaction took place. During the absorption of HCl, the colorless DMPU turned into a viscous yellowish liquid. The obtained HCl/DMPU solution was pipetted into an argon-flushed glass vessel with PTFE-lined cap. The concentration of the generated HCl/DMPU was approximately 43% by weight. This solution is slightly fuming but stable over months on a lab bench.

3.4.3. Synthesis of gold complexes (L-AuCl)

All gold complexes (L-AuCl) were synthesized using a slightly modified version of a literature method.⁹¹ These complexes were prepared via either one of the following general procedures, and the characterization of these gold complexes were previously reported by us.⁹²

Method 1: Sodium tetrachloroaurate(III) dihydrate (1 mmol) was dissolved in water, and the orange solution was cooled in ice. To this solution, 2,2'-thiodiethanol (3 mmol) was slowly added (ca. 10 min) with stirring. After stirring at 0°C for another 30 min, a solution of the phosphine ligand (1 mmol) in EtOH (if the ligand could not be dissolved, more

EtOH was used) was added dropwise to yield a white solid. The solid was filtered off, washed with water followed by EtOH, and ultimately dried in vacuum.

Method 2: Chloro(dimethylsulfide)gold(I) (1 mmol) was dissolved in dichloromethane in a vial and cooled in an ice bath. A solution of phosphine ligand (1 mmol) in dichloromethane was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred at room temperature for 3 h. After TLC indicated complete consumption of the starting material, the reaction solution was concentrated to dryness in the rotovap, and the gold complex product was further dried under high vacuum.

3.4.4. General procedure for homogeneous gold catalyzed hydrochlorination of alkynes

A glass screw cap vial equipped with a stir bar was charged with alkyne **3-1** (0.5 mmol). A 1:1 mixture of hexafluoroisopropanol (HFIP) and nitromethane (125 μ L) was added to dissolve it. **3-L6-Au-Cl** (7.3 mg, 2 mol %) was then added followed by HCl/DMPU (48 μ L, 0.6 mmol). The reaction mixture was stirred at rt (or 75 $^{\circ}$ C as the case may demand) and the progress of the reaction was monitored by GCMS or 1 H-NMR. Upon completion, reaction mixture was quenched with water and extracted with DCM. It was then dried over anhydrous Na_2SO_4 , filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

3.4.5. Procedure for synthesis of 3-4

Boronic acid (0.3 mmol, 49.8 mg), Pd(dppf)Cl_2 (5 mol %) and Na_2CO_3 (0.6 mmol, 63.6 mg) were placed into an oven-dried vial, then the vial was vacuumed and purged with argon for three times. Vinylchloride (0.2 mmol, 29.3 mg), EtOH (0.3 ml), toluene (0.3ml)

and H₂O (0.3 mL) were injected into the vial through syringe. The vial was placed into a preheated oil bath at 100 °C. The mixture was left to stir overnight. The reaction mixture was cooled down to room temperature and diluted with ethyl acetate (EA) (2 mL). Then the solution was washed with NaHCO₃ (aq.). The organic phase was dried over Na₂SO₄. Then Na₂SO₄ was filtered off. After evaporation of solvent, the residue was purified by flash chromatography on silica gel to obtain **3-4** (EA:Hex=1:15).

3.4.6. Procedure for synthesis of 3-5

Aniline (0.22 mmol, 27.1 mg), Pd₂(dba)₃ (3 mol %, 5.49 mg), BINAP (5 mol %, 6.23 mg) and *t*-BuONa (0.28 mmol, 26.9 mg) were placed into an oven-dried vial, then the vial was vacuumed and purged with argon for three times. Vinylchloride (0.2 mmol, 29.3 mg) and toluene (1 mL) were injected into the vial through syringe. The vial was placed into a preheated oil bath at 100 °C. The mixture was allowed to stir for overnight. The reaction mixture was cooled down to room temperature and toluene was evaporated, followed by adding DCM (1 mL) into the mixture. Then NaBH(OAc)₃ (0.4 mmol, 42.4 mg) and AcOH (0.4 mmol, 11.4 µL) were added. The reaction mixture was stirred for 24 h at room temperature, then quenched with 1 M NaOH solution, extracted by DCM (2 mL). The organic phase was washed with H₂O and brine, dried over Na₂SO₄. Na₂SO₄ was then filtered off, the solvent was evaporated and the residue was purified by flash chromatography on silica gel to obtain **5** (EA:Hex=1:8).

3.4.7. Characterization of products

(3-chlorobut-3-en-1-yl) benzene (**3-2a**)

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 5.14 (s, 1H), 5.08 (s, 1H), 2.96– 2.80 (t, *J* = 8.0 Hz, 2H), 2.69 – 2.57 (t, *J* = 8.0 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 141.9, 140.5, 128.4, 126.1, 112.5, 112.7, 41.0, 33.6. Colorless oil, 159.4 mg, 96 % yield.

5-chlorohex-5-enenitrile (**3-2b**)

¹H NMR (400 MHz, CDCl₃) δ 5.23 (s, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.02-1.89 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.9, 119.0, 114.3, 37.5, 22.6, 15.7. Colorless oil, 126.4 mg, 98 % yield.

(*Z*)-4-chlorooct-4-ene (**3-2c**)

¹H NMR (400 MHz, CDCl₃) δ 5.42 (t, *J* = 6.9 Hz, 1H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.13 (q, *J* = 7.2 Hz, 2H), 1.55 (dd, *J* = 14.7, 7.4 Hz, 2H), 1.39 (dd, *J* = 14.7, 7.4 Hz, 2H), 0.89 (dt, *J* = 9.7, 7.4 Hz, 6H). **¹³C NMR (126 MHz, CDCl₃)** δ 134.5, 125.1, 41.4, 30.5, 21.9, 20.5, 13.7, 12.9. Colorless oil, 132.9 mg, 91 % yield.

5-chlorohex-5-en-1-yl benzoate (**3-2d**)

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.55 (dd, *J* = 10.8, 4.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.16 (d, *J* = 7.4 Hz, 2H), 4.33 (t, *J* = 6.1 Hz, 2H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.87 – 1.67 (m, 4H). **¹³C NMR (100 MHz, CDCl₃)** δ 166.6, 142.3, 132.9, 130.3, 129.5, 128.3, 112.5, 64.5, 38.6, 27.6, 23.6. Colorless oil, 226.2 mg, 95 % yield.

2-(10-chloroundec-10-en-1-yl)isoindoline-1,3-dione (**3-2e**)

¹H NMR (400 MHz, CDCl₃) δ 7.82 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.1, 2.9 Hz, 2H), 5.09 (d, *J* = 8.4 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.61 (m, 2H), 1.57 – 1.48 (m, 2H), 1.35 – 1.26 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 168.4, 143.1, 133.8, 132.2, 123.1, 111.7, 39.1, 38.0, 29.3, 29.2, 29.1, 28.5, 28.4, 27.1, 26.8. **HRMS (ESI)** calcd. for [C₁₉H₂₄NCIONa⁺] ([M+Na⁺]) 356.1393; found 356.1385. White solid, 303.1 mg, 91 % yield.

(7-chlorooct-7-en-1-yl)(phenyl)sulfane (**3-2f**)

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.13 (m, 5H), 5.11 (d, *J* = 11.9 Hz, 2H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.60 – 1.50 (m, 2H), 1.49 – 1.38 (m, 2H), 1.37 – 1.26 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ = 142.9, 136.9, 128.9,

128.8, 125.7, 111.9, 39.0, 33.51, 28.9, 28.4, 28.0, 26.9. Colorless oil, 215.9 mg, 85 % yield.

(1-chlorovinyl) benzene (**3-2g**)

¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.55 (m, 2H), 7.39 – 7.34 (m, 3H), 5.77 (d, *J* = 1.7 Hz, 1H), 5.53 (d, *J* = 1.7 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.9, 136.9, 129.1, 128.3, 126.4, 112.4. Colorless oil, 126.9 mg, 92 % yield.

1-(1-chlorovinyl)-4-methylbenzene (**3-2h**)

¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.72 (d, *J* = 1.2 Hz, 1H), 5.47 (d, *J* = 1.1 Hz, 1H), 2.37 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.9, 139.2, 134.1, 128.9, 126.27, 111.7, 21.2. Colorless oil, 135.3 mg, 89 % yield.

1-(1-chlorovinyl)-3-methylbenzene (**3-2i**)

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.43 (m, 2H), 7.27 – 7.16 (m, 2H), 5.75 (s, 1H), 5.51 (s, 1H), 2.38 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 140.1, 137.9, 136.9, 129.8, 128.2, 127.1, 123.5, 112.5, 21.4. Colorless oil, 121.6 mg, 80 % yield.

1-(1-chlorovinyl)-2-methylbenzene (**3-2j**)

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.11 (m, 4H), 5.64 (d, *J* = 1.1 Hz, 1H), 5.34 (d, *J* = 1.1 Hz, 1H), 2.42 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.5, 138.7, 135.8, 130.4, 128.9, 125.7, 116.5, 116.4, 19.8. Colorless oil, 136.8, 90 % yield.

1-(tert-butyl)-4-(1-chlorovinyl) benzene (**3-2k**)

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 5.73 (s, 1H), 5.47 (s, 1H), 1.32 (s, 9H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.3, 139.9, 134.1, 126.1, 125.2, 111.8, 34.6, 31.2. Colorless oil, 192.1 mg, 99 % yield.

1-(1-chlorovinyl)-4-methoxybenzene (**3-2l**)

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.65 (d, *J* = 1.7 Hz, 1H), 5.41 (d, *J* = 1.7 Hz, 1H), 3.82 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 160.3, 139.6, 129.5, 127.7, 113.6, 110.8, 55.3. Colorless oil, 139.4 mg, 83 % yield.

1-(1-chlorovinyl)-4-fluorobenzene (**3-2m**)

¹H NMR (500 MHz, CDCl₃) δ 7.64 – 7.61 (m, 2H), 7.08 – 7.05 (m, 2H), 5.72 (d, *J* = 1.8 Hz, 1H), 5.52 (d, *J* = 1.8 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 163.2 (d, *J* = 199 Hz), 138.9, 133.1, 128.3, 115.3, 112.6. Colorless oil. **¹⁹F NMR (376 MHz, CDCl₃)** δ -112.28. Pale yellow oil, 135.7 mg, 87 % yield.

methyl 4-(1-chloroethenyl) benzoate (**3-2n**)

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 5.85 (d, *J* = 1.5 Hz, 1H), 5.60 (d, *J* = 1.5 Hz, 1H), 3.90 (s, 3H). **¹³C NMR (126 MHz, CDCl₃)** δ 166.4, 140.9, 138.9, 130.5, 129.5, 126.3, 114.6, 52.1. Yellow solid, 158.7 mg, 81 % yield.

1,4-di(1-chloroethenyl) benzene (**3-2o**)

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 1.0 Hz, 4H), 5.81 (d, *J* = 1.3 Hz, 2H), 5.56 (d, *J* = 1.3 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.1, 137.4, 126.3, 113.4. White solid, 148.5 mg, 75 % yield.

4-(1-chlorovinyl) benzonitrile (**3-2p**)

¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 5.88 (d, *J* = 2.0 Hz, 1H), 5.67 (d, *J* = 2.0 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.1, 132.7, 132.2, 126.9, 118.3, 115.8, 112.6. White solid, 130.4 mg, 80 % yield.

1-(1-chlorovinyl)-4-nitrobenzene (**3-2q**)

¹H NMR (400 MHz, CDCl₃) 2r: δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.79 (t, *J* = 9.4 Hz, 2H), 5.99 – 5.86 (m, 1H), 5.72 (d, *J* = 1.7 Hz, 1H). **¹³C NMR (126 MHz, CDCl₃) 2r/2r':** δ 142.7, 140.4, 129.9, 127.5, 127.3, 123.6, 123.5, 121.8, 116.41. Yellow solid, 135.4 mg, 74 % yield.

(*Z*)-2-(2-chlorovinyl) pyridine (**3-2r**)

¹H NMR (700 MHz, CDCl₃) δ 8.62 (d, *J* = 3.5 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.71 (td, *J* = 7.8, 1.6 Hz, 1H), 7.19 (dd, *J* = 6.5, 4.9 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 153.2, 149.5, 136.1, 130.4, 124.1, 122.6, 120.51. Yellow oil, 97.3 mg, 70 % yield.

3-(1-chlorovinyl) thiophene (**3-2s**)

¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H), 7.33 – 7.20 (m, 2H), 5.69 (s, 1H), 5.43 (s, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.9, 134.6, 126.4, 125.0, 124.3, 111.4. Yellow oil, 138.2 mg, 96 % yield.

(*Z*)-ethyl 3-chloro-3-phenylacrylate and (*E*)-ethyl 3-chloro-3-phenylacrylate (**3-2t**)

¹H NMR (500 MHz, CDCl₃) (*Z*) δ 7.71- 7.69 (m, 2H), 7.57 – 7.34 (m, 3H), 6.56 (s, 1H, *Z*), 6.37 (s, 1H, *E*), 4.29 (q, *J* = 7.1 Hz, 2H, *Z*), 4.07 (q, *J* = 7.1 Hz, 2H, *E*), 1.35 (t, *J* = 7.1 Hz, 3H, *Z*), 1.13 (t, *J* = 7.1 Hz, 3H, *E*). **¹³C NMR (126 MHz, CDCl₃) *Z/E*:** δ 164.2, 163.8, 149.7, 146.1, 137.3, 130.6, 129.9, 128.6, 128.4, 127.8, 127.2, 119.9, 116.4, 60.6, 14.2, 13.9. Colorless liquid, 138.6 mg, 66 % yield

(*S*)-methyl 2-(5-chlorohex-5-enamido)-3-phenylpropanoate (**3-2u**)

¹H NMR (400 MHz, CDCl₃) δ 7.28-7.25 (m, 3H), 7.09-7.07 (m, 2H), 7.57-7.54 (m, 1H), 5.86 (s, 1H), 5.11 (d, *J* = 24.0 Hz, 2H), 4.92-4.87 (m, 1H), 3.73 (s, 1H), 3.16-3.05 (m, 2H), 2.33 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 8.0 Hz, 2H), 1.90-1.85 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 172.1, 171.8, 141.8, 135.7, 129.2, 128.6, 127.2, 112.9, 52.9, 52.3, 38.1, 37.8, 34.6, 22.7. **HRMS (ESI)** calcd. for [C₁₆H₂₀NCIO₃Na⁺] ([M+Na⁺]) 332.1029; found 332.1031. Colorless oil, 213.3 mg, 69 % yield.

(8R,9S,13S,14S)-3-((7-chlorooct-7-en-1-yl)oxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (**3-2v**)

¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J*=8.0 Hz, 1H), 6.71-6.69 (m, 1H), 6.63 (s, 1H), 5.11 (d, *J* = 8.0 Hz, 2H), 3.91 (t, *J* = 8.0 Hz, 2H), 2.90-2.87 (m, 2H), 2.52-2.45 (m, 2H), 2.39-2.31 (m, 3H), 2.26-2.22 (m, 1H), 2.18-1.93 (m, 4H), 1.80-1.73 (m, 2H), 1.64-1.37 (m, 11H), 0.90 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 220.9, 157.1, 142.9, 137.7, 131.9, 126.3, 114.5, 114.5, 112.1, 111.9, 67.7, 50.4, 47.9, 43.9, 39.0, 38.4, 25.9, 31.6, 29.6, 29.2, 28.2, 27.1, 26.6, 25.9, 25.8, 21.6, 13.8. **HRMS (ESI)** calcd. for [C₂₆H₃₅ClO₂Na⁺] ([M+Na⁺]) 437.2223; found 437.2213. White solid, 393.5 mg, 95 % yield.

5-(oct-1-en-2-yl)benzo[d][1,3]dioxole(**3-4**)

¹H NMR (400 MHz, CDCl₃) δ 6.90-6.87 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 2H), 5.15 (s, 1H), 4.96 (s, 1H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.42 – 1.19 (m, 8H), 0.87 (t, *J* = 8.0 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 148.2, 147.6, 146.7, 135.8, 119.5, 111.1, 107.9, 106.7, 100.9, 35.6, 31.7, 28.9, 28.3, 22.6, 14.1. Colorless oil, 174.1 mg, 75 % yield.

4-methoxy-N-(octan-2-yl) aniline (**3-5**)

¹H NMR (400 MHz, CDCl₃) δ 6.76 (d, *J* = 8.0 Hz, 2H), 6.55 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 1H), 3.37-3.33 (m, 1H), 3.05 (s, 1H), 1.36-1.27 (m, 10H), 1.14 (d, *J* = 8.0 Hz, 3H), 0.88 (t, *J* = 8.0 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.8, 141.9, 114.9, 114.6, 55.9, 49.6, 37.2, 31.8, 29.4, 26.1, 22.6, 20.81, 14.0. Colorless oil, 157.6 mg, 67 % yield.

3.4.8. Copies of NMR spectra for compounds 3-2, 3-4 and 3-5

4. METEL-FREE CHLOROTHIOLATION OF ALKENES USING HCl AND SULFOXIDES

4.1 Introduction

Carbon-sulfur bond forming reactions are highly desirable because sulfur-containing compounds are commonly found in biologically important natural and synthetic products,⁹³ and functionalized materials.⁹⁴ These applications drive the investigation of new carbon-sulfur bond forming reactions.⁹⁵ The difunctionalization of alkenes is a fundamentally important transformation in organic synthesis.⁹⁶ More specifically, 1,2-chlorothiolation of olefins installs both the chloro- and thio-groups simultaneously. The resulting β -chlorothiolated compounds have been shown to possess insecticidal, antibacterial and antifungal properties.⁹⁷ Chlorothiolated compounds are commonly synthesized via electrophilic addition of sulfenylchlorides to olefins.^{97a, 98} Recently, chloromethylsulfide was shown to be the species responsible for the chlorothiolation of alkynes.⁹⁹ However, this method presents certain challenges: the instability and volatility of lower alkylsulfenyl chlorides require extremely low reaction temperatures.

Dimethylsulfoxide (DMSO), which is an environmentally benign and easy to handle reagent, has been utilized in the past decade as a one-carbon synthon for C-C homologation¹⁰⁰ and as the source of the thiomethyl moiety¹⁰¹ as well as other reactions.¹⁰² Several DMSO-Lewis acid combinations have been employed with chloride and bromide sources to achieve β -halothiolation.¹⁰³ Pagnoni and co-workers^{103c}

reported the transformation of alkenes to their corresponding β -chloromethylthiolated products using dialkylsulfoxide-trimethylchlorosilane [$R_2SO-(CH_3)_3SiCl$]. They subsequently used a dimethylsulfoxide-dimethylsulfide-sulfuryl chloride (DMSO-DMS- SO_2Cl_2) combination to achieve the same transformation (Scheme 6a). The importance of incorporating the thiomethyl moiety within molecules has engrossed research interests lately as demonstrated by the DMSO-mediated thiomethylation of arenes (Scheme 6b).^{95b-d} The above methods suffer from poor atom economy or use of strong oxidants and expensive transition metal catalysts. We reasoned that the reactive chlorosulfonium species can be generated *in situ* directly from a sulfoxide and a Brønsted acid like HCl, which can then react with unactivated alkenes to give β -chlorothiolated compounds in an atom-economical fashion (Scheme 6c).

Scheme 6. Chlorothiolation of alkenes and arenes

a) TMSCl mediated chloromethylthiolation of alkenes.

b) Directing group assisted metal-catalyzed methylthiolation of arenes

c) HCl mediated chlorothiolation of unactivated alkenes (**this work**).

4.2 Results and discussion

We began our investigation using allylbenzene (**4-1a**) as the model substrate (Table 7). Using ethyl acetate as choice solvent¹⁰⁴, no reaction took place when aqueous

concentrated aqueous HCl (37%) was employed (Table 7, entry 1). However, using our newly developed DMPU-HCl reagent,^{8, 105} we succeeded in generating the reactive methylsulfinyl chloride, which then reacted with allylbenzene to give the desired product (Table 7, entry 2). Increasing the amounts of DMSO (Table 7, entries 3-4) gave complete conversion in a shorter reaction time. When the reaction was run in more dilute conditions, the conversion was reduced (Table 7, entry 5). Concentrated aqueous HCl (37%) also resulted in moderate conversion at higher temperatures (Table 7, entry 6). Commercial 5M HCl/isopropanol solution (Table 7, entry 5) also gave good conversion, but suffered from the formation of side products due to further reaction with isopropanol.

Table 7. Optimization of reaction conditions

Ph-CH2-CH=CH2 (4-1a) $\xrightarrow[\text{EtOAc, 60 } ^\circ\text{C}]{\text{DMSO (X equiv), HCl source (2.4 equiv)}}$ Ph-CH2-CH(Cl)-CH2-S- (4-2a)

Entry	X (equiv)	HCl source	Solvent (mL)	Time (h)	Conversion ^b (%)
1	1.2	36.6-38% HCl (aq)	0.5	24	trace
2	1.2	HCl/DMPU (38-42 % w/w)	0.5	24	71
3	2.4	HCl/DMPU (38-42 % w/w)	0.5	5	100
4	4.8	HCl/DMPU (38-42 % w/w)	0.5	2	100
5	2.4	HCl/DMPU (38-42 % w/w)	1	5	95
6	2.4	36.6-38% HCl(aq)	1	24	54 ^c
7	4.8	HCl/DMPU (38-42 % w/w)	0.5	2	100
8	2.4	5M HCl/isopropanol	0.5	5	90

^a Reaction conditions: **4-1a** (0.5 mmol), HCl/DMPU (1.2 mmol), DMSO (1.2 mmol), EtOAc, 60 °C. ^b Determined by GC-MS with dodecane as the internal standard. ^c Reaction run at 70 °C.

The optimized reaction conditions were then tested on a range of alkenes (Table 8). A wide variety of functional groups were well tolerated giving moderate to excellent yields. 5-Hexene-1-ol (**4-1c**) gave the desired transformation with a simultaneous chloride substitution of the alcohol in 86% yield. Protected alcohols **4-1d**, **4-1e**, **4-1f**, **4-1i** and **4-1k** smoothly furnished the corresponding β -chloromethylthiolated products in 82%, 71%, 65%, 62% and 93% respectively. Phthalimides **4-1g** and **4-1h** gave the desired conversions in 87% and 59% respectively. Worthy of note is the significant loss in regioselectivity due to the neighboring group participation of carbonyl and ether oxygen adjacent to the alkene. As a result, the allylic substrates resulted in a mixture of regioisomers (Table 8, **4-2h** and **4-2i**).

Table 8. Alkene substrate scope for chlorothiolation

^aReaction conditions: **1** (0.5 mmol), HCl/DMPU (1.2 mmol), DMSO (1.2 mmol), EtOAc (0.5 mL), 60 °C, 1-5 h.

^bAll yields are isolated yields.

Other functionalities like carboxylic acids (**4-2j**), aldehydes (**4-2l**) and nitriles (**4-2n**) were equally tolerated furnishing products in moderate to excellent yields. Internal alkenes (**4-1q**, **4-1r**, **4-1s**, **4-1t**) also proceeded in 89%, 81%, 80% and 69% yields, respectively. The reaction is highly stereoselective giving exclusively the trans-addition products and single diastereomers. This result is consistent with the trans-addition product expected in the reaction of methylsulphenylchlorides to alkenes.^{103c, 106} Styrene substrates also worked well, but the labile benzylic chloride was hydrolyzed during work up to form **4-2s** and **4-2t** in 74% and 82 % yields respectively. The reactive 4-vinylanisole gave a complex mixture, possibly due to the instability of the product.

Given the prevalence of the arylsulfides in bioactive compounds, we sought to extend this methodology to the synthesis of substituted arylsulfides. Allylbenzene served as the model substrate for the reaction with various arylmethylsulfoxides (Table 9). Phenylmethylsulfoxide, p-tolylmethylsulfoxide, 4-bromophenylmethyl sulfoxide and 4-chlorophenylmethylsulfoxide gave the corresponding arylsulfides **4-3a**, **4-3b**, **4-3c** and **4-3d** in moderate yields.

However, the electron deficient arylmethylsulfoxides **4-3e** and **4-3f** gave poor yields. In these cases, the sulfoxides were mostly reduced to the corresponding sulfides. Reactions of dialkylsulfoxides such as dibutylsulfoxide was unsuccessful probably due to the slower formation of the reactive intermediate. The use of butylmethylsulfoxide gave the chloromethylthiolated product as the major adduct.

To further explore the scalability and application of this method, we performed a gram-scale reaction which, upon isolation, was efficiently oxidized to the corresponding sulfone, **4-4** (Scheme 7a), all in good yields.

Table 9. Sulfoxide substrate scope in the β -chloroarylthiolation of alkenes

^aReaction conditions: **1a** (0.5 mmol), HCl/DMPU (1.2 mmol), arylsulfoxide (1.2 mmol), EtOAc (0.5 mL), 75 °C, 24 - 48 h. ^b Isolated yields.

The process is also amenable to late stage functionalization, as demonstrated by the protected sugar **4-1v**, the chlorothiolated derivative of which **4-2v** was isolated in 46% yield (Scheme 7b). The rather unexpected result of **4-2w**, gave us another platform for further elaboration of our method: using *m*-vinylbenzoic acid (**4-1w**), we were pleased to observe an intramolecular cyclization to form the methylsulfide substituted isobenzofuranone. Using 4-fluorostyrene **4-1x**, we were able to produce an intermolecular β -carbomethylthiolation to produce **4-5** in good yields (Scheme 7c). The newly formed β -chloromethylsulfides should also be amenable to other synthetic processes such as the base-promoted elimination of HCl to give the corresponding vinyl thioether,¹⁰⁷ or transition metal catalyzed cross-coupling reactions with boronic acids.¹⁰⁸

The proposed mechanism (Scheme 8) involves the protonation of DMSO, generating sulfonium salt **I**, and subsequent elimination of water to form dimethylsulfonium chloride **II**. The reaction of this highly electrophilic species with another equivalent of HCl leads to

another electrophilic sulfur species **III**. **III** is then attacked by the alkene to generate the thiiranium intermediate **IV**, which is then trapped by the nucleophilic chloride to obtain the chlorothiolated product.

Scheme 7. Generality and applications of method

Both Kharasch¹⁰⁹ and Mueller^{106, 110} reported the formation of a thiiranium ion in the addition of sulfenylhalides to olefins.^{106, 111} The opening of the cyclic thiiranium ion **IV** by chloride would follow an S_N1-like pathway: the nucleophile (Cl⁻) preferentially attacks at the more hindered position resulting in the trans-addition product.^{106, 112} Notably, our HCl-DMSO system does not work for alkynes.¹¹³

Scheme 8. Proposed mechanism

4.3 Conclusion

In conclusion, we have achieved the chloromethylthiolation of alkenes, a transformation that affords biologically and synthetically relevant β -chlorothiolated compounds, using common and easy to handle starting materials: HCl-DMPU, DMSO and alkenes. The procedure shows good functional group compatibility-both terminal and internal alkenes are suitable substrates-and is suitable for gram scale synthesis.

4.4 Experimental

4.4.1. General

^1H and ^{13}C NMR spectra were recorded either at 400 MHz or 700 MHz, and 101 MHz using CDCl_3 or CD_2Cl_2 as a solvent. The chemical shifts are reported in δ (ppm) values (^1H and ^{13}C NMR relative to CHCl_3 , δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants (J), are reported in Hertz (Hz). The HRMS data was obtained from a Waters Micromass GCT Premier spectrometer. All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was

developed on silica gel 60 F254 aluminum sheets. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and used as received without any further purification.

4.4.2. General procedure for the β -chloromethyl/arylthiolation of alkenes

A glass vial equipped with a screw cap and a stirring bar was charged with alkene **4-1** (0.5 mmol). Then ethyl acetate was added (0.5 mL) followed by DMSO (1.2 mmol) and HCl/DMPU (102 μ L, 1.2 mmol). The reaction mixture was stirred at 65 $^{\circ}$ C (or 75 $^{\circ}$ C for less reactive substrates) and the progress of the reaction was monitored by GC-MS or TLC. Upon completion, the reaction mixture was quenched with water and extracted with DCM. The combined organic layers were then dried over anhydrous Na_2SO_4 , filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

4.4.3. Procedure for synthesis of sulfone, **4-4**

Product **4-2a**, prepared using general procedure (0.5 mmol, 100 mg), was measured into a screw cap vial equipped with a stir bar. Acetic acid (90.5 mL) was added and vial placed into an ice-bath to chill to 0 $^{\circ}$ C. H_2O_2 (170 μ L, 1.7 mmol) was added dropwise and the reaction mixture let to stir and warm up to rt. The reaction progress was monitored by GCMS and TLC. Upon completion, reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL), extracted with DCM (2 mL), washed twice with water (2 X 2 mL). The organic phase was dried over Na_2SO_4 , filtered off and solvent evaporated. The residue was purified by flash chromatography on silica gel to obtain **4-4** (1:9 EtOAc:Hex) to yield the desired product. Colorless oil, 113.6 mg, 98 %.

4.4.4. Procedure for the synthesis of 4-5

A glass screw cap vial equipped with a stir bar was charged with alkene **1** (0.5 mmol). Ethylacetate was added (0.5 mL). DMSO (1.2 mmol) and HCl/DMPU (102 μ L, 1.2 mmol). The reaction mixture was stirred at 65 °C and the progress of the reaction was monitored by GCMS or ¹H-NMR. Upon completion, the reaction mixture was cooled to rt then excess pyrrole (3.6 mmol, 0.25 mL) added and the reaction stirred for another 1 h. Upon full conversion, reaction mixture was quenched with saturated bicarbonate and extracted with DCM. It was then dried over anhydrous Na₂SO₄, filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

4.4.5. Characterization of products

(2-chloro-3-phenylpropyl) methyl sulfide (**4-2a**)

¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.18 (m, 5H), 4.30 – 4.14 (m, 1H), 3.32 (dd, J =14.2, 5.0, 1H), 3.00 (dd, J = 14.1, 8.0, 1H), 2.92 – 2.78 (m, 2H), 2.18 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 137.2, 129.4, 128.4, 126.8, 61.8, 42.8, 41.7, 16.6. **HRMS (EI⁺)** calcd. for [C₁₀H₁₃SCl]⁺ (M⁺) 200.0427; found 200.0425. Pale yellow oil, 89.4 mg, 89 % yield.

(2-chlorooctyl) methyl sulfide (**4-2b**)

¹H NMR (400 MHz, CD₂Cl₂) δ = 4.08 – 4.02 (m, 1H), 2.91 (dd, *J* = 13.8, 6.1, 1H), 2.83 (dd, *J* = 13.9, 7.4, 1H), 2.17 (s, 3H), 2.01 – 1.94 (m, 1H), 1.76 – 1.64 (m, 1H), 1.42 – 1.28 (m, 8H), 0.90 (t, *J* = 6.8, 3H). **¹³C NMR (100 MHz, CD₂Cl₂)** δ = 62.3, 42.4, 36.8, 31.6, 28.7, 26.2, 22.5, 16.2, 13.8. **HRMS (EI⁺)** calcd. for [C₉H₁₉SCl⁺] (*M*⁺) 194.0896; found 194.0894. Colorless oil, 92.2 mg, 95 % yield.

(2,6-dichlorohexyl) methyl sulfide (**4-2c**)

¹H NMR (400 MHz, CDCl₃) δ = 4.05 – 3.93 (m, 1H), 3.54 (t, *J* = 6.5, 2H), 2.90 (dd, *J* = 13.8, 5.7, 1H), 2.79 (dd, *J* = 13.8, 8.0, 1H), 2.15 (s, 3H), 2.05 – 1.98 (m, 1H), 1.84 – 1.53 (m, 6H). **¹³C NMR (126 MHz, CDCl₃)** δ = 61.4, 44.7, 42.3, 35.9, 31.9, 23.7, 16.6. **HRMS (EI⁺)** calcd. for [C₁₀H₁₃SCl₂⁺] (*M*⁺) 200.0193; found 200.0195. Colorless oil, 86.1 mg, 86 % yield.

(2-chloro-5-benzoylpentyl) methyl sulfide (**4-2d**)

¹H NMR (400 MHz, CDCl₃) δ = 8.03 (d, *J* = 7.6, 2H), 7.55 (t, *J* = 7.4, 1H), 7.43 (t, *J* = 7.6, 2H), 4.36 (t, *J* = 5.6, 2H), 4.14 – 3.99 (m, 1H), 2.93 (dd, *J* = 13.9, 5.6, 1H), 2.81 (dd, *J* = 13.8, 8.1, 1H), 2.22 – 2.04 (m, 5H), 1.95 – 1.77 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ = 166.5, 132.9, 130.2, 129.5, 128.4, 64.2, 61.1, 42.4, 33.2, 25.6, 16.5. **HRMS (EI⁺)** calcd. for [C₁₀H₁₇O₂SCl⁺] (*M*⁺) 272.0638; found 272.0630. Yellow oil, 111.5 mg, 82 % yield.

(2-chloro-2-methyl-4-phenoxybutyl) methyl sulfide (**4-2e**)

¹H NMR (400 MHz, CDCl₃) δ = 7.30 (dd, *J* = 8.5, 7.5, 2H), 6.99 – 6.90 (m, 3H), 4.23 (ddd, *J*=8.3, 5.8, 2.5, 2H), 3.07 (d, *J* = 13.8, 1H), 2.99 (d, *J* = 13.8, 1H), 2.47- 2.30 (m, 2H), 2.25 (s, 3H), 1.73 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 158.5, 129.5, 120.8, 114.5, 72.7, 64.4, 49.3, 41.3, 29.9, 18.5. **HRMS (EI+)** calcd. for [C₁₂H₁₇OSCl⁺] (M⁺) 244.0689; found 244.0691. Colorless liquid, 86.7 mg, 71 % yield.

(2-chloro-4-phenoxybutyl) methyl sulfide (**4-2f**)

¹H NMR (400 MHz, CDCl₃) δ = 7.28 (dd, *J* = 15.0, 7.5, 2H), 7.04 – 6.81 (m, 3H), 4.40 – 4.29 (m, 1H), 4.23 – 4.12 (m, 2H), 3.00 (dd, *J* = 13.9, 6.7, 1H), 2.90 (dd, *J* = 13.9, 7.7, 1H), 2.60- 2.52 (m, 1H), 2.20 (s, 3H), 2.13- 2.04 (m, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ = 158.6, 129.5, 120.9, 114.5, 64.3, 58.3, 42.5, 36.4, 16.5. **HRMS (ESI) HRMS (EI+)** calcd. for [C₁₁H₁₅OSCl⁺] 230.0532; found 230.0536. Colorless oil, 74.6 mg, 65 % yield.

2-(2-chloro-3-(methylthio)hexyl)isoindoline-1,3-dione (**4-2g**)

¹H NMR (400 MHz, CDCl₃) δ = 7.81 (dt, *J* = 8.2, 3.9, 2H), 7.74 – 7.62 (m, 2H), 4.00- 3.94 (m, 1H), 3.68 (t, *J* = 7.1, 2H), 2.88 (dd, *J* = 13.8, 5.7, 1H), 2.77 (dd, *J* = 13.8, 7.9, 1H), 2.13 (s, 3H), 2.10 – 1.97 (m, 1H), 1.79 – 1.58 (m, 5H), 1.54 – 1.38 (m, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ = 168.3, 133.9, 132.1, 123.2, 61.4, 42.4, 37.6, 36.1, 27.9, 23.5,

16.5. **HRMS (EI+)** calcd. for $[C_{15}H_{18}O_2NSCl^+]$ 311.0427; found 311.0425. Colorless oil, 135.3 mg, 87 % yield.

2-(2-chloro-3-(methylthio)propyl)isoindoline-1,3-dione (**4-2h/2h'**)

1H NMR (400 MHz, $CDCl_3$) 1H NMR (700 MHz, $cdcl_3$) δ = 7.87 – 7.80 (m, 4H), 7.72 (ddd, J = 6.2, 4.7, 3.0, 4H), 4.47– 4.44 (m, 1H, Markonnikov's product), 4.15 (dd, J = 8.6, 4.8, 1H), 4.09 – 3.99 (m, 2H), 3.86 (dd, J = 14.2, 8.6, 1H), 3.80 (dd, J = 11.4, 4.8, 1H), 3.66 (dd, J = 11.4, 8.3, 1H), 3.33– 3.29 (m, 1H, anti-Markovnikov product), 2.95 (dd, J = 14.2, 5.9, 1H), 2.89 (dd, J = 14.2, 7.7, 1H), 2.20 (s, 3H), 2.13 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 168.0, 134.1, 131.8, 123.5, 57.2, 46.6, 45.5, 43.1, 39.9, 39.0, 16.3, 13.4. **HRMS (EI+)** calcd. for $[C_{12}H_{12}SO_2NCl^+]$ (M^+) 269.0277; found 269.0271. Colorless oil, 79.4 mg, 59 % yield.

(2-chloro-4-phenoxypropyl) methyl sulfide (**4-2i, 4-2i'**)

1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 4H), 7.10 – 6.86 (m, 6H), 4.38 – 4.19 (m, 5H), 3.95 – 3.87 (m, 2H), 3.22 – 3.13 (m, 1H), 3.12 – 2.95 (m, 2H), 2.25 (s, 3H), 2.20 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.3, 158.1, 129.6, 121.4, 114.7, 69.7, 67.4, 58.0, 47.9, 44.3, 38.7, 16.8, 14.9. **HRMS (EI+)** calcd. for $[C_{10}H_{13}OSCl^+]$ (M^+) 216.0376; found 216.0371. Colorless oil, 67.1 mg, 62 % yield.

10-chloro-11-(methylthio)undecenoic acid (**4-2j**)

¹H NMR (400 MHz, CDCl₃) δ = 4.13 – 4.08 (m, 2H), 4.02- 3.98 (m, 1H), 2.88 (dd, J = 13.8, 5.8, 1H), 2.79 (dd, J = 13.8, 7.7, 1H), 2.27 (t, J = 7.5, 2H), 2.15 (s, 3H), 1.95 (td, J = 8.6, 4.3, 1H), 1.71 – 1.47 (m, 5H), 1.38- 1.22 (m, 7H). **¹³C NMR (100 MHz, CDCl₃)** δ = 173.8, 61.9, 60.1, 42.5, 36.7, 34.3, 29.1, 28.9, 26.2, 24.9, 16.5, 14.2. **HRMS (EI+)** calcd. for [C₁₂H₂₃O₂SCl⁺] (M⁺)266.0227; found 266.0225. Colorless oil, 121.1, 91 % yield.

(2-chloro-2-methyl-4-benzoylbutyl) methyl sulfide (**4-2k**)

¹H NMR (400 MHz, CDCl₃) δ = 8.02 (d, J = 7.4, 2H), 7.53 (t, J = 7.4, 1H), 7.41 (t, J = 7.6, 2H), 4.54 (t, J = 6.7, 2H), 3.04 (dd, J = 13.8, 6.1, 1H), 2.94 (dd, J = 13.9, 7.4, 1H), 2.42- 2.26 (m, 2H), 2.20 (s, 3H), 1.70 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 166.4, 132.9, 130.0, 129.6, 128.4, 71.9, 61.7, 49.2, 40.7, 29.7, 18.4. **HRMS (EI+)** calcd. for [C₁₃H₁₇O₂SCl⁺] (M⁺) 272.0638; found 272.0630. Pale yellow oil, 126.5 mg, 93 % yield.

2-formylphenyl 4-chloro-5-(methylthio) pentanoate (**4-2l**)

¹H NMR (400 MHz, CDCl₃) δ = 10.06 (s, 1H), 7.86 (d, J = 7.7, 1H), 7.62 (t, J = 7.8, 1H), 7.40 (t, J = 7.5, 1H), 7.17 (d, J = 8.1, 1H), 4.18 (d, J = 8.2, 1H), 3.00- 2.81 (m, 4H), 2.66 – 2.50 (m, 1H), 2.16 (s, 3H), 2.09- 2.00 (m, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ = 188.8,

171.1, 151.1, 135.3, 131.8, 127.9, 126.5, 123.4, 60.4, 42.2, 31.4, 30.9, 16.4. **HRMS** (**EI+**) calcd. for $[C_{13}H_{17}O_2SCl]^+$ (M^+) 286.0430; found 286.0432. Colorless oil, 70.1 mg, 49 % yield.

(2-chloro-4-(naphthalen-2-yloxy)hexyl) methyl sulfide (**4-2m**)

1H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, J = 9.5, 1H), 7.55 (dd, J = 7.1, 4.6, 2H), 7.33 (d, J = 8.9, 1H), 7.20 (t, J = 7.5, 1H), 6.68 (d, J = 9.5, 1H), 4.38 – 4.19 (m, 2H), 4.00 (dd, J = 10.0, 6.7, 1H), 2.89 (dd, J = 13.9, 5.7, 1H), 2.79 (dd, J = 13.8, 7.9, 1H), 2.14 (s, 3H), 1.89 – 1.44 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 162.1, 139.0, 130.6, 129.0, 121.8, 121.7, 121.4, 120.9, 114.0, 61.5, 42.4, 42.0, 36.3, 26.8, 23.7, 16.5. **HRMS** (**EI+**) calcd. for $[C_{16}H_{20}O_2SNCl]^+$ (M^+) 309.1187; found 309.1196. Yellow solid, 80.4 mg, 52 % yield.

(2-chloro-6-cyanoethyl) methyl sulfide (**4-2n**)

1H NMR (400 MHz, $CDCl_3$) δ = 4.06 – 3.90 (m, 1H), 2.90 (dd, J = 13.8, 6.1, 1H), 2.78 (dd, J = 13.9, 7.4, 1H), 2.36 (t, J = 6.5, 2H), 2.15 (s, 3H), 2.07 – 1.98 (m, 1H), 1.76- 1.55 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 119.5, 60.9, 42.3, 35.7, 25.5, 24.9, 17.1, 16.6. **HRMS** (**EI+**) calcd. for $[C_8H_{14}SNCl]^+$ (M^+) 191.0535; found 191.0530. Colorless liquid, 77.4 mg, 81 % yield.

(5-chlorooctan-4-yl)(methyl)sulfide (**4-2o**)

¹H NMR (400 MHz, CDCl₃) δ = 4.11 (d, J =10.0, 1H), 2.73 (s, 1H), 2.13 (s, 3H), 1.99 – 1.55 (m, 6H), 1.41 (m, 3H), 0.94 (t, J = 7.0, 6H). **¹³C NMR (100 MHz, CDCl₃)** δ = 66.1, 54.1, 35.5, 32.5, 20.8, 20.4, 15.5, 13.9, 13.8, 13.5. **HRMS (EI+)** calcd. for [C₉H₁₉SCl⁺] 194.0896; found 194.0887. Colorless liquid, 86.4 mg, 89 % yield.

(2-chlorocyclohexyl)(methyl)sulfide (**4-2p**)

¹H NMR (700 MHz, CDCl₃) δ = 4.09 – 3.93 (m, 1H), 2.77– 2.72 (m, 1H), 2.35 – 2.13 (m, 5H), 1.83 – 1.60 (m, 3H), 1.51 (dd, J = 13.6, 9.0, 1H), 1.44 – 1.29 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ = 63.3, 51.9, 34.3, 30.6, 23.9, 23.5, 14.9. **HRMS (EI+)** calcd. for [C₇H₁₃SCl⁺] (M⁺) 164.0427; found 164.0434. Yellow oil, 66.3 mg, 81 % yield.

(3-chlorobicyclo[2.2.1]heptan-2-yl)(methyl)sulfide (**4-2q**)

¹H NMR (400 MHz, CDCl₃) δ = 4.07– 3.99 (m, 1H), 2.57 (t, J = 3.0, 1H), 2.46 (s, 1H), 2.26 – 2.13 (m, 4H), 2.02 – 1.91 (m, 1H), 1.78 (d, J = 10.4, 1H), 1.75 – 1.62 (m, 1H), 1.52 – 1.30 (m, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 68.3, 58.5, 44.3, 43.1, 36.0, 29.1, 21.7, 14.9. **HRMS (EI+)** calcd. for [C₈H₁₃SCl⁺] (M⁺) 176.0427; found 176.0426. Colorless oil, 70.4 mg, 80 % yield.

3-chloro-4-(methylthio)tetrahydrothiophene 1,1-dioxide (**4-2r**)

¹H NMR (400 MHz, CDCl₃) δ = 4.53– 4.48 (m, 1H), 3.85 (dd, J = 13.9, 6.9, 1H), 3.75 (dd, J = 13.7, 7.7, 1H), 3.60 (q, J = 7.2, 1H), 3.39 (dd, J = 13.9, 6.4, 1H), 3.15 (dd, J = 13.6, 7.1, 1H), 2.26 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 58.9, 56.2, 56.1, 50.0, 15.2. **HRMS (EI+)** calcd. for [C₁₃H₁₇O₂SCl⁺] 199.9733; found 199.9729. Yellow liquid, 67.6 mg, 68 % yield

2-(methylthio)-1-phenylethanol (**4-2s**)

¹H NMR (400 MHz, CD₂Cl₂) δ = 7.44 – 7.27 (m, 5H), 4.77 (d, J = 9.0, 1H), 2.94 (s, 1H), 2.88 (dd, J = 13.9, 3.6, 1H), 2.72 (dd, J = 13.8, 9.3, 1H), 2.13 (s, 3H). **¹³C NMR (100 MHz, CD₂Cl₂)** δ = 142.8, 128.3, 127.6, 125.8, 70.9, 44.0, 15.2 **HRMS (EI+)** calcd. for [C₉H₁₂OS⁺] (M⁺) 168.0609; found 168.0608. Yellow liquid, 62.2 mg, 74 % yield

1-(4-fluorophenyl)-2-(methylthio)ethanol (**4-2t**)

¹H NMR (700 MHz, CD₂Cl₂) δ = 7.25 (s, 2H), 6.95 (d, *J* = 6.6, 2H), 4.63 (d, *J* = 6.8, 1H), 2.85 (dd, *J* = 13.9, 3.8, 1H), 2.00 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** **¹³C NMR (100 MHz, CD₂Cl₂)** δ = 163.4, 161.0, 138.7, 127.5, 115.3, 70.4, 44.0, 15.2. **¹⁹F NMR (376 MHz, CD₂Cl₂)** δ = -116.8. **HRMS (EI+)** calcd. for [C₉H₁₁OSF⁺] (M⁺) 186.0515; found 186.0519. Yellow liquid, 76.2 mg, 82 % yield.

(2R,3S,4S,5R,6R)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-(5-chloro-6-(methylthio)hexyloxy)tetrahydro-2H-pyran (**4-2v**)

¹H NMR (400 MHz, CDCl₃) **¹H NMR (400 MHz, cdcl₃)** δ = 7.39 – 7.10 (m, 20H), 5.04 – 4.34 (m, 10H), 3.98 (t, *J* = 9.1, 2H), 3.84 – 3.34 (m, 8H), 2.92 – 2.72 (m, 2H), 2.13 (s, 3H), 2.01 (dd, *J* = 9.6, 4.4, 1H), 1.78 – 1.61 (m, 4H). **¹³C NMR (100 MHz, CDCl₃)** δ = 138.8, 138.6, 138.3, 138.1, 137.9, 128.4, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 103.6, 97.0, 84.7, 82.2, 82.1, 80.0, 77.9, 77.7, 75.7, 75.1, 75.0, 74.8, 74.7, 73.5, 73.2, 70.1, 69.7, 68.9, 68.5, 67.9, 61.7, 42.4, 36.5, 29.3, 28.9, 23.1, 16.6. White solid, 162.0 mg, 46 % yield.

3-((methylthio)methyl)isobenzofuran-1(3H)-one (**4-2w**)

¹H NMR (400 MHz, CDCl₃) δ = 7.91 (d, *J* = 7.6, 1H), 7.71 – 7.65 (m, 1H), 7.61 (d, *J* = 7.1, 1H), 7.55 (t, *J* = 7.5, 1H), 5.64 (t, *J* = 5.6, 1H), 3.17 (d, *J* = 110.3, 2H), 2.86 (d, *J* = 126.7, 2H), 2.20 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 169.9, 148.6, 134.0, 129.5, 126.4, 125.7, 122.4, 80.3, 38.4, 17.1. **HRMS (EI+)** calcd. for [C₁₀H₁₀O₂S⁺] (M⁺) 194.0402; found 194.0395. Colorless liquid, 92.2 mg, 95 % yield.

(2-chloro-3-phenylpropyl)(phenyl)sulfide (**4-3a**)

¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.13 (m, 10H), 4.20 – 4.09 (m, 1H), 3.40 – 3.28 (m, 2H), 3.18 (dd, *J* = 13.9, 7.8, 1H), 3.01 (dd, *J* = 14.2, 7.9, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ = 137.1, 134.9, 130.1, 129.5, 129.2, 128.4, 126.9, 126.8, 61.1, 42.6, 41.3. **HRMS (EI+)** calcd. for [C₁₅H₁₅SCl⁺] 262.0583; found 262.0590. Yellow liquid, 66.8 mg, 51 % yield.

(2-chloro-3-phenylpropyl)(p-tolyl)sulfide (**4-3b**)

¹H NMR (400 MHz, CDCl₃) δ = 7.38 – 7.07 (m, 9H), 4.17 – 4.10 (m, 1H), 3.42 – 3.29 (m, 2H), 3.15 (dd, *J* = 13.9, 8.0, 1H), 3.00 (dd, *J* = 14.3, 8.1, 1H), 2.34 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 137.2, 131.5, 131.1, 130.9, 129.9, 129.8, 129.7, 129.6, 128.4, 126.9, 61.2, 42.5, 42.0, 21.1. **HRMS (EI+)** calcd. for [C₁₆H₁₇SCl⁺] (M⁺) 276.0555; found 276.0547. Yellow liquid, 89.7 mg, 65 % yield.

(4-bromophenyl)(2-chloro-3-phenylpropyl)sulfide (**4-3c**)

¹H NMR (400 MHz, CDCl₃) δ = 7.46 – 7.16 (m, 9H), 4.19 – 4.08 (m, 1H), 3.36 – 2.99 (m, 4H). **¹³C NMR (100 MHz, CDCl₃)** δ = 136.9, 134.2, 132.4, 132.3, 131.5, 129.5, 128.5, 127.1, 120.7, 60.7, 42.8, 41.3. **HRMS (EI+)** calcd. for [C₁₅H₁₄SClBr⁺] (M⁺) 339.9688; found 339.9687. Yellow oil, 101.9 mg, 60 % yield.

(2-chloro-3-phenylpropyl)(4-chlorophenyl)sulfide (**4-3d**)

¹H NMR (400 MHz, CDCl₃) δ = 7.41 – 7.09 (m, 9H), 4.16 – 4.09 (m, 1H), 3.38 – 2.93 (m, 4H). **¹³C NMR (100 MHz, CDCl₃)** δ = 136.9, 133.5, 132.9, 131.4, 129.5, 129.3, 128.5, 127.0, 60.9, 42.7, 41.5. **HRMS (EI+)** calcd. for [C₁₅H₁₄SCl₂⁺] (M⁺) 266.1505; found 296.1517. Yellow liquid, 81.4 mg, 55 % yield.

(2-chloro-3-(methylsulfonyl)propyl)benzene (**4-4**)

¹H NMR (400 MHz, CDCl₃) δ = 7.39 – 7.17 (m, 5H), 4.65– 4.59 (m, 1H), 3.45 – 3.32 (m, 2H), 3.25 – 3.14 (m, 2H), 3.06 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ = 135.4, 129.5,

128.9, 128.8, 127.6, 61.3, 54.9, 44.3, 43.2. **HRMS (EI+)** calcd. for $[C_{10}H_{13}O_2SCl]^+$ (M^+) 232.0325; found 232.0323. Colorless oil, 113.6 mg, 98 % yield.

2-(1-(4-fluorophenyl)-2-(methylthio)ethyl)-1H-pyrrole (**4-5**)

1H NMR (400 MHz, CD_2Cl_2) δ = 8.17 (s, 1H), 7.29 – 7.16 (m, 2H), 7.04 (t, J = 8.6, 2H), 6.68 (s, 1H), 6.11 (d, J = 2.4, 1H), 5.99 (s, 1H), 4.19 (t, J = 7.4, 1H), 3.21 (dd, J = 13.1, 7.2, 1H), 3.00 (dd, J = 13.1, 7.7, 1H), 2.05 (s, 3H). **^{13}C NMR (100 MHz, CD_2Cl_2)** δ = 162.9, 160.5, 138.5, 133.5, 129.5, 117.0, 115.3, 108.0, 105.6, 43.8, 40.3, 15.9. **^{19}F NMR (376 MHz, CD_2Cl_2)** δ = -116.8. Colorless liquid, 89.7 mg, 65 % yield.

4.4.6. Copies of NMR spectra for compounds 4-2, 4-3, 4-4 and 4-5

5. A 5+1 PROTIC ACID-ASSISTED AZA-PUMMERER APPROACH FOR SYNTHESIS OF 4-CHLOROPIPERIDINES FROM HOMOALLYLIC AMINES

5.1 Background

Functionalized piperidines are ubiquitous in natural products¹¹⁴ and pharmaceuticals (Figure 9).¹¹⁵ Despite an extensive literature on piperidine syntheses,¹¹⁶ there are still demands for more efficient syntheses. The common strategies for the synthesis of piperidine skeletons involve intra-¹¹⁷ and intermolecular¹¹⁸ cyclization reactions, ring expansion processes¹¹⁹ and reduction of pyridines.¹²⁰ Cycloaddition is the predominant approach. This is achieved either by a nucleophilic substitution process (Scheme 9a),^{116c, 121} transition metal catalysis (Scheme 9b),^{116a, b, 122} or an electrophile- or radical-induced cyclization (Scheme 9c).¹²³ The use of designed or protected substrates and expensive transition metals limit the application of some of these methods. Another notable method for obtaining 4-chloropiperidines is through the aza-Prins cyclization method (Scheme 1e).^{54b, 118a, 124} This method usually requires transition metal or Lewis acid catalysis. In our search for applications of the newly formulated HCl/DMPU,^{9, 105} a highly concentrated, bench stable, readily prepared and easily dispensable anhydrous source of HCl, we observed the activation of DMSO. Activation of dimethyl sulfoxide by electrophiles¹²⁵ has been widely reported and has led to application of DMSO as a viable synthon,^{101b} as noted by the increased use of DMSO as a one carbon source in the

recent literature (Scheme 9d).^{94c, 126} In this chapter, we describe an application of our HCl/DMPU-mediated DMSO activation to prepare 4-chloropiperidines.

Figure 9. Examples of piperidine-containing natural products and drug molecules

Despite the tremendous progress made in alkene amino cyclization reactions,^{117, 124a, 127} there are still limitations in the substrate scope for intramolecular construction of piperidines. We wanted to avoid the use of toxic formaldehyde as a one carbon synthon. To address these limitations, we surmised one possible solution would be to exploit formation of (thiomethyl)methyl carbenium ion from DMSO in the presence of homoallylic amines (Scheme 9e).¹²⁸ The thiocarbenium ion generation could arise from a Pummerer fragmentation through the interaction of the sulfoxide with an electrophile. Such activations are common in activated, high-molecular weight sulfoxides.¹²⁹ However, the use of protic acid activation of DMSO has not been widely explored.^{100b, 130} We envisioned that reaction of the thiocarbenium ion with a homoallylic amine might initiate an intramolecular cyclization to form a piperidine ring. Specifically, tandem electrophilic capture of the DMSO-derived (thiomethyl)methyl carbenium ion by the homoallylic amine followed by intramolecular reaction of the pendant vinyl system with subsequent counterion trapping of the resulting electrophilic center could afford access

to 4-substituted piperidines. Such an approach would provide a nice compliment to current halo-piperidation techniques.^{118a, 124a, 131}

Scheme 9. Literature background

Synthesis of piperidines

a) Nucleophilic process

b) Transition metal catalyzed hydroamination

c) Electrophile induced cyclization

DMSO as a one carbon source

Aza-Prins methods

Our approach

5.2. Results and discussion

Table 10. Reaction condition optimization

Entry	Solvent	HCl source	Conc.	Conv. /% ^a
1	DCE	HCl•DMPU	1.0	64
2	CH ₃ CN	HCl•DMPU	1.0	22
3	CH ₃ NO ₃	HCl•DMPU	1.0	30
4	EtOAc	HCl•DMPU	1.0	90
5	DMSO	HCl•DMPU	1.0	18
6	EtOAc	HCl•DMPU	0.5	89
7	EtOAc	HCl•DMPU	0.2	99
8	EtOAc	HCl, Et ₂ O	0.2	32 (98) ^b
9	EtOAc	HCl, 2-propanol	0.2	99 ^c
10	EtOAc	HCl, dioxane	0.2	65 (94) ^b
11	EtOAc	HCl, AcOH	0.2	99 ^c
12	EtOAc	HCl, H ₂ O	0.2	29 (65) ^b
13	EtOAc	CH ₃ COCl/EtOH	0.2	99
14	EtOAc	TMSCl/MeOH	0.2	95

^aDetermined by GC-MS with dodecane as the internal standard. ^b 24 h, ^c combined with thiolated side product.

We began our investigation using the homoallylic amine **5-1a**, HCl•DMPU (2.4 equiv) and DMSO (2.4 equiv) in DCE at 65 °C (Table 10). We were pleased to observe that the

desired cyclized product **5-2a** was obtained in a decent yield. A solvent screening (Table 10, entries 1-5) indicated a better conversion in ethyl acetate, albeit with poor selectivity. The reaction progress appeared to be retarded by more polar solvents, possibly due to solvolysis. Reaction concentration played an important role in selectivity (Table 10, entries 6 and 7) as lower concentration favored the piperidine formation. Longer reaction times led to complete conversion (Table 10, entry 8). We also investigated other HCl sources. As expected, the lower concentration sources were sluggish (Table 10, entries 9 and 11) while the more concentrated sources gave appreciable conversions with lower ratios of the desired product (Table 10, entries 10 and 12). Use of aqueous HCl gave a dismal outcome; however, the conversions with *in situ* generated HCl (Table 10, entries 14 and 15) proceeded with comparable selectivity to the ready-made HCl•DMPU reagent. Encouraged by these results, we examined the substrate scope of this new cyclization reaction with the optimum condition (Table 11).

We first examined the scope of homoallylic anilines. The study revealed that there was broad tolerance of substituents with diverse electronic properties on all positions on the aromatic ring giving good to excellent yields. An array of para-substituted anilines containing groups such as methyl (**5-2b**), halo (**5-2d**, **5-2e**, **5-2f**), trifluoromethyl (**5-2j**), methoxy (**5-2k**), cyano (**5-2l**), trifluoromethoxy (**5-2m**), nitro (**5-2n**), phenyl (**5-2r**) and acetyl (**5-2t**) all proceeded in excellent yields. Single crystal X-ray structure of the 4-nitrophenyl derivative (**5-2n**), was obtained showing the chlorine atom locked in the axial position (Figure 10). The inclusion of similar substituents at the ortho (**5-2i**, **5-2o**, **5-2s**) and meta (**5-2c**, **5-2g**, **5-2h**, **5-2q**) positions did not affect the yields. The method displayed good functional group tolerance to groups like nitrile (**5-2l**), ester (**5-2w**), ethers (**5-2k**, **5-2m**, **5-2v**) and ketones (**5-2t**, **5-2u**). Interestingly, homoallylic sulfonamides (**5-2aa**, **5-2ab**, **5-2ac**) underwent the transformation in excellent yields.

Table 11. Substrate scope for synthesis of 4-chloropiperidines

^a **1** (0.2 mmol), HCl·DMPU (2.4 equiv), DMSO (2.4 equiv), 65 °C, 9-24 h. All yields are isolated yields.

Heteroaromatic amines containing benzodioxole (**5-2v**), thiophene (**5-2w**), pyridine (**5-2x**, **5-2y**) and pyrazine (**5-2z**) moieties also gave desired cyclization products in good yields. While meta-polysubstitution (**5-2p**) was highly selective resulting to a yield of 90%, the trisubstituted substrate (**5-2ai**) gave an inseparable 3:2 mixture of piperidine and pyrrolidine respectively. The scope was extended to aliphatic amines. Though

strongly basic, we were delighted to observe satisfactory product yields of 51-64%. Benzyl (**5-2ag**, **5-2ah**) and longer aliphatic chain (**5-2ad**, **5-2ae**, **5-2af**) substrates were also tolerated.

Figure 10. ORTEP representation of (**2n**) with thermal ellipsoids shown at the 50% probability level

Unfortunately, the method was unsuccessful with the hydrazide (**5-2aj**), hydroxylamine (**5-2ak**) and indole (**5-2al**) substrates likely due to substrate intolerance and product instability (Figure 11).

Figure 11. Failed substrates

Next, we investigated the scope of the alkene chain (Table 12). Both terminal and internal substituted alkenes afforded desired products. The disubstituted alkenes (**5-5-3a**, **5-3b**, **5-3c**, **5-3d**) furnished the desired cyclized products (**5-4a**, **5-4b**, **5-4c**, **5-4d**) in good yields of 81%, 84%, 53% and 65% respectively. The major diastereomer, **5-4d**, exhibited an anti-stereochemistry. The sterically hindered homoallylic amine derivative of nopol (**3c**) underwent the cyclization in a modest 53% yield. Good yields and diastereoselectivity were achieved for the *trans*-internal alkene. Due to steric demands, the 1,1,2-trisubstituted alkene substrate (**5-3e**) failed to achieve desired outcomes.

Rather it formed the kinetically favored pyrrolidine product in 64% yield. Also, the cyclic alkene substrate (**5-3f**) was unsuccessful probably because of ring strain barrier associated with its formation.

Table 12. Scope for synthesis of 4-chloropiperidines

Ph-NH-R^1 (**3**) $\xrightarrow[\text{EtOAc, 65 } ^\circ\text{C}]{\text{HCl}\cdot\text{DMPU (2.4 equiv), DMSO (2.4 equiv)}}$ $\text{Ph-N-CH}_2\text{-CH}_2\text{-CH(R}^2\text{)-CH}_2\text{-CH}_2\text{-Cl}$ (**4**)

entry	3	4	Yield ^a
1			4a , 81%
2			4b , 84%
3			4c , 53%
4			4d , 65%, 3:1 dr
5			4e , 64% ^b
6			4f , unsuccessful

^a **3** (0.2 mmol), HCl·DMPU (2.4 equiv), DMSO (2.4 equiv), 65 °C, 9-18 h, isolated yields, ^b ¹H NMR with CH₂Br₂ as internal standard.

To demonstrate the practicality of the method, a 10 mmol reaction (Scheme 10, eq 1) of **5-1a** was performed without any further modifications. We were gratified to find that desired product **5-2a** was obtained in high yield. To probe the mechanism of the process, a deuterium labeling experiment using deuterated DMSO was performed. High

deuterium incorporation of over 99% was observed for the resulting piperidine (Scheme 10, eq 2). This indicates that the extra carbon arises from DMSO. Zhong and co-workers¹³² reported that DMSO can serve as a formaldehyde surrogate. It is however, inconclusive that it is the case here because as earlier referenced, DMSO can equally serve as a one-carbon source. Given the abundance of chloride ion during the reaction, the *in-situ* generation of chloromethyl methyl sulfide (**IIb**) as an intermediate is possible. Indeed, reaction of the starting amine with commercially available chloromethyl methyl sulfide led to the formation of **5-2a** in 64% yield (Scheme 10, eq 3). Finally, to seek insight as to the intermediacy of an iminium ion prior to cyclization, we performed the reaction with tertiary amine **5-7** and observed no cyclization to give **5-2a**. Rather the chlorothiolated product **5-8**¹⁰ was formed in 67% (Scheme 10, eq 4).

Scheme 10. Gram scale reaction and mechanistic study

Based on the above results, a plausible mechanism is proposed (Scheme 11). Electrophilic activation of DMSO by HCl generates sulfonium salt I, which undergoes base-assisted elimination of water to generate (thiomethyl)methyl carbenium ion IIa. Interchangeable formation of chloromethyl methyl sulfide (IIb) may also be operative. IIa/b reacts with the starting amine to ultimately generate iminium ion V from ammonium salt IV via proton transfer (P.T.) and elimination of methyl mercaptan. A 6-endo-trig cyclization¹³³ followed by nucleophilic addition of chloride ion gives the desired product.

Scheme 11. Proposed mechanism

5.3. Conclusion

In summary, we have developed a convenient protic acid-catalyzed formation of (thiomethyl)methyl carbenium ion from DMSO under mild conditions. In the presence of homoallylic amines, the *in situ*-generated species reacts in aza-Pummerer fashion to generate an iminium ion intermediate that cyclizes to form 4-chloropiperidines in good

yield. The method is applicable to both aromatic and aliphatic amines. The use of HCl•DMPU as protic acid, non-nucleophilic base and chloride source provides an environmentally benign method for piperidine formation. The reaction has a broad substrate scope and is scalable.

5.4. Experimental

5.4.1. General

^1H and ^{13}C NMR spectra were recorded either at 400 MHz or 500 MHz, and 101 MHz using CDCl_3 or CD_2Cl_2 as a solvent. The chemical shifts are reported in δ (ppm) values (^1H and ^{13}C NMR relative to CHCl_3 , δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants (J), are reported in Hertz (Hz). The HRMS data was obtained from an Agilent Technologies QTOF spectrometer. All reagents and solvents were employed without further purification. The products were purified using a commercial flash chromatography system. TLC was developed on silica gel 60 F254 aluminum sheets.

5.4.2. General procedure for preparing homoallylic amines, **1** and **3**¹³⁴.

To a round bottomed flask equipped with a stirring bar was charged with aryl or alkylamine **5-1** or **5-3** (1.2 mmol, 1.2 equiv), K_2CO_3 (2 mmol, 2 equiv) and dry DMF (3 mL). Homoallyl bromide (1 mmol, 1 equiv) was slowly added to the mixture and heated to 110 °C. The progress of the reaction was monitored by GC-MS and/or TLC. Upon completion, the reaction mixture was cooled to room temperature and water (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were then dried

over anhydrous Na₂SO₄, filtered, concentrated and eventually purified silica gel column chromatography with hexanes/ethyl acetate or petroleum ether/ethyl acetate as eluent.

5.4.3. Procedure for synthesis of 4-chloropiperidines, 5-2 and 5-4.

A glass vial equipped with a screw cap and a stirring bar was charged with alkene **5-1** (0.5 mmol). Then ethyl acetate was added (2.5 mL) followed by DMSO (2.4 mmol) and HCl/DMPU (102 μ L, 2.4 mmol). The reaction mixture was stirred at 65 °C and the progress of the reaction was monitored by GC-MS or TLC. Upon completion, the reaction mixture was quenched with water and extracted with DCM. The combined organic layers were then dried over anhydrous Na₂SO₄, filtered and solvent evaporated. The crude product was purified by silica gel column chromatography (hexanes/ethyl acetate).

5.4.4. Characterization of starting materials and products

N-(but-3-en-1-yl)aniline (**5-1a**)

¹H NMR (400 MHz, CDCl₃) δ 7.19 (t, J = 7.9 Hz, 2H), 6.72 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 2H), 5.85– 5.79 (m, 1H), 5.21 – 5.07 (m, 2H), 3.63 (s, 1H), 3.20 (t, J = 6.7 Hz, 2H), 2.40 (q, J = 6.7 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.4, 136.0, 129.4, 117.6, 117.3, 113.1, 43.0, 33.8.

N-(but-3-en-1-yl)-4-methylaniline (**5-1b**)

¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 5.87–5.78 (m, 1H), 5.17 – 5.10 (m, 2H), 3.52 (s, 1H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.38 (q, *J* = 6.7 Hz, 2H), 2.25 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 146.1, 136.0, 129.8, 126.68, 117.1, 113.2, 43.3, 33.8, 20.5.

N-(but-3-en-1-yl)-3-methylaniline (**5-1c**)

¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 7.7 Hz, 2H), 5.86 – 5.78 (m, 1H), 5.17 – 5.10 (m, 2H), 3.60 (s, 1H), 3.18 (t, *J* = 6.7 Hz, 2H), 2.42 – 2.32 (m, 2H), 2.28 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.2, 138.9, 135.7, 129.0, 118.2, 116.9, 113.6, 109.9, 42.7, 33.6, 21.5.

N-(but-3-en-1-yl)-4-fluoroaniline (**5-1d**)

¹H NMR (400 MHz, CDCl₃) δ 6.88 (t, *J* = 8.8 Hz, 2H), 6.54 (dd, *J* = 9.0, 4.4 Hz, 2H), 5.85 – 5.76 (m, 1H), 5.17 – 5.10 (m, 2H), 3.54 (s, 1H), 3.14 (t, *J* = 6.7 Hz, 2H), 2.37 (q, *J* = 6.7 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 156.8, 144.6, 135.7, 117.2, 115.7, 115.6, 113.7, 43.5, 33.6. **¹⁹F NMR (376 MHz, CDCl₃)** δ -128.35.

N-(but-3-en-1-yl)-4-chloroaniline (**5-1e**)

¹H NMR (500 MHz, CDCl₃) δ 7.11(d, *J* = 7.8, 2H), 6.53 (d, *J* = 7.9, 2H), 5.81 – 5.77 (m, 1H), 5.15 – 5.10 (m, 2H), 3.66 (s, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.37 (q, *J* = 6.7, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 146.8, 135.5, 129.0, 121.9, 117.3, 113.9, 42.9, 33.5.

4-bromo-N-(but-3-en-1-yl)aniline (**5-1f**)

¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 5.97 – 5.88 (m, 1H), 5.29 – 5.23 (m, 2H), 3.80 (s, 1H), 3.27 (t, *J* = 6.7 Hz, 2H), 2.50 (q, *J* = 6.7 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 147.3, 135.6, 132.0, 117.4, 114.5, 108.9, 42.9, 33.5.

N-(but-3-en-1-yl)-3-iodoaniline (**5-1g**)

¹H NMR (500 MHz, CDCl₃) δ 7.02 (d, *J* = 7.7 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.88 (t, *J* = 8.0 Hz, 1H), 6.56 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.29 – 4.97 (m, 2H), 3.69 (s, 1H), 3.16 (dd, *J* = 11.9, 6.4 Hz, 2H), 2.39 (dt, *J* = 7.9, 6.1 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 149.4, 135.4, 130.6, 126.1, 121.3, 117.4, 112.2, 95.3, 42.5, 33.4.

3-bromo-N-(but-3-en-1-yl)aniline (**5-1h**)

¹H NMR (500 MHz, CDCl₃) δ 7.02 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.1 Hz, 1H), 6.75 (d, *J* = 1.7 Hz, 1H), 6.52 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.75-5.63 (m, 1H), 5.15 (t, *J* = 13.2 Hz, 2H), 3.74 (s, 1H), 3.17 (dd, *J* = 12.2, 6.4 Hz, 2H), 2.39 (q, *J* = 6.7 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 149.5, 135.4, 130.5, 123.3, 120.0, 117.4, 115.3, 111.6, 42.6, 33.4.

N-(but-3-en-1-yl)-2-iodo-4-methylaniline (**5-1i**)

¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 1.7 Hz, 1H), 7.02 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.48 (d, *J* = 8.2 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.05

(s, 1H), 3.20 (t, J = 6.7 Hz, 2H), 2.43 (q, J = 6.8 Hz, 2H), 2.21 (s, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 144.9, 139.1, 135.3, 129.8, 127.8, 117.3, 110.5, 85.3, 43.3, 33.3, 19.6.

N-(but-3-en-1-yl)-4-(trifluoromethyl)aniline (**5-1j**)

^1H NMR (400 MHz, CDCl_3) δ 7.45 - 7.30 (m, 2H), 6.68 (d, J = 8.3 Hz, 2H), 6.59 (d, J = 8.5 Hz, 2H), 5.81 (dd, J = 17.1, 10.2 Hz, 2H), 5.14 (dd, J = 12.7, 11.0 Hz, 3H), 3.97 (s, 3H), 3.21 (t, J = 6.7 Hz, 3H), 2.39 (d, J = 6.7 Hz, 3H). **^{13}C NMR (100 MHz, CDCl_3)** δ 150.4, 135.2, 126.6, 126.5, 117.4, 112.0, 42.4, 33.3. **^{19}F NMR (376 MHz, CDCl_3)** δ -61.02.

N-(but-3-en-1-yl)-4-methoxyaniline (**5-1k**)

^1H NMR (400 MHz, CDCl_3) δ 6.80 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 5.87 – 5.80 (m, 1H), 5.19 – 5.07 (m, 2H), 3.75 (s, 3H), 3.32 (s, 1H), 3.15 (t, J = 6.7 Hz, 2H), 2.38 (q, J = 6.7 Hz, 2H). **^{13}C NMR (100 MHz, CDCl_3)** δ 152.2, 142.6, 136.0, 117.1, 115.0, 114.3, 55.8, 43.9, 33.8.

4-(but-3-en-1-ylamino)benzonitrile (**5-1l**)

¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.20 – 5.08 (m, 2H), 4.24 (s, 1H), 3.22 (t, *J* = 6.7 Hz, 2H), 2.39 (q, *J* = 6.7, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.2, 135.0, 133.7, 120.5, 117.7, 112.2, 98.6, 42.0, 33.2.

N-(but-3-en-1-yl)-4-(trifluoromethoxy)aniline (**5-1m**)

¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 9.0 Hz, 2H), 5.87 – 5.78 (m, 1H), 5.25 – 5.14 (m, 2H), 3.78 (s, 1H), 3.21 (t, *J* = 6.7 Hz, 2H), 2.43 (q, *J* = 6.7 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 146.9, 140.3, 135.4, 124.5, 122.3, 121.9, 119.4, 117.2, 116.8, 112.9, 42.8, 33.4. **¹⁹F NMR (376 MHz, CDCl₃)** δ -58.31.

N-(but-3-en-1-yl)-4-nitroaniline (**5-1n**)

¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 9.2 Hz, 2H), 6.53 (d, *J* = 9.2 Hz, 2H), 5.87 – 5.77 (m, 1H), 5.26 – 5.11 (m, 2H), 4.50 (s, 1H), 3.29 (dd, *J* = 12.1, 6.6 Hz, 2H), 2.43 (q, *J* = 6.7 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 153.3, 149.7, 138.2, 134.9, 126.6, 118.2, 111.2, 42.3, 33.3.

N-(but-3-en-1-yl)-2-(trifluoromethyl)aniline (**5-1o**)

¹H NMR (400 MHz, CDCl₃) δ 7.79 - 7.19 (m, 2H), 6.95 - 6.62 (m, 2H), 5.92-5.80 (m, 1H), 5.69 - 5.02 (m, 2H), 4.55 (s, 1H), 3.39 (t, *J* = 6.4 Hz, 2H), 2.59 (ddd, *J* = 6.7, 6.2, 1.2 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 145.8, 135.2, 133.2, 126.8, 126.7, 124.0, 117.7, 115.9, 111.9, 42.5, 33.4. **¹⁹F NMR (376 MHz, CDCl₃)** δ -62.44.

N-(but-3-en-1-yl)-3,5-bis(trifluoromethyl)aniline (**5-1p**)

¹H NMR (400 MHz, CDCl₃) δ 7.04 (s, 1H), 6.83 (s, 2H), 5.72 (td, *J* = 16.8, 6.6 Hz, 1H), 5.16 - 5.03 (m, 2H), 4.01 (s, 1H), 3.14 (dd, *J* = 12.1, 6.3 Hz, 2H), 2.33 (q, *J* = 6.7 Hz, 2H), 1.45 (s, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.3, 134.5, 124.5, 121.8, 117.5, 111.4, 109.7, 41.9, 32.8. **¹⁹F NMR (376 MHz, CDCl₃)** δ -63.54.

N-(but-3-en-1-yl)-3-(trifluoromethyl)aniline (**5-1q**)

¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, *J* = 9.2, 6.6 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.84 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.87 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.44 – 4.88 (m, 2H), 3.91 (s, 1H), 3.26 (s, 2H), 2.57 – 2.29 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.4, 135.4, 131.7, 131.4, 129.6, 125.7, 123.0, 117.5, 115.8, 113.7, 113.7, 108.9, 108.9, 42.5, 33.4. **¹⁹F NMR (376 MHz, CDCl₃)** δ -62.90.

N-(but-3-en-1-yl)-[1,1'-biphenyl]-4-amine (**5-1r**)

¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.20 – 7.10 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 5.86 – 5.61 (m, 1H), 5.03 (t, *J* = 14.5 Hz, 2H), 3.63 (s, 1H), 3.11 (t, *J* = 6.7 Hz, 2H), 2.29 (q, *J* = 6.6 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 147.5, 141.1, 135.6, 130.1, 128.5, 127.8, 126.1, 125.9, 117.0, 113.0, 42.7, 33.5.

N-(but-3-en-1-yl)-[1,1'-biphenyl]-2-amine (**5-1s**)

¹H NMR (500 MHz, CDCl₃) δ 7.48 – 7.31 (m, 5H), 7.28 – 7.21 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.73 – 6.68 (m, 1H), 5.94 – 5.50 (m, 1H), 5.00 (dd, *J* =

8.6, 6.5 Hz, 2H), 3.99 (s, 1H), 3.18 (dd, J = 11.8, 6.4 Hz, 2H), 2.32 (q, J = 6.7 Hz, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 145.0, 139.4, 135.6, 130.1, 129.4, 128.8, 128.7, 127.7, 127.1, 117.0, 116.8, 110.4, 42.8, 33.5.

1-(4-(but-3-en-1-ylamino)phenyl)ethanone (**5-1t**)

^1H NMR (500 MHz, CDCl_3) δ = 7.84 (d, J =8.8, 2H), 6.60 – 6.50 (m, 2H), 5.78-5.66 (m, 1H), 5.21 - 5.08 (m, 2H), 4.21 (s, 1H), 3.27 (dd, J =12.2, 6.6, 2H), 2.50 (d, J =6.9, 2H), 2.42 (dd, J =13.5, 6.8, 1H). **^{13}C NMR (126 MHz, CDCl_3)** δ 152.0, 135.1, 130.8, 117.6, 111.4, 42.1, 33.4, 26.0.

(3-(but-3-en-1-ylamino)phenyl)(phenyl)methanone (**5-1u**)

^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.29 - 7.24 (m, 1H), 7.06 (d, J = 6.5 Hz, 2H), 6.82 (d, J = 8.3 Hz, 1H), 5.77-5.66 (m, 1H), 5.14 (t, J = 13.2 Hz, 2H), 3.81 (s, 1H), 3.22 (t, J = 6.7 Hz, 2H), 2.46 - 2.31 (m, 2H). **^{13}C NMR (100 MHz, CDCl_3)** δ 197.2, 148.2, 138.6, 137.9, 135.5, 132.2, 130.0, 128.9, 128.1, 119.6, 117.4, 116.9, 113.5, 42.7, 33.5.

N-(but-3-en-1-yl)benzo[d][1,3]dioxol-5-amine (**5-1v**)

¹H NMR (500 MHz, CDCl₃) δ 6.67 (d, *J* = 8.3 Hz, 1H), 6.26 (s, 1H), 6.07 (d, *J* = 8.3 Hz, 1H), 5.97 - 5.74 (m, 3H), 5.10-5.01 (m, 2H), 3.45 (s, 1H), 3.13 (td, *J* = 6.7, 1.4 Hz, 2H), 2.44 - 2.31 (m, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 148.3, 144.1, 139.6, 135.7, 117.1, 108.6, 104.5, 100.5, 96.1, 43.8, 33.6.

methyl 3-(but-3-en-1-ylamino)thiophene-2-carboxylate (**5-1w**)

¹H NMR (500 MHz, CDCl₃) δ 7.33 (d, *J* = 5.5 Hz, 1H), 6.76 (s, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 5.86 - 5.79 (m, 1H), 5.18 - 5.11 (m, 2H), 3.81 (s, 3H), 3.34 (d, *J* = 2.7 Hz, 2H), 2.50 - 2.28 (m, 2H).. **¹³C NMR (100 MHz, CDCl₃)** δ 165.4, 156.1, 135.1, 132.2, 117.4, 116.2, 98.5, 51.1, 44.4, 34.3.

N-(but-3-en-1-yl)-6-chloropyridin-3-amine (**5-1x**)

¹H NMR (500 MHz, CDCl₃) δ 7.77 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.6, 1H), 5.76-5.64 (m, 1H), 5.16 (dd, *J* = 13.3, 6.3 Hz, 2H), 3.74 (s, 1H), 3.18 (dd, *J* = 12.5, 6.4

Hz, 2H), 2.40 (q, J = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, CDCl_3)** δ 143.2, 139.0, 135.0, 134.5, 124.0, 122.2, 117.7, 42.5, 33.3.

N-(but-3-en-1-yl)-4-chloropyridin-2-amine (**5-1y**)

^1H NMR (500 MHz, CDCl_3) δ 8.03 (s, 1H), 7.36 (d, J = 8.8, 1H), 6.33 (d, J = 8.9 Hz, 1H), 5.93 – 5.69 (m, 1H), 5.34 – 4.99 (m, 2H), 4.53 (s, 1H), 3.41 – 3.27 (m, 2H), 2.38 (dt, J = 6.6, 5.5 Hz, 2H). **^{13}C NMR (100 MHz, CDCl_3)** δ 143.4, 138.8, 135.1, 134.5, 124.1, 122.3, 117.7, 42.6, 33.4.

N-(but-3-en-1-yl)-5-chloropyrazin-2-amine (**5-1z**)

^1H NMR (500 MHz, CDCl_3) δ 8.00 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 5.76-5.65 (m, 1H), 5.32 – 4.98 (m, 2H), 4.68 (s, 1H), 3.40 (dd, J = 12.4, 6.6 Hz, 2H), 2.40 (q, J = 6.7 Hz, 2H). **^{13}C NMR (126 MHz, CDCl_3)** δ 153.3, 141.2, 136.0, 135.0, 129.9, 117.7, 40.7, 33.4.

N-(but-3-en-1-yl)-4-methylbenzenesulfonamide (**5-1aa**)

¹H NMR (500 MHz, CDCl₃) δ 6.67 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.26 (t, *J* = 1.8 Hz, 1H), 6.06 (ddd, *J* = 11.6, 6.8, 4.8 Hz, 1H), 5.92 – 5.77 (m, 3H), 5.15-5.05 (m, 2H), 3.69 - 3.21 (m, 1H), 3.13 (td, *J* = 6.7, 1.4 Hz, 2H), 2.49 - 2.25 (m, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 148.3, 144.1, 139.6, 135.7, 117.1, 108.6, 104.5, 100.5, 96.1, 43.8, 33.6.

N-(but-3-en-1-yl)-4-methoxybenzenesulfonamide (**5-1ab**)

¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.72 - 5.39 (m, 1H), 5.13 – 4.78 (m, 2H), 4.65 (d, *J* = 6.0 Hz, 1H), 3.80 (d, *J* = 0.6 Hz, 3H), 3.07 – 2.71 (m, 2H), 2.13 (q, *J* = 6.8 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 162.8, 134.1, 131.4, 129.1, 117.9, 114.2, 55.6, 42.0, 33.5.

4-bromo-N-(but-3-en-1-yl)benzenesulfonamide (**5-1ac**)

¹H NMR (500 MHz, CDCl₃) δ 7.77 - 7.69 (m, 2H), 7.68 - 7.62 (m, 2H), 5.58-5.46 (m, 1H), 5.16 - 4.95 (m, 2H), 4.90 (s, 1H), 3.03 (dd, *J* = 12.9, 6.7 Hz, 2H), 2.22 (qt, *J* = 6.8, 1.3 Hz, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 139.0, 133.9, 132.3, 128.6, 127.5, 118.2, 42.1, 33.6.

N-(but-3-en-1-yl)-2-ethylhexan-1-amine (**5-1ad**)

¹H NMR (400 MHz, CDCl₃) δ 5.78 (m, *J* = 13.7, 10.2, 5.1 Hz, 1H), 5.18 - 4.93 (m, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.49 (d, *J* = 6.2 Hz, 2H), 2.32 - 2.13 (m, 2H), 1.52 - 1.36 (m, 1H), 1.35 - 1.20 (m, 7H), 0.88 (m, 6H). **¹³C NMR (100 MHz, CDCl₃)** δ 136.6, 116.1, 53.1, 49.2, 39.4, 34.3, 31.4, 29.0, 24.5, 23.1, 14.1, 10.8.

N-phenethylbut-3-en-1-amine (**5-1ae**)

¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.33 (m, 5H), 5.99 - 5.90 (m, 1H), 5.30 - 5.15 (m, 2H), 3.13 - 3.05 (m, 2H), 3.03 - 2.97 (m, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 2.44 (q, *J* = 6.9 Hz, 2H), 1.31 (s, 1H). **¹³C NMR (100 MHz, CDCl₃)** δ 140.2, 136.5, 128.8, 128.5, 126.2, 116.4, 51.2, 48.9, 36.5, 34.4.

N-(4-methoxyphenethyl)but-3-en-1-amine (**5-1af**)

¹H NMR (400 MHz, CDCl₃) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.79 - 5.67 (m, 1H), 5.25 - 4.97 (m, 2H), 3.87 (s, 2H), 2.98 - 2.90 (m, 2H), 2.86 - 2.74 (m, 2H),

2.32 (q, J = 6.9 Hz, 2H), 1.83 (s, 1H). **^{13}C NMR (100 MHz, CDCl_3)** δ 158.1, 136.4, 132.1, 129.7, 116.4, 113.9, 55.3, 51.3, 48.8, 35.5, 34.3.

N-benzylbut-3-en-1-amine (**5-1ag**)

^1H NMR (400 MHz, CDCl_3) δ = 7.39 – 7.19 (m, 5H), 5.84 – 5.74 (m, 1H), 5.16 – 4.98 (m, 2H), 3.79 (s, 2H), 2.70 (t, J =6.8, 2H), 2.28 (dt, J =6.9, 6.2, 2H), 1.29 (s, 1H). **^{13}C NMR (100 MHz, CDCl_3)** δ 140.4, 136.5, 128.4, 128.1, 126.9, 116.3, 53.9, 48.3, 34.3.

(R)-N-(1-phenylethyl)but-3-en-1-amine (**5-1ah**)

^1H NMR (400 MHz, CDCl_3) δ 8.15 – 6.33 (m, 5H), 5.69 – 5.58 (m, 1H), 5.31 – 4.69 (m, 2H), 3.76 (q, J = 6.6 Hz, 1H), 2.72 – 2.36 (m, 2H), 2.29 – 2.07 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H), 1.27 (s, 1H). **^{13}C NMR (100 MHz, CDCl_3)** δ 145.7, 136.5, 128.4, 126.8, 126.5, 116.2, 58.2, 46.5, 34.3, 24.3.

N-(3-methylbut-3-en-1-yl)aniline (**5-3a**)

¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 5.54 -5.41 (m, 1H), 5.50 - 5.37 (m, 1H), 4.13 (s, 1H), 3.65 (s, 1H), 3.13 (t, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 6.7 Hz, 2H), 1.70 (d, *J* = 6.0 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.4, 129.2, 128.2, 127.7, 117.2, 112.8, 77.3, 77.0, 76.7, 43.3, 32.4, 18.0.

N-(3-bromobut-3-en-1-yl)aniline (**5-3b**)

¹H NMR (500 MHz, CDCl₃) δ 7.26 - 7.17 (m, 2H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 - 6.58 (m, 2H), 5.75 - 5.63 (m, 1H), 5.55 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 1H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.74 (t, *J* = 6.5 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 147.6, 131.3, 129.3, 118.9, 117.7, 113.0, 41.6, 40.9.

N-(2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl)aniline (**5-3c**)

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.11 (m, 2H), 6.72 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.65 – 6.55 (m, 2H), 5.37 (dt, *J* = 4.2, 1.3 Hz, 1H), 3.66 (s, 1H), 3.27 – 2.93 (m, 2H), 2.41 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.36 – 2.24 (m, 4H), 2.17 – 1.99 (m, 2H), 1.41 – 1.22 (m, 5H), 0.93 – 0.81 (m, 4H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.4, 145.6, 129.2, 118.7, 117.2, 112.9, 45.4, 41.2, 40.8, 38.0, 36.5, 31.8, 31.4, 26.3, 22.7, 21.2, 14.2.

(E)-N-(pent-3-en-1-yl)aniline (**5-3d**)

¹H NMR (400 MHz, CDCl₃) δ 7.18 (t, *J* = 7.9 Hz, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 5.54-5.44 (m, 1H), 5.50 - 5.37 (m, 1H), 3.65 (s, 1H), 3.13 (t, *J* = 6.7 Hz, 2H), 2.31 (q, *J* = 6.7 Hz, 2H), 1.70 (d, *J* = 6.0 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.4, 129.2, 128.2, 127.7, 117.2, 112.8, 43.3, 32.4, 18.0.

N-(4-methylpent-3-en-1-yl)aniline (**5-3e**)

¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.7 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 5.28 (t, *J* = 7.2 Hz, 1H), 3.76 (s, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.44 (d, *J* = 7.0 Hz, 2H), 1.86 (s, 3H), 1.77 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 148.5, 134.4, 129.3, 121.4, 117.3, 113.0, 43.9, 28.2, 25.9, 18.0.

4-chloro-1-phenylpiperidine (**5-2a**)

¹H NMR (400 MHz, CDCl₃) δ 7.23 (t, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.82 (t, *J* = 7.3 Hz, 1H), 4.25 – 4.14 (m, 1H), 3.54 – 3.45 (m, 2H), 3.07 – 2.97 (m, 2H), 2.25 – 2.15

(m, 2H), 2.03 – 1.92 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.1, 129.2, 119.8, 116.6, 57.2, 47.5, 35.1. **HRMS (EI+)** calcd. for [C₁₁H₁₄NCl] (MH⁺) 196.1044; found 196.1041. Colorless oil, 92.6 mg, 95% yield.

4-chloro-1-(p-tolyl)piperidine (**5-2b**)

¹H NMR (400 MHz, CDCl₃) δ = 7.05 (d, *J*=7.7, 2H), 6.83 (d, *J*=7.5, 2H), 4.16 (*bs*, 1H), 3.42 – 3.44 (m, 2H), 2.99 – 2.95 (m, 2H), 2.29 – 2.12 (m, 5H), 2.00 – 1.98 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 149.0, 129.6, 129.3, 116.9, 57.1, 48.1, 35.2, 20.4. **HRMS (EI+)** calcd. for [C₁₂H₁₇NCl] (MH⁺) 210.1044; found 210.1042. Colorless oil, 89.1 mg, 85% yield.

4-chloro-1-(m-tolyl)piperidine (**5-2c**)

¹H NMR (400 MHz, CDCl₃) δ 7.16 (t, *J* = 7.7 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 7.4 Hz, 1H), 4.23 – 4.17 (m, 1H), 3.55 – 3.47 (m, 2H), 3.09 – 2.99 (m, 2H), 2.32 (s, 3H), 2.26 – 2.17 (m, 2H), 2.06 – 1.95 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.1, 138.9, 129.0, 120.8, 117.5, 113.7, 57.2, 47.7, 35.1, 21.8. **HRMS (EI+)** calcd. for [C₁₂H₁₇NCl] (MH⁺) 210.1044; found 210.1042. Colorless oil, 97.5 mg, 93% yield.

4-chloro-1-(4-fluorophenyl)piperidine (**5-2d**)

¹H NMR (400 MHz, CDCl₃) δ 7.01 – 6.84 (m, 4H), 4.19 (tt, *J* = 8.0, 3.9 Hz, 1H), 3.45 – 3.31 (m, 2H), 3.02 – 2.93 (m, 2H), 2.22 (dtd, *J* = 10.4, 7.0, 3.6 Hz, 2H), 2.09 – 1.95 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 158.3, 155.9, 147.7, 118.4, 115.5, 115.3, 56.7, 48.3, 35.0. **¹⁹F NMR (376 MHz, CDCl₃)** δ = -124.31 (s, 1H). **HRMS (EI⁺)** calcd. for [C₁₁H₁₃ClFN] (M⁺) 213.0719; found 213.0714. Colorless oil, 89.5 mg, 84% yield.

4-chloro-1-(4-chlorophenyl)piperidine (**5-2e**)

¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.21 (tt, *J* = 7.6, 3.7 Hz, 1H), 3.52 – 3.35 (m, 2H), 3.13 – 2.97 (m, 2H), 2.27 – 2.11 (m, 2H), 2.06 – 1.92 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 149.6, 129.0, 124.6, 117.7, 56.8, 47.4, 34.8. **HRMS (EI⁺)** calcd. for [C₁₁H₁₄NC₂] (MH⁺) 230.0498; found 230.0496. Colorless oil, 104.7 mg, 91 % yield.

1-(4-bromophenyl)-4-chloropiperidine (**5-2f**)

¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.21 (tt, *J* = 7.8, 3.9 Hz, 1H), 3.51 – 3.39 (m, 2H), 3.12 – 2.94 (m, 2H), 2.20 (dtd, *J* = 10.5, 7.0, 3.6 Hz, 2H), 2.06 – 1.94 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 150.0, 131.9, 129.1, 118.1, 56.8, 47.2, 34.7. **HRMS (EI+)** calcd. for [C₁₁H₁₄NBrCl] (MH⁺) 273.9993; found 273.9989. Colorless oil, 109.9 mg, 80% yield.

4-chloro-1-(3-iodophenyl)piperidine (**5-2g**)

¹H NMR (400 MHz, CDCl₃) δ 7.25 – 7.23 (m, 1H), 7.18 – 7.13 (m, 1H), 6.98 – 6.93 (m, 1H), 6.87 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 4.21 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.12 – 3.01 (m, 2H), 2.18 (ddd, *J* = 13.1, 6.8, 3.3 Hz, 2H), 2.03 – 1.92 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.1, 130.5, 128.4, 125.2, 115.6, 95.2, 56.8, 46.9, 34.7. **HRMS (EI+)** calcd. for [C₁₁H₁₃ClIN] (M⁺) 320.9781; found 320.9775. Colorless oil, 112.3 mg, 70% yield.

1-(3-bromophenyl)-4-chloropiperidine (**5-2h**)

¹H NMR (400 MHz, CDCl₃) δ 7.11 (t, *J*=8.1, 1H), 7.05 (t, *J*=2.1, 1H), 6.96 (ddd, *J*=7.8, 1.8, 0.8, 1H), 6.87 – 6.81 (m, 1H), 4.22 (tt, *J*=7.8, 3.8, 1H), 3.57 – 3.45 (m, 2H), 3.15 – 3.04 (m, 2H), 2.25 – 2.15 (m, 2H), 2.05 – 1.93 (m, 2H). **¹³C NMR (100 MHz CDCl₃)** δ 152.2, 130.4, 123.2, 122.2, 119.1, 114.8, 56.8, 46.8, 34.6. **HRMS (EI⁺)** calcd. for [C₈H₁₄NBrClF₂] (MH⁺) 275.9970; found 275.9969. Colorless oil, 137 mg, 86% yield.

4-chloro-1-(2-iodo-4-methylphenyl)piperidine (**5-2i**)

¹H NMR (400 MHz, CDCl₃) δ 7.67 (s, 1H), 7.10 (d, *J*=8.1, 1H), 6.93 (d, *J*=8.1, 1H), 4.21 (bs, 1H), 3.19 – 3.14 (m, 2H), 2.81 – 2.77 (m, 2H), 2.28 – 2.20 (m, 5H), 2.14 – 2.03 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.7, 129.0, 126.4, 125.9, 125.6, 123.2, 120.5, 114.8, 58.6, 45.9, 34.3. **HRMS (EI⁺)** calcd. for [C₁₂H₁₅ClIN] (M⁺) 334.994; found 334.9943. Colorless oil, 137.3 mg, 82% yield.

4-chloro-1-(4-(trifluoromethyl)phenyl)piperidine (**5-2j**)

¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.28 – 4.28 (m, 1H), 3.64 – 3.53 (m, 2H), 3.25 – 3.15 (m, 2H), 2.23 – 2.17 (m, 2H), 2.04 – 1.91 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.7, 129.0, 126.4, 125.9, 125.6, 123.2, 120.5,

114.8, 58.6, 45.9, 34.3. **¹⁹F NMR (376 MHz, CDCl₃)** δ -61.35. **HRMS (EI+)** calcd. for [C₁₂H₁₃ClF₃N] (M⁺) 263.0691; found 263.0686. Colorless oil, 106.5 mg, 81% yield.

4-chloro-1-(4-methoxyphenyl)piperidine (**5-2k**)

¹H NMR (400 MHz, CDCl₃) δ = 6.93 (d, *J*=9.0, 2H), 6.85 (d, *J*=8.9, 2H), 4.24 – 4.12 (m, 1H), 3.79 (s, 3H), 3.46 – 3.34 (m, 2H), 3.00 – 2.90 (m, 2H), 2.22 (s, 2H), 2.12 – 2.00 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 153.9, 145.6, 118.8, 114.4, 57.1, 55.5, 49.1, 35.4. **HRMS (EI+)** calcd. for [C₁₂H₁₇ONCl] (MH⁺) 226.0993; found 226.0990. Colorless oil, 101.5 mg, 90% yield.

4-(4-chloropiperidin-1-yl)benzonitrile (**5-2l**)

¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.31 – 4.26 (m, 1H), 3.69 – 3.57 (m, 2H), 3.32 – 3.26 (m, 2H), 2.21 – 2.14 (m, 2H), 2.00 – 1.92 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.7, 133.4, 119.8, 114.3, 100.0, 56.3, 44.9, 34.1. **HRMS (EI+)** calcd. for [C₁₂H₁₄N₂Cl] (MH⁺) 221.0840; found 221.0837. Colorless oil, 79.4 mg, 72% yield.

4-chloro-1-(4-(trifluoromethoxy)phenyl)piperidine (**5-2m**)

¹H NMR (400 MHz, CDCl₃) δ = 7.11 (d, J =8.7, 2H), 6.90 (d, J =8.9, 2H), 4.22 (dt, J =11.7, 3.8, 1H), 3.53 – 3.44 (m, 2H), 3.13 – 3.03 (m, 2H), 2.21 (dd, J =14.6, 11.6, 2H), 2.06 – 1.96 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 149.7, 141.9, 124.2, 121.8, 119.2, 117.1, 114.4, 112.8, 56.6, 47.3, 34.7. **¹⁹F NMR (376 MHz, CDCl₃)** δ = -58.32. **HRMS (EI+)** calcd. for [C₁₂H₁₄ONClF₃] (MH⁺) 280.0711; found 280.0708. Colorless oil, 126 mg, 90 % yield.

4-chloro-1-(4-nitrophenyl)piperidine (**5-2n**)

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 9.4 Hz, 2H), 6.82 (d, J = 9.4 Hz, 2H), 4.32 (dq, J = 10.8, 3.7 Hz, 1H), 3.78 – 3.65 (m, 2H), 3.40 (ddd, J = 11.5, 7.3, 3.6 Hz, 2H), 2.26 – 2.11 (m, 2H), 2.01 – 1.93 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 154.4, 138.4, 126.1, 112.9, 56.3, 44.9, 34.3. **HRMS (EI+)** calcd. for [C₁₁H₁₃ClN₂ O₂] (M⁺) 240.0669; found 240.0664. Yellow solid crystal, 72.0 mg, 60% yield.

4-chloro-1-(2-(trifluoromethyl)phenyl)piperidine (**5-2o**)

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 4.23 (bs, 1H), 3.21 – 3.02 (m, 2H), 2.81 (ddd, *J* = 11.2, 7.7, 3.2 Hz, 2H), 2.21 (ddd, *J* = 13.5, 6.9, 3.4 Hz, 2H), 2.09 – 1.97 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 152.8, 132.9, 128.6, 127.3, 127.0, 125.5, 125.0, 124.2, 122.8, 120.1, 57.4, 51.4, 35.9. **¹⁹F NMR (376 MHz, CDCl₃)** δ -60.5, -62.21 (side product). **HRMS (EI+)** calcd. for [C₁₂H₁₄NCIF₃] (MH⁺) 264.0761; found 264.0758. Colorless oil, 105.4 mg, 80% yield.

1-(3,5-bis(trifluoromethyl)phenyl)-4-chloropiperidine (**5-2p**)

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.21 (m, 3H), 4.28 (tt, *J* = 7.4, 3.7, 1H), 3.64 – 3.55 (m, 2H), 3.29 – 3.19 (m, 2H), 2.22 (ddt, *J* = 14.3, 7.4, 3.6, 2H), 2.06 – 1.96 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.3, 132.8, 132.5, 132.2, 131.8, 127.5, 124.8, 122.1, 119.4, 115.0, 112.0, 56.0, 46.0, 34.3. **¹⁹F NMR (376 MHz, CDCl₃)** δ = -63.10. **HRMS (EI+)** calcd. for [C₁₃H₁₃NCIF₆] (MH⁺) 332.0635; found 332.0632. Colorless oil, 149.2 mg, 90% yield.

4-chloro-1-(3-(trifluoromethyl)phenyl)piperidine (**5-2q**)

¹H NMR (400 MHz, CDCl₃) δ 7.35 (t, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.24 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.60 – 3.48 (m, 2H), 3.20 – 3.08 (m, 2H), 2.29 – 2.15 (m, 2H), 2.07 – 1.94 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.1, 131.9, 131.6, 131.3, 130.9, 129.6, 125.6, 122.9, 119.2, 115.9, 114.6, 112.6, 56.6, 46.8, 34.7. **¹⁹F NMR (376 MHz, CDCl₃)** δ -62.83. **HRMS (EI+)** calcd. for [C₁₂H₁₄NCIF₃] (MH⁺) 264.0761; found 264.0760. Colorless oil, 95 mg, 72% yield.

1-([1,1'-biphenyl]-4-yl)-4-chloropiperidine (**5-2r**)

¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.19 (dd, *J* = 14.7, 7.2 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.16 – 4.10 (m, 1H), 3.51 – 3.43 (m, 2H), 3.08 – 2.97 (m, 2H), 2.19 – 2.08 (m, 2H), 1.99 – 1.87 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 150.1, 140.7, 132.2, 128.6, 127.7, 126.4, 126.4, 116.5, 57.0, 47.3, 34.8. **HRMS (EI+)** calcd. for [C₁₇H₁₉NCI] (MH⁺) 272.1201; found 272.1200. White solid, 111.4 mg, 82% yield.

1-([1,1'-biphenyl]-2-yl)-4-chloropiperidine (**5-2s**)

¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.60 (m, 2H), 7.42 (dd, *J*=10.5, 4.7, 2H), 7.34 – 7.24 (m, 3H), 7.08 (ddd, *J*=11.9, 9.2, 4.6, 2H), 4.13 – 3.97 (m, 1H), 3.18 – 3.07 (m, 2H), 2.70 (ddd, *J*=11.8, 8.8, 2.9, 2H), 2.01 – 1.93 (m, 2H), 1.86 – 1.71 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 150.2, 141.0, 135.1, 131.3, 128.6, 128.1, 126.7, 122.7, 118.5, 57.3, 49.4, 35.6. **HRMS (EI+)** calcd. for [C₁₇H₁₉NCI] (MH⁺) 272.1201; found 272.1199. Colorless oil, 114.1 mg, 84% yield.

1-(4-(4-chloropiperidin-1-yl)phenyl)ethanone (**5-2t**)

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J*=9.0, 2H), 6.87 (d, *J*=9.0, 2H), 4.28 (tt, *J*=7.6, 3.8, 1H), 3.68 (ddd, *J*=12.8, 7.3, 3.6, 2H), 3.29 (ddd, *J*=13.2, 7.8, 3.5, 2H), 2.52 (s, 3H), 2.05–1.95 (m, 2H), 1.96 (dtd, *J*=11.3, 7.7, 3.6, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 196.4, 153.6, 130.4, 127.5, 113.6, 56.7, 45.3, 34.4, 26.1. **HRMS (EI+)** calcd. for [C₁₃H₁₇ONCI] (MH⁺) 238.0993; found 238.0991. Colorless oil, 97.4 mg, 82% yield.

(3-(4-chloropiperidin-1-yl)phenyl)(phenyl)methanone (**5-2u**)

¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (s, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 14.1, 7.7 Hz, 2H), 4.23 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.19 – 3.09 (m, 2H), 2.21 (bs, 2H), 2.07 – 1.96 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 196.9, 150.8, 138.4, 137.6, 132.3, 130.0, 128.8, 128.1, 121.7, 120.4, 117.1, 56.7, 47.0, 34.7. **HRMS (EI+)** calcd. for [C₁₈H₁₉ONCl] (MH⁺) 300.1150; found 300.1150. Colorless liquid, 111 mg, 74 % yield.

1-(benzo[d][1,3]dioxol-5-yl)-4-chloropiperidine (**5-2v**)

¹H NMR (400 MHz, CDCl₃) δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.90 (s, 2H), 4.17 (td, *J* = 8.0, 4.0 Hz, 1H), 3.40 – 3.27 (m, 2H), 2.92 (ddd, *J* = 12.0, 8.4, 3.4 Hz, 2H), 2.20 (dd, *J* = 16.4, 3.5 Hz, 2H), 2.08 – 1.94 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 110.0, 109.7, 108.1, 100.9, 100.5, 84.4, 57.0, 49.2, 35.3. **HRMS (EI+)** calcd. for [C₁₂H₁₄O₂NCl] (MH⁺) 239.0713; found 239.0707. Yellow liquid, 81.3 mg, 68 % yield.

methyl 3-(4-chloropiperidin-1-yl)thiophene-2-carboxylate (**5-2w**)

¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, *J* = 5.4 Hz, 1H), 6.84 (d, *J* = 5.4 Hz, 1H), 4.37 – 4.19 (m, 1H), 3.84 (s, 3H), 3.57 – 3.45 (m, 2H), 3.23 – 3.11 (m, 2H), 2.28 (ddd, *J* = 13.9, 7.4, 3.9 Hz, 2H), 2.12 – 1.98 (m, 2H). **¹³C NMR (126 MHz, CDCl₃)** δ 162.1, 157.6, 156.7, 131.1, 121.0, 56.9, 51.6, 49.8, 35.2. **HRMS (EI⁺)** calcd. for [C₁₈H₁₉ONCl] (MH⁺) 260.0434; found 264.0431. Pale yellow oil, 80.3 mg, 62 % yield.

2-chloro-5-(4-chloropiperidin-1-yl)pyridine (**5-2x**)

¹H NMR (400 MHz, CDCl₃) δ 8.15 – 8.03 (m, 1H), 7.41 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 4.27 (tt, *J* = 7.8, 3.8 Hz, 1H), 3.87 (ddd, *J* = 13.0, 7.1, 3.7 Hz, 2H), 3.41 (ddd, *J* = 13.3, 8.1, 3.5 Hz, 2H), 2.20 – 2.08 (m, 2H), 1.96 – 1.82 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 157.3, 146.3, 137.2, 120.0, 107.8, 57.2, 43.2, 34.4. **HRMS (EI⁺)** calcd. for [C₁₀H₁₃N₂Cl₂] (MH⁺) 231.0450; found 231.0447. Yellow liquid, 91.3 mg, 79 % yield.

4-chloro-2-(4-chloropiperidin-1-yl)pyridine (**5-2y**)

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J*=1.5, 1H), 7.31 (s, 1H), 7.25 – 7.19 (m, 1H), 4.29 (tt, *J*=7.5, 3.8, 1H), 3.58 – 3.47 (m, 2H), 3.23 – 3.12 (m, 2H), 2.26 (ddt, *J*=14.2, 7.3, 3.6, 2H), 2.11 – 2.00 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 146.0, 141.3, 137.9, 126.2, 124.0, 56.2, 46.5, 34.4. **HRMS (EI+)** calcd. for [C₁₀ H₁₂Cl₂N₂] (M⁺) 230.0382; found 230.0378. Colorless oil, 87.4 mg, 76% yield.

2-chloro-5-(4-chloropiperidin-1-yl)pyrazine (**5-2z**)

¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.88 (s, 1H), 4.34 – 4.28 (m, 1H), 3.89 – 3.81 (m, 2H), 3.55 – 3.47 (m, 2H), 2.18 – 2.11 (m, 2H), 1.97 – 1.89 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 153.4, 141.0, 136.0, 129.2, 56.6, 42.4, 34.2. **HRMS (EI+)** calcd. for [C₉H₁₂N₃Cl₂] (MH⁺) 232.0403; found 232.0400. Brown oil, 91.7 mg, 79% yield.

4-chloro-1-tosylpiperidine (**5-2aa**)

¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.16 – 4.09 (m, 1H), 3.21 – 3.07 (m, 4H), 2.44 (s, 3H), 2.16 – 2.09 (m, 2H), 1.98 – 1.89 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 143.5, 132.8, 129.6, 127.4, 55.2, 42.7, 33.8, 21.4. **HRMS (EI+)** calcd. for [C₁₂H₁₇O₂NCIS] (MH⁺) 274.0663; found 274.0660. White solid. 89.1 mg, 85% yield.

4-chloro-1-((4-methoxyphenyl)sulfonyl)piperidine (**5-2ab**)

¹H NMR (400 MHz, (CDCl₃) δ 7.60 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.07 – 3.97 (m, 1H), 3.78 (s, 3H), 3.11 – 3.05 (m, 2H), 3.03 – 2.95 (m, 2H), 2.10 – 1.97 (m, 2H), 1.88 – 1.80 (m, 2H).. **¹³C NMR (100 MHz, (CDCl₃)** δ 162.9, 129.5, 127.6, 114.1, 55.5, 55.2, 42.7, 33.9. **HRMS (EI+)** calcd. for [C₁₂H₁₇O₃NCIS] (MH⁺) 290.0612; found 290.0610. White solid, 113 mg, 78 % yield.

1-((4-bromophenyl)sulfonyl)-4-chloropiperidine (**5-2ac**)

¹H NMR (400 MHz, CD₃Cl₃) 7.68 (d, *J* = 8.6, 2H), 7.62 (d, *J* = 8.6, 2H), 4.17 – 4.13 (m, 1H), 3.15 (t, *J* = 5.4 Hz, 4H), 2.17 – 2.10 (m, 2H), 1.97 – 1.91 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 135.4, 132.6, 129.2, 128.2, 55.2, 42.9, 34.1. **HRMS (EI+)** calcd. for

[C₁₁H₁₃O₂NBrClNaS] (M+Na) 359.9431; found 359.9429. White solid, 120.2mg, 71 % yield.

4-chloro-1-(2-ethylhexyl)piperidine (**5-2ad**)

¹H NMR (500 MHz, CDCl₃) δ 4.01 (bs, 1H), 2.71 (bs, 2H), 2.13 (dd, *J* = 6.6, 4.4 Hz, 5H), 1.98 – 1.81 (m, 3H), 1.44 (bs, 2H), 1.29 – 1.23 (m, 7H), 0.88 (dt, *J* = 14.9, 7.1 Hz, 7H). **¹³C NMR (126 MHz, CDCl₃)** δ 62.7, 58.0, 52.2, 36.5, 35.8, 31.5, 28.9, 24.7, 23.1, 14.1, 10.8. **HRMS (EI+)** calcd. for [C₁₃H₂₆ClN] (M⁺) 231.1756; found 231.1751. Colorless oil, 64.4 mg, 54% yield.

4-chloro-1-(4-methoxyphenethyl)piperidine (**5-2ae**)

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.10 (m, 5H), 4.01 (s, 1H), 2.78 – 2.72 (m, 4H), 2.54 (dd, *J*=9.7, 6.5, 2H), 2.27 (bs, 2H), 2.07 (d, *J*=12.4, 2H), 1.94 – 1.80 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 140.2, 128.6, 128.3, 125.9, 60.3, 57.3, 51.2, 35.5, 33.7. **HRMS (EI+)** calcd. for [C₁₃H₁₈ClN] (M⁺) 223.1232; found 223.1228. Colorless oil, 56.9 mg, 51% yield.

4-chloro-1-(4-methoxyphenethyl)piperidine (**5-2af**)

¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.12 – 4.00 (m, 1H), 3.79 (s, 3H), 2.88 – 2.79 (m, 2H), 2.78 – 2.67 (m, 3H), 2.61 – 2.52 (m, 2H), 2.38 – 2.25 (m, 2H), 2.18 – 2.08 (m, 2H), 2.00 – 1.86 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 158.0, 132.3, 129.6, 113.8, 60.6, 57.4, 55.3, 51.3, 35.6, 32.9. **HRMS (EI+)** calcd. for [C₁₄H₂₀ClNO] (M⁺) 253.1232; found 253.1228. Colorless oil, 73.4 mg, 58% yield.

1-benzyl-4-chloropiperidine (**5-2ag**)

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.12 (m, 5H), 4.03 (bs, 1H), 3.49 (bs, 2H), 2.80 – 2.67 (m, 2H), 2.23 (s, 2H), 2.13 – 2.02 (m, 2H), 1.96 – 1.84 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ 138.3, 129.0, 128.2, 127.0, 62.8, 57.5, 51.3, 35.6. **HRMS (EI+)** calcd. for [C₁₂H₁₆ClN] (M⁺) 209.0973; found 209.0967. Colorless oil, 64 mg, 61% yield.

4-chloro-1-(1-phenylethyl)piperidine (**5-2ah**)

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.21 (m, 5H), 3.98 (bs, 1H), 3.44 (q, *J*=6.7, 1H), 2.86 (bs, 1H), 2.78 – 2.66 (m, 1H), 2.29 – 2.12 (m, 2H), 2.14 – 1.99 (m, 2H), 1.97 – 1.80 (m, 2H), 1.37 (d, *J*=6.7, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 143.8, 128.2, 127.5, 126.9, 64.4, 57.8, 48.6, 35.9, 19.4. **HRMS (EI+)** calcd. for [C₁₃H₁₉NCI] (MH⁺) 224.1201; found 224.1197. Colorless liquid, 72.7 mg, 65% yield.

4-chloro-4-methyl-1-phenylpiperidine (**5-4a**)

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.22 (m, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.85 (t, *J* = 7.0 Hz, 1H), 3.51 (d, *J* = 12.8 Hz, 2H), 3.25 – 3.12 (m, 2H), 1.95 (ddd, *J* = 22.6, 18.0, 8.3 Hz, 4H), 1.68 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)** δ 151.1, 129.1, 119.5, 116.4, 69.5, 46.0, 40.3, 33.2. **HRMS (EI+)** calcd. for [C₁₂H₁₇NCI] (MH⁺) 210.1044; found 210.1040. Colorless liquid, 84.9 mg, 81% yield.

4-bromo-4-chloro-1-phenylpiperidine (**5-4b**)

¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.45 – 3.28 (m, 4H), 2.68 (ddd, *J* = 13.7, 7.1, 3.7 Hz, 2H), 2.55 (ddd, *J* = 13.7, 7.0, 3.7 Hz, 2H). **¹³C NMR (100 MHz CDCl₃)** δ 150.2, 129.1, 120.0, 116.4, 78.9,

47.5, 46.4. **HRMS (EI+)** calcd. for $[C_{11}H_{13}BrClN]$ (M^+) 272.9917; found 274.9890.

Colorless liquid, 114.7 mg, 84% yield.

4a-chloro-6,6-dimethyl-2-phenyldecahydro-5,7-methanoisoquinoline (**5-4c**)

1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 8.1 Hz, 2H), 6.79 (t, J = 7.2 Hz, 1H), 3.70 – 3.60 (m, 3H), 2.79 (td, J = 12.6, 3.0 Hz, 1H), 2.45 – 2.38 (m, 1H), 2.23 (td, J = 12.1, 6.4 Hz, 1H), 2.10 (td, J = 12.8, 4.5 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.79 (d, J = 10.7 Hz, 1H), 1.61 – 1.54 (m, 1H), 1.35 (d, J = 11.2 Hz, 1H), 1.08 (s, 3H), 1.01 (s, 3H), 0.92 (dt, J = 13.0, 4.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 151.1, 129.0, 118.9, 116.3, 77.7, 55.2, 51.8, 47.5, 47.3, 39.4, 34.8, 30.5, 30.4, 29.9, 27.7, 23.2. **HRMS (EI+)** calcd. for $[C_{18}H_{24}ClN]$ (M^+) 289.1595; found 289.1590. Colorless oil, 76.62 mg, 53% yield.

4-chloro-3-methyl-1-phenylpiperidine (**5-4d**)

1H NMR (400 MHz, $CDCl_3$) Major (anti-) diastereomer: δ 7.31 – 7.22 (m, 2H), 6.96 – 6.90 (m, 2H), 6.86 (t, J = 7.3 Hz, 1H), 3.73 – 3.57 (m, 3H), 2.80 (td, J = 12.5, 2.7 Hz, 1H), 2.50 (dd, J = 12.9, 10.6 Hz, 1H), 2.31 – 2.21 (m, 1H), 2.14 – 1.95 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.7, 129.1, 119.7, 116.5, 64.7, 56.4, 49.4,

39.5, 35.8, 16.9. **HRMS (EI+)** calcd. for $[C_{12}H_{17}NCl]$ (MH^+) 210.1044; found 210.1042.

Colorless oil, 68.1 mg, 65% yield.

3.4.5 Copies of NMR spectra for compounds 5-1, 5-2, 5-3 and 5-4

3.4.6 X-ray data for 5-2n

Table 5.1. Crystal data and structure refinement for 5-2n.

Identification code	5-2n	
Empirical formula	C ₁₁ H ₁₃ Cl N ₂ O ₂	
Formula weight	240.68	
Temperature	101.95(10) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P nma	
Unit cell dimensions	a = 17.2486(2) Å	α = 90°.
	b = 10.17867(17) Å	β = 90°.
	c = 6.17147(11) Å	γ = 90°.
Volume	1083.51(3) Å ³	
Z	4	
Density (calculated)	1.475 Mg/m ³	
Absorption coefficient	0.338 mm ⁻¹	
F(000)	504	
Crystal color, habit	yellow plate	
Crystal size	0.39 x 0.38 x 0.05 mm ³	
Theta range for data collection	3.51 to 33.12°.	
Index ranges	-26 ≤ h ≤ 25, -15 ≤ k ≤ 15, -9 ≤ l ≤ 9	
Reflections collected	26127	
Independent reflections	2160 [R(int) = 0.0265]	
Completeness to theta = 33.12°	99.9 %	
Absorption correction	SCALE 3 ABSPACK	
Max. and min. transmission	1.000 and 0.906	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2160 / 0 / 102	
Goodness-of-fit on F ²	1.042	
Final R indices [I > 2σ(I)]	R1 = 0.0320, wR2 = 0.0722	
R indices (all data)	R1 = 0.0364, wR2 = 0.0746	
Largest diff. peak and hole	0.489 and -0.344 e.Å ⁻³	

Table 5.2. Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$) for 5-2n.
 $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
Cl(1)	0.3167(1)	0.2500	0.6844(1)	0.033(1)
O(1)	-0.466(1)	0.1437(1)	-0.5484(1)	0.025(1)
N(1)	0.1383(1)	0.2500	0.3151(2)	0.018(1)
N(2)	-0.272(1)	0.2500	-0.4688(2)	0.018(1)
C(1)	0.3040(1)	0.2500	0.3903(2)	0.025(1)
C(2)	0.2604(1)	0.1265(1)	0.3244(2)	0.024(1)
C(3)	0.1761(1)	0.1318(1)	0.3992(2)	0.021(1)
C(4)	0.1019(1)	0.2500	0.1168(2)	0.015(1)
C(5)	0.0810(1)	0.1313(1)	0.0126(1)	0.017(1)
C(6)	0.0394(1)	0.1313(1)	-0.1790(1)	0.017(1)
C(7)	0.0182(1)	0.2500	-0.2727(2)	0.015(1)

Table 5.3. Bond lengths [Å] and angles [°] for 5-2n.

Cl(1)-C(1)	1.8285(14)
O(1)-N(2)	1.2347(8)
N(1)-C(4)	1.3753(15)
N(1)-C(3)#1	1.4632(11)
N(1)-C(3)	1.4632(11)
N(2)-O(1)#1	1.2347(8)
N(2)-C(7)	1.4417(15)
C(1)-C(2)#1	1.5206(13)
C(1)-C(2)	1.5206(13)
C(1)-H(1)	0.972(19)
C(2)-C(3)	1.5270(13)
C(2)-H(2A)	0.941(13)
C(2)-H(2B)	0.977(13)
C(3)-H(3A)	0.955(13)
C(3)-H(3B)	0.998(13)
C(4)-C(5)	1.4155(10)
C(4)-C(5)#1	1.4155(10)
C(5)-C(6)	1.3824(11)
C(5)-H(5)	0.936(12)
C(6)-C(7)	1.3886(10)
C(6)-H(6)	0.935(12)
C(7)-C(6)#1	1.3885(10)
C(4)-N(1)-C(3)#1	121.26(5)
C(4)-N(1)-C(3)	121.26(5)
C(3)#1-N(1)-C(3)	110.57(10)
O(1)-N(2)-O(1)#1	122.48(10)
O(1)-N(2)-C(7)	118.75(5)
O(1)#1-N(2)-C(7)	118.75(5)
C(2)#1-C(1)-C(2)	111.56(11)
C(2)#1-C(1)-Cl(1)	108.93(7)
C(2)-C(1)-Cl(1)	108.93(7)
C(2)#1-C(1)-H(1)	111.2(5)
C(2)-C(1)-H(1)	111.2(5)
Cl(1)-C(1)-H(1)	104.8(11)
C(1)-C(2)-C(3)	111.16(8)
C(1)-C(2)-H(2A)	111.1(8)
C(3)-C(2)-H(2A)	110.0(8)
C(1)-C(2)-H(2B)	107.1(8)
C(3)-C(2)-H(2B)	109.2(8)
H(2A)-C(2)-H(2B)	108.2(11)
N(1)-C(3)-C(2)	110.27(8)
N(1)-C(3)-H(3A)	111.6(8)
C(2)-C(3)-H(3A)	111.5(8)
N(1)-C(3)-H(3B)	108.1(8)
C(2)-C(3)-H(3B)	109.5(7)
H(3A)-C(3)-H(3B)	105.7(10)
N(1)-C(4)-C(5)	121.39(5)
N(1)-C(4)-C(5)#1	121.39(5)
C(5)-C(4)-C(5)#1	117.16(10)
C(6)-C(5)-C(4)	121.40(8)
C(6)-C(5)-H(5)	117.7(7)
C(4)-C(5)-H(5)	120.9(7)
C(5)-C(6)-C(7)	119.54(8)

C(5)-C(6)-H(6)	119.7(7)
C(7)-C(6)-H(6)	120.7(7)
C(6)#1-C(7)-C(6)	120.90(10)
C(6)#1-C(7)-N(2)	119.55(5)
C(6)-C(7)-N(2)	119.55(5)

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z

Table 5.4. Anisotropic displacement parameters ($\text{\AA}^2$) for 5-2n. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	0.022(1)	0.050(1)	0.025(1)	0.000	-0.008(1)	0.000
O(1)	0.028(1)	0.022(1)	0.024(1)	-0.007(1)	-0.006(1)	0.000(1)
N(1)	0.018(1)	0.020(1)	0.017(1)	0.000	-0.002(1)	0.000
N(2)	0.017(1)	0.020(1)	0.016(1)	0.000	0.000(1)	0.000
C(1)	0.017(1)	0.037(1)	0.021(1)	0.000	0.003(1)	0.000
C(2)	0.023(1)	0.027(1)	0.021(1)	0.001(1)	0.001(1)	0.007(1)
C(3)	0.020(1)	0.023(1)	0.019(1)	0.005(1)	-0.003(1)	-0.001(1)
C(4)	0.013(1)	0.017(1)	0.015(1)	0.000	0.001(1)	0.000
C(5)	0.019(1)	0.014(1)	0.018(1)	0.001(1)	0.000(1)	0.001(1)
C(6)	0.018(1)	0.015(1)	0.017(1)	-0.001(1)	0.001(1)	-0.001(1)
C(7)	0.015(1)	0.016(1)	0.014(1)	0.000	0.000(1)	0.000

Table 5.5. Hydrogen coordinates and isotropic displacement parameters ($\text{\AA}^2$) for 5-2n.

	x	y	z	U(eq)
H(1)	0.3564(11)	0.2500	0.3320(30)	0.030
H(2A)	0.2846(7)	0.0508(13)	0.3800(20)	0.028
H(2B)	0.2619(8)	0.01218(13)	0.1660(20)	0.028
H(3A)	0.1485(7)	0.0541(13)	0.3590(20)	0.025
H(3B)	0.1742(7)	0.1354(13)	0.5610(20)	0.025
H(5)	0.0941(7)	0.0499(12)	0.0727(19)	0.021
H(6)	0.0262(7)	0.0516(12)	-0.2440(20)	0.020

Table 6. Torsion angles [$^\circ$] for 5-2n.

C(2)#1-C(1)-C(2)-C(3)	-50.40(13)
Cl(1)-C(1)-C(2)-C(3)	69.88(9)
C(4)-N(1)-C(3)-C(2)	88.96(11)
C(3)#1-N(1)-C(3)-C(2)	-62.21(12)
C(1)-C(2)-C(3)-N(1)	55.97(11)
C(3)#1-N(1)-C(4)-C(5)	165.40(9)
C(3)-N(1)-C(4)-C(5)	17.28(15)
C(3)#1-N(1)-C(4)-C(5)#1	-17.28(15)

C(3)-N(1)-C(4)-C(5)#1	-165.40(9)
N(1)-C(4)-C(5)-C(6)	175.18(9)
C(5)#1-C(4)-C(5)-C(6)	-2.25(15)
C(4)-C(5)-C(6)-C(7)	0.55(13)
C(5)-C(6)-C(7)-C(6)#1	1.26(16)
C(5)-C(6)-C(7)-N(2)	-178.08(9)
O(1)-N(2)-C(7)-C(6)#1	-178.93(9)
O(1)#1-N(2)-C(7)-C(6)#1	-0.42(15)
O(1)-N(2)-C(7)-C(6)	0.42(15)
O(1)#1-N(2)-C(7)-C(6)	178.93(9)

Symmetry transformations used to generate equivalent atoms: #1 $x, -y+1/2, z$

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APPENDIX A: LIGAND EFFECTS IN THE GOLD CATALYZED HYDRATION OF ALKYNES

Background

The hydration of alkynes is a straightforward and atom-economical method to prepare carbonyl compounds.^{135,136} Hg,¹³⁷ Fe,¹³⁸ Ru,¹³⁹ Pd,¹⁴⁰ Ir,¹⁴¹ Pt,¹⁴² Ag,¹⁴³ Cu¹⁴⁴ based catalysts as well as other system¹⁴⁵ have been developed for this purpose. Among them, gold catalysts appeared to be especially efficient.^{136, 146} State of the art methods include Nolan and coworkers' [IPr-Au]⁺-catalyzed alkyne hydration at ppm level gold catalyst loadings (Scheme 12a), although high temperatures (e.g. 120 °C) are needed to achieve high efficacy.¹³⁶ Another example is Corma and coworkers' isolable SPhos based gold(I) complex catalyzed alkyne hydration at room temperature without acidic promoters,¹⁴⁷ although a relatively high gold catalyst loading (0.5-5%) was needed (Scheme 12b).

Scheme 12. State of the art methods for gold catalyzed hydration of alkynes.

Low gold catalyst loading is essential for larger scale synthesis and the use of relative low temperatures is important for the synthesis of complex target molecules, which usually contain sensitive functional groups. Our goal was to find a gold hydration catalyst

with a suitable ligand that is efficient at low loading (ppm level) and at low temperature (e.g., room temperature).

Results and discussion

Ligands are known to play a crucial role in modulating the reactivity of cationic gold catalysts.^{86b, 148} To study the effects of ligands we used the hydration of 1-octyne **A-1a** as model reaction (Figure 12). The ligands used by Nolan (IPr, **A-L1**) and Corma (SPhos, **A-L5**) were indeed efficient, both **A-L1** and **A-L5** catalytic systems accomplished the hydration of alkyne **A-1** at room temperature in 24 h. To our surprise, most ligands performed similarly, even the very electron poor ligand $P(OPh)_3$ was an equally good ligand. In contrast to many gold catalyzed reactions, like hydroamination,¹⁴⁸ the electronic effect of the ligand played only a small role in the kinetics of alkyne hydration.¹⁴⁹ For example, an electron poor ligand (**A-L8**) behaved very similarly to an electron rich ligand (**A-L5**). Conversely, the steric effects of ligands played a crucial role in alkyne hydration; for example, a bulkier ligand (*t*-BuX-Phos, **A-L3**) led to a faster reaction rate compared to JohnPhos (**A-L2**). We found that the most sterically demanding Buchwald ligand **A-L4** ($Me_3(OMe)tBuXPhos$, it is a mixture of two regioisomers)¹⁵⁰ was the best for this reaction. It should be noted that this reaction is not a pure water addition process, it may involve a combination of hydroalkoxylation (methanol addition) and the subsequent hydrolysis of the enol ether/acetal by water *in situ*. A rationale for the role of steric hindrance in the performance of these ligands is not yet clear. It has been reported that the high affinity of gold for both gold and silver, causes various Au-Ag,^{151,152} Au-Au¹⁵³ intermediates to be formed in gold catalyzed reactions (Figure 13); these intermediates often behave as off-cycle species.¹⁵³

Figure 12. Screening for the optimal ligand for hydration of alkyne 1a.

It is likely that sterically hindered ligands discourage the formation of these off-cycle gold intermediates, which in turn lead to the high turnover of gold catalysts.

Figure 13. Au-Ag, Au-Au intermediates in catalytic cycle.

With the best catalytic system (**A-L4**-Au-OTf) for alkyne hydration in hand, we explored the substrate scope (Table 13). The **A-L4**-Au-OTf system was able to catalyze the hydration of most alkynes at low catalyst loading (0.02%) and relatively low temperature (80°C). Both terminal and internal alkynes worked well and many common functional groups such as alcohol (Table 13, entry 12), ester (Table 13, entries 13, 15), and carboxylic acid¹⁵⁴ (Table 13, entry 14) were tolerated.

In many gold catalyzed reactions, the use of acidic promoters has been shown to ease the reaction conditions.¹⁵⁵ When we used acidic promoters with our optimized catalytic system we found that the hydration of 1-octyne took place under both, lower catalyst loading and reduced reaction temperature (Table 14). It should be noted that without an acid promoter, **A-L4**-Au-OTf (0.1%) was not able to complete the reaction at room temperature (Table 14, entry 1). Most acids sped up the reaction but strong acids such as H₃PW₁₂O₄₀ and TfOH performed best (Table 14, entries 6, 9). Complete conversions were achieved at very low gold loading.

Table 13. Hydration of alkynes without acid promoter

Entry	2	Time/ h	Yield (%) ^b	Entry	2	Time/ h	Yield (%) ^b
1		19	>99	9		96	17
2		6	>99	10 ^c		72	90
3		24	99	11 ^c		14	>99
4		6	>99	12 ^c		17	>99
5		20	>99	13		24	>99
6		24	>99	14		16	>99
7		100	>99	15		24	>99
8		72	89 (11 ^d)				

^a Reaction conditions; **1** (1 mmol), H₂O (2 equiv), MeOH (0.3 mL), **L4-Au-Cl** (0.02 mol%), AgOTf (0.03 mol%), 80 °C; ^b ¹H NMR yield; ^c [Au] = 0.03 mol%; ^d yield for monohydrated product.

Table 14. Hydration of alkynes in the presence of acid promoter

entry	[Au]	additive	time	conversion
1	0.1%	None	24 h	< 5%
2	0.1%	Cu(OTf) ₂ (0.2%)	24 h	15%
3	0.1%	Eu(OTf) ₃ (0.2%)	24 h	< 5%
4	0.1%	H ₃ PW ₁₂ O ₄₀ (0.2%)	24 h	>99%
5	0.01%	H ₃ PW ₁₂ O ₄₀ (0.15%)	24 h	>99%
6	0.01%	H ₃ PW ₁₂ O ₄₀ (0.15%)	12 h	>99%
7	0.01%	HNTf ₂ (0.15%)	21 h	69%
8	0.01%	HOTf (0.15%)	21 h	93%
9	0.01%	HOTf (0.45%)	21 h	>99%
10	-	HOTf (0.45%)	24 h	0%

catalyst loading (0.01%) at room temperature. An acid alone cannot catalyze the reaction at room temperature (Table 14, entry 10).

We examined the substrate scope for our L4-Au-OTf/acid system (Table 15). For most terminal alkynes, the reaction proceeded very well at very low gold catalyst loading (0.01%) at room temperature (Table 15, entries 1-9). For internal alkynes, a higher temperature and catalyst loading (0.03%) was needed to achieve high conversion (Table 15, entries 10-11).

Table 15. Scope of gold/acid co-catalyzed hydration

$\text{R}^1\text{---}\text{C}\equiv\text{C}\text{---}\text{R}^2 \xrightarrow[\text{MeOH/ H}_2\text{O, H}^+, \text{rt}]{\text{A-L4-Au-Cl (0.01 mol\%)} / \text{AgOTf (0.015 mol\%)}} \text{R}^1\text{---CH}_2\text{---C(=O)---R}^2$							
Entry	2	time	yield (%) ^b	Entry	2	time	yield (%) ^b
1	A-2a	19 h	>99	7	A-2g	48 h	>99
2	A-2b	21 h	>99	8	A-2h	27 h	90
3	A-2c'	24 h	>99	9	A-2i	19 h	>99
4	A-2d	21 h	>99	10 ^c	A-2j	72 h	>99
5	A-2e	24 h	>99	11 ^c	A-2p	72 h	>99
6	A-2f	48 h	>99	12 ^d	A-2q	48 h	89

^aReaction conditions: **1** (1 mmol), H₂O/ MeOH (1:20) (0.3 mL), **L4**-Au-Cl (0.01 mol%), AgOTf (0.015 mol%), HOTf (0.45 mol%); ^b ¹H NMR yield; ^c the reaction was conducted at 80 °C, [Au] = 0.03 mol %; [HOTf] = 1.35 mol%; ^d the reaction was conducted at 50 °C.

Conclusion

In summary, a gold catalyst containing a highly sterically hindered and commercially available phosphine ligand (**A-L4**) was able to catalyze the alkyne hydration of a wide range of substrates in good yields using only ppm loading levels and relatively low temperatures.

Experimental

General Methods and Materials

All commercial reagents and solvents were obtained from the commercial provider and used without further purification. ^1H and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz (or 400 MHz and 101 MHz) respectively using CDCl_3 as a solvent. The chemical shifts are reported in δ (ppm) values (^1H and ^{13}C NMR relative to CHCl_3 , δ 7.26 ppm for ^1H NMR and δ 77.0 ppm for ^{13}C NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hexet), m (multiplet) and br (broad). Coupling constants (J) are reported in Hertz (Hz). The product formation was monitored by ^1H NMR using aliquots containing the solvent mixture.

Synthesis of gold complexes (L-AuCl)

All gold complexes (L-AuCl) were synthesized using a slightly modified version of a literature method.^{91, 156} These complexes were prepared via either one of the following general procedures:

Method 1: Sodium tetrachloroaurate(III) dihydrate (1 mmol) was dissolved in water, and the orange solution was cooled in ice. To this solution, 2,2'-thiodiethanol (3 mmol) was slowly added (ca. 10 min) with stirring. After stirring at 0°C for another 30 min, a solution of the phosphine ligand (1 mmol) in EtOH (if the ligand could not be dissolved, more EtOH was used) was added dropwise to yield a white solid. The solid was filtered off, washed with water followed by EtOH, and ultimately dried in vacuum to obtain the complex quantitatively.

Method 2: To a vial Chloro(dimethylsulfide)gold(I) (1 mmol) was dissolved in dichloromethane and cooled in an ice bath. A solution of phosphine ligand (1 mmol) in

dichloromethane was added dropwise, and the resulting solution was allowed to warm to room temperature and stirred at room temperature for 3 h. After TLC indicated complete consumption of the starting material, the reaction solution was concentrated to dryness in the rotovap, and the gold complex product was further dried under high vacuum to yield the complex quantitatively.

Typical procedure for the acid free hydration (condition A): A glass vial equipped with a screw cap and a stir bar was charged with 1-octyne **A-1a** (112 mg, 150 μ L, 1 mmol) dissolved in a mixture of MeOH (0.3 mL) and water (36 μ L, 2 mmol). A stock solution of AgOTf (0.01 M in methanol, 30 μ L, 0.0003 mmol) and a stock solution of **A-L4-Au-Cl** (0.01 M in methanol, 20 μ L, 0.0002 mmol) were introduced to the reaction mixture. The reaction was stirred at 80 °C and the progress of reaction was monitored by GCMS or $^1\text{H-NMR}$. Upon completion, reaction mixture was filtered through a celite plug, dried over anhydrous Na_2SO_4 , filtered and solvent evaporated. The crude product was purified by silica gel column chromatography with EtOAc: Hex (1:5) as eluent.

Typical procedure for acid co-catalyzed hydration (condition B): A glass vial equipped with a screw cap and a stir bar was charged with 1-octyne **A-1a** (112 mg, 150 μ L, 1 mmol) dissolved in 0.3 mL MeOH/water (25:1) mixture. A stock solution of acid promoter TfOH (0.01 M in methanol, 450 μ L, 0.0045 mmol), a stock solution of AgOTf (0.01 M in methanol, 15 μ L, 0.00015 mmol) and a stock solution of **A-L4-Au-Cl** (0.01 M in methanol, 10 μ L, 0.0001 mmol) were introduced to the reaction mixture. The reaction mixture was stirred at room temperature and the progress of reaction was monitored by GCMS and $^1\text{H NMR}$. Upon completion, the reaction mixture was quenched with saturated bicarbonate (1 mL) and extracted with EtOAc (2 X 1 mL). The organics are dried over anhydrous Na_2SO_4 , filtered and solvent evaporated using a rotoevaporator.

The crude product was subjected to silica gel column chromatography with EtOAc: Hex (1:5) as eluent.

¹H NMR, ¹³C NMR and ³¹P NMR data of L4-AuCl and ¹H NMR data hydration products

The hydration products (ketones 2): **2a** (CAS#111-13-7)¹⁵⁷, **2b** (CAS #591-78-6)¹⁵⁸, **2c** (CAS#13505-34-5)¹⁵⁹, **2c'**(1193-18-6)¹⁶⁰, **2d** (2550-26-7)¹⁶¹, **2e** (CAS#932-66-1)¹⁶², **2f** (CAS#403-42-9)¹⁵⁸, **2g** (CAS#100-06-1)¹⁵⁸, **2h** (CAS#1009-61-6)¹⁵⁸, **2i** (CAS#577-16-2)¹⁶³, **2j** (cas # 589-63-9)¹⁶⁴, **2k** (cas # 693-54-9¹⁶⁵, 928-80-3¹⁶⁶), **2l**¹⁶⁷, **2m** (cas #19275-80-3)¹⁶⁸, **2n** (cas # 13984-50-4)¹⁶⁹, **2o** (cas #24889-15-4)¹⁷⁰, **2p** (CAS#451-40-1)¹⁵⁸, **2q** (cas # 1123-27-9)¹⁷¹ are commercially available and reported compounds and their spectroscopic data agree well with the reported literature.

A-L4-AuCl: White solid;

Major isomer: **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.05 (s, 2 H), 3.79 (s, 3 H), 2.99 (m, 1 H), 2.62 (s, 3 H), 2.34 - 2.47 (m, 2 H), 2.23 (s, 3 H), 1.55-1.57 (m, 21 H), 1.29-1.31 (d, 12 H), 0.89-0.90 (d, 6 H)

Minor isomer: **¹H NMR (400 MHz, CDCl₃)** δ ppm 7.05 (s, 2 H), 3.68 (s, 3 H), 2.99 (m, 1H), 2.59 (s, 3 H), 2.34 - 2.47 (m, 2 H), 2.23 (s, 3 H), 1.49-1.53 (m, 21 H), 1.37-1.39 (d, 12 H), 0.85-0.87 (d, 6 H). **¹³C NMR (CDCl₃, 100 MHz)** δ 13.5, 17.2, 21.5, 23.7, 25.2, 30.3, 33.3, 38.7, 41.7, 59.4, 59.7, 68.1, 122.6, 126.3, 129.9, 133.1, 136.5, 139.5, 144.4, 148.6, 156.4, 156.5, 159.5, 159.6. **³¹P NMR (162 MHz, CDCl₃)** δ 75.96, 75.81

2-octanone (**A-2a**)¹⁵⁷

Colorless oil, 116.5 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ 2.41 (t, J = 7.5 Hz, 2H), 2.13 (s, 3H), 1.55 (dd, J = 14.4, 7.2 Hz, 2H), 1.38 – 1.17 (m, 6H), 0.87 (t, J = 6.7 Hz, 3H).

2-hexanone (**A-2b**) ¹⁵⁸

Colorless oil, 91.4 mg, 91%. ^1H NMR (400 MHz, CDCl_3) δ = 2.36 (t, J =7.5, 2H), 2.06 (s, 3H), 1.52- 1.45 (m, 2H), 1.30 – 1.18 (m, 2H), 0.83 (t, J =7.3, 3H).

Heptane-2,6-dione (**A-2c**) ¹⁵⁹

Colorless liquid, 113.2 mg, 89%. ^1H NMR (400 MHz, CDCl_3) δ = 2.42 (t, J =7.1, 4H), 2.08 (s, 6H), 1.77 (p, J =7.1, 2H).

3-methyl-2-cyclohexene-1-one (**A-2c'**) ¹⁵⁹

^1H NMR (400 MHz, CDCl_3) δ 6.01 – 5.60 (m, 1H), 2.41 – 2.19 (m, 4H), 2.08 – 1.81 (m, 5H). yellow oil, 93.5 mg, 85%

4-phenylbutan-2-one (**A-2d**) ¹⁶¹

Colorless oil, 130.8 mg, 88%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33 – 7.15 (m, 2H), 2.90 (t, $J = 7.6$ Hz, 1H), 2.76 (t, $J = 7.6$ Hz, 1H), 2.14 (s, 1H).

1-acetyl-1-cyclohexene (**A-2e**)¹⁶²

Light yellow oil, 114.8 mg, 92%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.85 (t, $J = 3.8$ Hz, 1H), 2.31 – 2.05 (m, 7H), 1.70 – 1.39 (m, 4H).

1-(4-fluorophenyl)ethan-1-one (**A-2f**)¹⁵⁸

Colorless oil, 107.8 mg, 78%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.98 (dd, $J = 8.3, 5.8$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 2.58 (s, 3H).

4'-methoxyacetophenone (**A-2g**)¹⁵⁸

White solid, 142.3 mg, 95%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.86 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 3.78 (s, 3H), 2.47 (s, 3H).

1,4-diacetylbenzene (**A-2h**)¹⁵⁸

White solid, 144.3, 89%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.03 (s, 4H), 2.65 (s, 6H).

2-methylacetophenone (**A-2i**)¹⁶³

Colorless oil, 117.5 mg, 88%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.76 (d, J = 11.0 Hz, 2H), 7.44 – 7.29 (m, 2H), 2.59 (s, 3H), 2.41 (s, 3H).

4-octanone (**A-2j**)¹⁶⁴

Colorless oil, 106 mg, 82%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 2.35 (td, J =7.3, 5.2, 4H), 1.55 (dp, J =22.7, 7.5, 4H), 1.33 – 1.22 (m, 2H), 0.87 (td, J =7.4, 2.7, 6H).

Mixture of 2- and 3-decanone (**A-2k**)^{165,166}

Colorless oil, 148 mg, 95%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 2.43 – 2.32 (m, 4H), 2.10 (s, 2-decanone, 3H), 1.53 (m, 2- and 3-decanone mixture, 3H), 1.26 (m, 2- and 3-decanone mixture, 15H), 1.01 (t, J =7.3, methyl of 3-decanone, 1H), 0.84 (t, J =6.9, 2- and 3-decanone mixture, 5H).

1-hydroxy-3-octanone (**A-2l**)¹⁶⁷

Clear liquid, 124 mg, 86%. ¹H NMR (400 MHz, CDCl₃) δ = 3.61 (s, 1H), 2.56 – 1.63 (m, 6H), 1.58 – 1.42 (m, 2H), 1.33 – 1.20 (m, 2H), 0.91 – 0.82 (t, 3H).

2-oxo-1-phenylpropyl acetate (**A-2m**)¹⁶⁸

Colorless liquid, 181 mg, 93%. ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 5H), 5.97 (s, 1H), 2.18 (s, 3H), 2.10 (s, 3H).

methyl-5-oxohexanoate (**A-2n**)¹⁶⁹

Colorless liquid, 110 mg, 76%. ¹H NMR (400 MHz, CDCl₃) δ = 3.65 (s, 3H), 2.49 (t, *J*=7.2, 2H), 2.36 – 2.29 (m, 2H), 2.13 (s, 3H), 1.88 (p, *J*=7.2, 2H).

Dimethyl-2-(2-oxopropyl) malonate (**A-2o**)¹⁷⁰

Colorless oil, 180.4 mg, 95%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 3.86 (t, $J=7.1$, 1H), 3.73 (s, 6H), 3.05 (d, $J=7.2$, 2H), 2.18 (s, 3H).

1,2-diphenylethan-1-one (**A-2p**)¹⁵⁸

White solid, 165.9 mg, 84%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.02 (dd, J = 5.3, 3.3 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.51 – 7.42 (m, 2H), 7.38 – 7.22 (m, 5H), 4.29 (s, 2H).

1-acetylcyclohexanol (**A-2q**)¹⁷¹

Yellow oil, 95.2 mg, 67%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.61 (s, 1H), 2.21 (s, 3H), 1.28-1.73 (m, 10H).

^1H NMR, ^{13}C NMR and ^{31}P NMR spectra of L4-AuCl and ^1H NMR spectra of products

SUMMARY AND OUTLOOK

We have developed HBr/DMPU and HCl/DMPU reagents which will serve a good alternative to existing of hydrogen bromide and chloride solutions. The advantages of these reagents lie in the ease of handling, high concentration and especially unique reactivities towards alkenyl and alkynyl systems. The HBr reagent has been used in the hydrobromination of alkenes and alkynes without competition reactions caused by rearrangement or solvolysis. It also served as an effective substitution to other bromides in bromination transformations.

HCl/DMPU reagent presented us with the first efficient regioselective homogeneous gold-catalyzed hydrochlorination of unactivated alkynes. This overcame the traditional incompatibility between conventional cationic gold catalysts and chloride.

It was also shown to promote the chlorothiolation of alkenes, a transformation that affords biologically and synthetically relevant β -chlorothiolated compounds, using common and easy to handle starting materials like DMSO and less expensive feedstock; alkenes. The procedure showed good functional group compatibility—both terminal and internal alkenes are suitable substrates—and is scalable.

Finally, HCl/DMPU induces the formation of (thiomethyl)methyl carbenium ion from DMSO under mild conditions. Homoallylic amines react with this electrophile to generate 4-chloropiperidines in good yields. The method is applicable to both aromatic and aliphatic amines. The use of HCl•DMPU as both non-nucleophilic base and chloride source constitutes an environmentally benign alternative for piperidine formation. With

this mildly generated carbosulfonium ion, this chemistry will be exploited to access a wide range of homologation cyclization reactions by altering reaction nucleophiles.

Remarkably, the combination of HCl/DMPU and DMSO showed reactivity that is substrate dependent (Scheme 13). We observed that chloromethylthiolation is obtained for many (un)functionalized alkenes that do not have neighboring competing nucleophilic substituent. However, secondary amino alkenes will undergo a competitive cyclization reaction. For example, under similar conditions, secondary homoallylic amines afforded piperidines *via* iminium ion and a 6-exo-trig cyclization.

Scheme 13. Dual reactivity of HCl/DMPU and DMSO with alkenes

APPENDIX B: LIST OF ABBREVIATIONS

DCE:	1,2-Dichloroethane
DCM:	Dichloromethane
DMPU:	N, N'-Dimethylpropyleneurea
DMSO:	Dimethylsulfoxide
dr:	Diastereomeric ratio
EI:	Electrospray Ionization
EtOAc:	Ethyl acetate
GC:	Gas liquid chromatography
h:	Hour
HBD:	Hydrogen bond donor
HBA:	Hydrogen bond acceptor
HCl:	Hydrogen chloride
HBr:	Hydrogen bromide
HF:	Hydrogen fluoride
HFIP:	1,1,1,3,3,3-Hexafluoro-2-propanol
HOAc:	Acetic acid
HRMS:	High resolution mass spectroscopy
Hz:	Hertz
IR:	Infrared
M:	Molar
<i>m</i>:	meta
mg:	milligram
min:	minute
mL:	milliliter
mmol:	millimole
MsOH:	Methanesulfonic acid
NBS:	N-Bromosuccinimide

NCS: N-Chlorosuccinimide

NMR: Nuclear magnetic resonance spectroscopy

o: Ortho

p: Para

ppm: Parts per million

Py: Pyridine

tert: Tertiary

TMS: Trimethylsilyl

TFA: Trifluoroacetic acid

TfOH: Trifluoromethanesulfonic acid

THF: Tetrahydrofuran

TLC: Thin layer chromatography

APPENDIX C: COPYRIGHT PERMISSION

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Ebule, Rene Elad; Hammond, Gerald B

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1. Li, Z.; **Ebule, R.**; Kostyo, J.; Hammond, G. B.; Xu, B., HBr–DMPU: The First Aprotic Organic Solution of Hydrogen Bromide. *Chem. Eur. J.* **2017**, 23, 12739-12743.

<https://doi.org/10.1002/chem.201703457>

2. **Ebule, R.**; Liang, S.; Hammond, G. B.; Xu, B., Chloride-Tolerant Gold(I) Catalyzed Regioselective Hydrochlorination of Alkynes, *ACS Catal.* **2017**, 7, 6798-6801.

<https://pubs.acs.org/doi/abs/10.1021%2Facscatal.7b02567>

3. **Ebule, R.**; Hammond, G. B.; Xu, B., Metal-free Chlorothiolation of Alkenes using HCl and Sulfoxides, *Eur. J. Org. Chem.* **2018**, 2018, 4705-4708.

<https://doi.org/10.1002/ejoc.201800973>

4. **Ebule, R.**; Malhotra, D.; Hammond, G. B.; Xu, B., Ligand Effects in the Gold Catalyzed Hydration of Alkynes. *Adv. Synth. Catal* **2016**, 358, 1478-1481.

<https://doi.org/10.1002/adsc.201501079>

CURRICULUM VITAE

Rene E. Ebule

3306 RIVER CHASE CT., APT G, LOUISVILLE, KY 40218. Email:
ebulerene@yahoo.com or rene.ebule@louisville.edu. Phone: (502) 533-2007

PROFILE

- Resilient, self-motivated and skilled candidate with demonstrated research expertise in organic synthesis, interpretation and characterization.
- Have experience in chemical formulation; I designed and formulated new organic aprotic halogenation reagents which have been explored for efficient halogenation transformations.
- Highly knowledgeable in NMR, GC-MS, IR, UV-Vis, Chromatography and Schlenk techniques.
- Vast experience in teaching and mentoring high school, undergraduate and junior graduate students.
- Possess an advanced understanding of the use of softwares like Agilent ChemStation, Mestre Nova, Xshell, for data analysis.

EDUCATION

PhD Organic Chemistry 2013- 2018

University of Louisville, Louisville, KY

Advisor: Professor G.B.Hammond

Dissertation: Investigating the unique reactivity of novel HX (X=Cl, Br) reagents with alkenes and alkynes.

MS Applied Chemistry 2010- 2012

New Mexico Highlands University, Las Vegas, NM

Advisor: Dr. Rodolfo A. Martinez

Thesis: The synthesis of various C-13 labeled vinyl-systems from diethyl phenylsulfinyl [¹³C]methyl phosphonate.

BS (Hons) in Chemistry; Minor Materials Science 2000- 2003

University of Buea, Buea, Cameroon

RESEARCH EXPERIENCE

University of Louisville, KY

2013- Present

- Prepared highly concentrated, bench stable hydrogen halide reagents used for green and atom economical hydrohalogenation reactions.
- Investigated the reactivity of hydrogen halide-DMPU reagents in various transformations of unsaturated systems
- Explored protic acid-assisted homologation and alkene cyclization reactions.
- Designed and synthesized ligands to study their effects in the homogenous gold and other transition-metal catalysis.
- Evaluated the efficacy of various ligands on other transition metal-catalyzed transformations.
- Taught and mentored undergraduate and first year graduate students into designing a new project.

New Mexico Highlands University (MS)

2010- 2012

- Synthesized isotopically enriched vinyl systems from basic synthons like $^{13}\text{CH}_3\text{I}$ and $^{13}\text{CH}_3\text{OH}$.
- Performed the Synthesis chromophores to test for Non-linear Optical application.

PUBLICATIONS.

1. **Ebule, R.**; Mudshinge, S, Hammond, G. B.; Xu, B., A 5+1 Protic Acid-Assisted *aza*-Pummerer Approach for Synthesis of 4-Chloropiperidines From Homoallylic Amines. (Manuscript submitted).
2. **Ebule, R.**; Hammond, G. B.; Xu, B., Metal-free Chlorothiolation of Alkenes using HCl and Sulfoxides, *Eur. J. Org. Chem.* **2018**, *2018*, 4705-4708.
3. **Ebule, R.**; Liang, S.; Hammond, G. B.; Xu, B., Chloride-Tolerant Gold(I) Catalyzed Regioselective Hydrochlorination of Alkynes, *ACS Catal.* **2017**, *7*, 6798-6801.
4. Li, Z.; **Ebule, R.**; Kostyo, J.; Hammond, G. B.; Xu, B., HBr–DMPU: The First Aprotic Organic Solution of Hydrogen Bromide. *Chem. Eur. J.* **2017**, *23*, 12739-12743
5. Liang, S.; **Ebule, R.**; Hammond, G. B.; Xu, B., A Chlorinating Reagent Yields Vinyl Chlorides with High Regioselectivity under Heterogeneous Gold Catalysis. *Org. Lett.* **2017**, *19*, 4524-4527
6. **Ebule, R.**; Malhotra, D.; Hammond, G. B.; Xu, B., Ligand Effects in the Gold Catalyzed Hydration of Alkynes. *Adv. Synth. Catal* **2016**, *358*, 1478-1481.

AWARDS / HONORS

- COACH workshop travel award recipient at the 45th Annual NOBCChE meeting, September 16, 2018, Orlando, FL.
- 2018 Selected presenter at the Graduate Research Symposium, July 26- 29, 2018, Bloomington, IN.
- Advancing science conference grant recipient of the 45th Annual NOBCChE meeting from NOBCChE, September 17- 20th 2018.
- Advancing science conference grant recipient of the 45th Annual NOBCChE meeting from NOBCChE, October 30th – November 3rd, 2017.
- Travel award from the Graduate Network in Arts and Sciences (GNAS), University of Louisville to attend the 44th Annual NOBCChE meeting, October 2017.
- Travel award to the 254th ACS annual meeting in Washington, DC from the University of Louisville graduate student committee (GSC). August 2017.
- Best graduate teaching assistant in the department of chemistry, University of Louisville, KY 2016.
- Outstanding performance at the graduate level courses at New Mexico highlands University, NM 2011
- Highest achievement award at General Certificate of Education, Ordinary and Advanced levels examinations 1998 and 2000
- Salutatorian recognition at the Department of Chemistry at the University of Buea for the 2003 Convocation.
- Instructor Award for 100% success of students in the Cameroon General Certificate of Education Advanced Levels (CGCE) examination. 2007-2008

CONFERENCES

- An HCl/DMPU Mediated Metal-Free Chlorothiolation and Methylenation of Alkenes and Homoallylic Amines Using Dimethylsulfoxide as Thiomethyl and Methylene Source

Rene Ebule (Oral Presentation); 44th Annual NOBCChE National Meeting, Orlando, FL, September 17 -20, 2018.

- Synthesis of 4-Chloropiperidines via Protic Acid-Assisted Cyclization of Homoallylic Amines with DMSO: An aza-Pummerer Approach

Rene Ebule (Poster Presentation); Graduate Research Symposium, Bloomington, IN, July 26-29, 2018.

- Mild and environmentally benign reactivity of a novel, highly concentrated, organic HCl reagent for 1, 2-alkene difunctionalization

Rene Ebule (Oral Presentation); 255th ACS National Meeting & Exposition, New Orleans, LA, March 18-22, 2018.

- Exploring the Reactivity of Novel Environmentally Benign Aprotic Hydrogen Halide Solutions with Unsaturated Systems

Rene Ebule (Oral Presentation) 11th Annual Graduate Regional Research Conference, Louisville, KY, March 2-3, 2018.

- Investigating the reactivity of HCl/DMPU and HBr/DMPU reagents with unsaturated systems

Rene Ebule (Poster Presentation); 44th Annual NOBCChE National Meeting, Minneapolis, MN, October 30- November 3, 2017.

- Investigating the reactivity of HCl/DMPU and HBr/DMPU reagents with unsaturated systems

Rene Ebule (Poster Presentation); 254th ACS National Meeting & Exposition, Washington, DC, August 20-24, 2017.

- Synthesis and X-ray studies of triene chromophores containing the cyclohexene ring structure for nonlinear optical applications

Rene Ebule (Poster Presentation); 23rd Rocky Mountain Regional Meeting of the ACS, Westminster, CO, October 17-20, 2012.

TECHNICAL/LAB SKILLS

- Highly knowledgeable in NMR, GC-MS, IR, UV-Vis, Chromatography and Schlenk techniques; being able to run, interpret data and troubleshoot when needed.
- Vast experience in teaching and mentoring high school, undergraduate and junior students.
- Possess an advanced understanding of the use of softwares like Agilent ChemStation, Mestre Nova, Xshell, for data analysis.

TEACHING EXPERIENCE

University of Louisville, KY

2013- 2017

Graduate Teaching Assistant: Taught undergraduate Organic Chemistry I and II laboratory courses.

New Mexico Highlands University Las Vegas, NM

2010- 2012

Adjunct Instructor for undergraduate general chemistry and organic Chemistry I laboratory courses (Spring 2013)

Graduate Teaching Assistant: Taught undergraduate Organic Chemistry I and II laboratory courses where I performed the following tasks;

- Prepared materials and solutions to be used during laboratory sessions.
- Critique and grade laboratory reports submitted by student's weekly.
- Supervise laboratory sessions and answer all inquiries presented by students.
- Collaborate with other professors during lecture and laboratory sessions
- Lead class discussions during introductory lessons that are given prior to the actual experiment.
- Conduct and demonstrate experiments for students in explicit, teacher-directed models of Instruction.

Sacred Heart College, Douala and Bishop Rogan College, Buea (Cameroon)
2003- 2009

Chemistry Instructor and Head of Chemistry Department; Coordinated the department of Chemistry by providing supervision and recommendations for instructional methods to all teachers within the department.

- Submitted annual reports to the Superintendent of the College that assessed the academic year instruction and test scores, as well as submitted requests for new material and equipment, as well as instruction resources based on teacher input.
- Taught Chemistry for the secondary and high school; supervising practical lessons for higher level students.
- Conducted monthly meetings for staff and faculty members of the department where faculty was given the opportunity to express ideas, complaints, or needs for the department. Followed up on requests through work orders with higher officials.

Leadership and Outreach activities

University of Louisville, KY

2014- 2015

Secretary general of the association of Chemistry graduate students: Took meeting notes and forwarded for execution by the public relations officer

New Mexico Highlands University Student Senator

2011- 2012

Student Senator, Graduate Committee and Steering Committee member to run the student government.

Member of the UNICEF NMHU chapter; Created awareness, sensitized the community on the Rights of the child through community radio and designed ways of raising funds to be sent to the UNICEF headquarters in saving the lives of children dying every day from preventable causes.

University of Buea, Cameroon 2000- 2003

Secretary General of the Government Bilingual High School, TIKO Ex-Students Association University of Buea branch.

Financial Secretary for the Catholic Community of the University of Buea; I kept records of the finances of the community after every event and gave monthly updates.

GOVERNMENT BILINGUAL HIGH SCHOOL, TIKO 1998- 1999

Student representative to the school administration. 1999- 2000

School delegate to the nationally televised inter-school quiz competition. 1999

REFERENCES.

Available upon request.