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DEVELOPMENT OF RECYCLABLE GOLD NANOPARTICLES FOR ROUTINE BENCHTOP CATALYSIS IN ORGANIC TRANSFORMATIONS

By

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B.S., Shanxi University, China 2006
M.S., Hunan University, China, 2009

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Louisville, Kentucky

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A Dissertation Approved on

April 18th, 2017

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ABSTRACT

DEVELOPMENT OF RECYCLABLE GOLD NANOPARTICLES FOR ROUTINE BENCHTOP CATALYSIS IN ORGANIC TRANSFORMATIONS

Shengzong Liang

April 18th, 2017

Homogeneous gold catalysis is a popular research area due to its high efficiency. Various gold catalysts have been utilized in organic synthesis and their reaction mechanisms are also well understood. However, most gold catalysis suffers from high catalyst loading or catalyst decay problems. In addition, homogeneous gold catalysts are not recyclable. These disadvantages have limited their application in large-scale synthesis and also caused a serious waste of this precious metal. A solution for these problems is to use a recyclable heterogeneous gold catalyst. So in this study, with the aim of making gold chemistry greener we successfully used heterogeneous gold nanoparticles (Au/TiO₂) as catalyst on several types of organic transformations where they functioned as a “Swiss army knife” multipurpose heterogeneous catalyst. On the one hand, similarly as homogeneous gold catalysis, small amount of cationic gold species on Au/TiO₂ could act as soft Lewis acid for the activation of C-C unsaturated bonds especially triple bond, promoting the facile nucleophilic addition of various nucleophiles. For example, the nucleophilic attack of catalytical amount of morpholine followed by hydration of the resulting imine intermediate could lead to an overall efficient alkyne hydration catalyzed by Au/TiO₂ under basic conditions. This method

could tolerate substrates bearing highly acid-sensitive functional groups like silyl ethers or ketals that usually can't survive in conventional acidic alkyne hydration systems. In addition, amines could also serve as nucleophile to furnish corresponding amine products after reduction which is derived from alkyne hydroamination reaction. Moreover, a novel chlorinating reagent HCl/DMPU was designed by our group, in the presence of Au/TiO₂, it could deliver chlorine onto alkynes to give vinylchlorides in good regioselectivity. On the other hand, the main component of gold nanoparticles: gold(0) species could efficiently dissociate transfer hydrogen reagents such as ammonium formate and formic acid, thus the resulting gold hydride species could easily mediate the highly stereoselective semireduction of alkynes and reductive amination of carbonyl compounds respectively. It is noteworthy that the gold nanoparticles could be recycled easily without significant loss of activity in most of cases.

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1. INTRODUCTION

1.1 Introduction of homogeneous gold catalysis

Gold with symbol (Au) and atomic number 79 in the periodic table of the elements is a transition metal and a group 11 element. It is found mostly in rocks, veins and alluvial deposits in elemental form, and less commonly it can also be found in minerals such as quartz, pyrite, sylvanite as well as tellurium. For centuries, it was considered as one of the most stable and least reactive elements due to its strong resistance to most acids, chemical reactions and oxidants. However regardless of its “uselessness” from chemistry point of view, gold has shown its great values in many other aspects. For instance, the most common use of gold is for decoration products such as jewelry, which consumes around 50% of gold. In addition, its high electrical and thermal conductivity make it an important material in industry.¹

Although gold is an inert element, it still has ionic forms. A large scope of oxidation state of gold ranging from -1 to +5 has been observed, among which Au(I) and Au(III) are the dominant ones. As a matter of fact, these two gold species initiate the homogeneous cationic gold catalysis which is a landmark addition to the field of organic synthesis. It is viewed as one of the most important breakthroughs during last decades. The commonly used homogeneous gold catalyst is Au(I) organogold compounds with a coordination number 2 and a linear molecular geometry.² AuCl stands for the simplest Au(I) catalyst which is readily reduced to Au(0), therefore, in order to increase the stability of gold catalyst, a wide range of ligands are involved to coordinate with gold center such as organophosphine based ligands and N-heterocyclic carbene (NHC) Ligands.³ To further tune

the reactivity of gold catalysts, more ionic characteristics counterions such as OTf, NTf₂ and SbF₆ are utilized instead of chloride. Moreover, the reactivity of gold catalysts can also be modified through fine tune either the electronic or the steric properties of organophosphine ligands.

Numerous reactions catalyzed by homogeneous gold have been increasingly emerging and various strategies facilitating the efficiency of gold catalysis also appeared in the literature.⁴ Most of them were based on the propensity of gold to function as a soft and carbophilic Lewis acid in the activation of carbon-carbon π -bonds. Especially, computational studies show that the binding energy between gold catalysts and alkynes is the strongest among various electrophiles.^{3b, 5} The unusual activity of gold compared with its neighboring atoms in the periodic table was rationalized by its relativistic effects,⁶ resulting in a contracted 6s orbital which is responsible for the greatly increased π -acidity of gold. Based on the unique alkynophilic ability of gold catalyst, a two-stages gold catalytic cycle has been well accepted (Scheme 1).⁷ In stage 1, the cationic gold species will activate triple bond and followed by a nucleophilic attack on the gold activated π -complex alkyne **A** to give a trans-alkenyl gold intermediate **B**. In stage 2, the resulting vinyl gold complex will react with a proton to furnish the final product through protodeauration, and meanwhile the cationic gold species is regenerated through this

Scheme 1. Typical two-stages gold catalytic cycle

step. However, in most of the gold-catalyzed reactions, the gold catalysts suffer from decay or deactivation issues which are caused mainly by the disproportionation of cationic gold.⁸

The versatility of homogeneous gold catalysis regarding to organic synthesis is attributed to the various nucleophilic additions onto the activated alkynes for purpose of establishing new carbon-carbon or carbon-heteratom bonds. For instance, the oxygen could serve as nucleophiles to access various valuable synthetic functionalities such as alcohols,⁹ ethers,¹⁰ ketones,¹¹ esters¹² and ketals¹³. One notable example is the hydration of alkynes reported by Nolan and coworkers in 2014 (Scheme 2a).¹⁴ They developed a highly efficient NHC gold catalyst which could catalyze the hydration of alkynes in 50 ppm level. Halogens are also suitable nucleophiles for construction of carbon-halogen bonds.¹⁵ Our group has reported a novel gold phthalimide precatalyst mediated fluorination of alkynes to synthesize alkenyl fluoride compounds (Scheme 2b).^{15a} The newly designed nucleophilic fluorinating reagent HF/DMPU was able to deliver fluorine smoothly onto

Scheme 2. Remarkable examples of homogeneous gold catalyzed reactions

alkynes to furnish the corresponding alkenyl fluorides with both good yields and regioselectivity. In addition, C-N bond could also be established via gold mediated hydroamination of alkynes through either intramolecular or intermolecular hydroamination of alkynes.¹⁶ One of such remarkable examples was described by Shi and coworkers that in the presence of their specially designed triazole gold catalyst, a variety of amine products could be generated from hydroamination of alkynes after reduction (Scheme 2c).^{16d} Moreover, carbon-carbon bond formation could also be achieved with the same strategy.¹⁷ For example, the same group also reported a Nakamura Reaction between terminal alkynes and dione compounds with their triazole gold catalysts (Scheme 2d).^{17a} Lastly, other uncommon carbon-heteroatom bond such as sulfur¹⁸ and phosphine¹⁹ were also constructed by different research groups.

1.2 Introduction of heterogeneous gold catalysis

Despite of the wide attentions homogeneous gold has received, some obvious disadvantages of it can't be ignored: 1) homogeneous gold catalysts are usually not stable; 2) the separation process is usually complicated; 3) homogeneous gold catalysts are not recyclable. Therefore, searching for more stable and recyclable heterogeneous gold catalysts might be a good solution to solve these problems.

Although bulk gold has been considered as an inert catalyst, gold particles with size of nanometers (gold nanoparticles, Au NPs) have been recognized as active and extraordinary effective green catalysts.²⁰ Mostly, gold nanoparticles are supported on metal oxide surfaces (Au/M_xO_y, e.g., Au/TiO₂ or Fe₃O₄ or Al₂O₃ or ZnO, etc.), while some of them are coated on activated carbon or specially designed polymers. The existence of supporting material could make Au NPs very stable and easy to handle. The first breakthrough using Au NPs as catalyst occurred in the oxidation of CO to CO₂ under atmospheric air.²¹ This oxidation process has led to some practical applications, such as

the use of Au NPs as additives in gas masks or sensors in analytical instruments. In addition, many valuable potential industrial processes catalyzed by nanogold particles have been developed, such as the aerobic oxidation of methanol to methyl formate,²² vinyl acetate and vinyl chloride that are important raw material for polymer synthesis.²³ Following the oxidation of CO methodology, more and more potential oxidative reactions with Au NPs have been extensively explored such as oxidation of alcohol,²⁴ aldehydes,²⁵ amines,²⁶ alkanes,²⁷ as well as epoxidation of alkenes.²⁸ Apart from the excellent performance of Au NPs in oxidative reactions, other catalytic potentials were also well studied. It was found that hydrosilanes and silylboranes can be efficiently activated by Au NPs and added to alkyne substrates to form valuable building blocks-alkenyl silanes.²⁹ Gold is a less active catalyst regarding to cross-coupling reactions as compared to its palladium competitors, however, such reactions like Suzuki and Sonogashira reactions were able to be accomplished by using Au NPs as catalysts, which makes these reactions much greener because of the good recyclability of Au NPs.³⁰ In addition, Au NPs are also efficient catalysts in the case of reduction of specific functional groups. A general method about Au NPs catalyzed selective hydrogenation of nitrobenzenes has been established by Corma and coworkers in 2006, excellent functional group tolerance was exhibited in the presence of other reducible functionalities such as olefin, aldehyde, nitrile, and amide.³¹ Using propanol as hydrogen donor, a transfer hydrogenation process could also take place to produce alcohols from corresponding aromatic ketones.³² Another excellent example regarding to the reductive catalytic property of Au NPs was the deoxygenation of epoxides. Fan's group reported a protocol for reduction of epoxides to produce olefins in the presence of reductant (H_2O and CO) under ambient conditions.³³ Although the application of gold nanoparticles in alkyne activation is still underdeveloped, their use in such transformations will lead to a more economical and environmental friendly process. Some remarkable methodologies have been developed during the last decade. For

instance, Garcia and co-workers found that Au NPs with various supports could catalyze the benzannulation of o-alkynylbenzaldehyde with high selectivity and yields.³⁴ In Hashmi's work, heterogeneous Au/CeO₂ were able to mediate the formation of phenols from ω -alkynylfurans through an isomerization process.³⁵ Another application of Au NPs on the alkyne activation was reported by Stratakis in 2011, where the cyclization of aryl propargyl ethers was achieved with minor dimerized byproduct using Au NPs supported by TiO₂.³⁶ A methodology of three-component coupling among aldehyde, amine, and alkyne to form propargyl amines was also evaluated, nanogold particles deposited on CeO₂ and ZrO₂ showed the best activity and could be easily reused.³⁷

1.3 Rationality, scenario and summary of thesis research

Supported gold nanoparticles are usually expected to be composed of exclusive metallic gold clusters, however, they also contain minor cationic gold species in either oxidative state of +1 or +3 (Scheme 3).³⁸ These cationic gold species are formed either by incomplete reduction of HAuCl₄ or NaAuCl₄ during the preparation of Au NPs or by oxidization of small nanogold clusters with certain oxidants.³⁹ So we hypothesized that these support-stabilized cationic gold species [Au]^{δ+} may function as homogeneous gold catalysts to activate C-C unsaturated bonds, especially alkynes, for various nucleophilic

Scheme 3. Cationic gold species observation in commercially Au/TiO₂ through XPS

Scheme 4. Similarity of gold nanoparticles and homogeneous gold in gold catalytic cycle additions (Scheme 4).

Based on this hypothesis, we deeply studied gold nanoparticles, more specifically, the cationic gold species on gold nanoparticles mediated alkyne activation and nucleophilic addition to construct C-O, C-N and C-Cl bonds. First of all, we found that gold nanoparticles (Au/TiO₂) could catalyze the hydration of alkyne using morpholine as a basic co-catalyst. Compared with conventional acid catalyzed alkyne hydration, in our protocol, due to the presence of base, it was compatible with various acid-sensitive functional groups, which is highly valuable from organic synthesis point of view. We also examined alkyne hydroamination catalyzed by Au/TiO₂, and discovered that a wide range of terminal alkynes were able to be regioselectively converted to amines through intermolecular hydroamination. On the other hand, the hydroamination in intramolecular manner could furnish indole derivatives in high yields. Lastly, based on the concept of hydrogen bonding basicity, we successful designed and synthesized a novel chlorinating reagent: HCl/DMPU, with which a highly regioselective hydrochlorination of alkynes mediated by Au/TiO₂ was accomplished.

In addition, regarding to the fact that the high surface areas of metallic nanosize of gold particles in Au/TiO₂ could greatly facilitate the dissociation of hydrogen sources for

reduction of functional groups as mentioned in section **1.2**, we also explored a highly efficient catalytic system for *cis*-selective semihydrogenation of alkynes. A cost-effective and easy-to-handle transfer hydrogen reagent ammonium formate was selected as reductant. Good stereoselectivity was obtained in both non-fluorinated and *gem*-difluorinated alkyne substrates. Beside semireduction of alkynes, we also used the similar strategy to conduct reductive amination of carbonyl compounds in which a wide range of secondary and tertiary amines were synthesized in good to excellent yields.

2. Au/TiO₂ CATALYZED ALKYNES HYDRATION UNDER BASIC CONDITIONS AND ALKYNES HYDRATION THROUGH ACID-ASSISTED BRØNSTED ACID CATALYSIS

2.1 Au/TiO₂ catalyzed hydration of alkynes under basic conditions

2.1.1 Background

Cationic gold catalysts are regarded as the most powerful catalysts for the electrophilic activation of alkynes toward a variety of nucleophiles.^{5a} However, a cationic gold catalytic system may not be compatible with substrates containing highly acid-sensitive functional groups such as silyl ethers or ketals because of the acidity of cationic gold catalysts and the acid promoters that are used to generate cationic gold. Although addition of bases to the reaction system may stabilize substrates containing acid-sensitive functional groups, more often than not, a base will quench the reactivity of cationic gold catalysts by inhibiting or slowing down multiple stages in the cationic gold catalytic cycle.⁷

As mentioned in introduction, the catalytic activity of Au NPs towards electrophilic activation of alkynes could be attributed to its partial oxidation, by oxygen or other oxidants, to higher valence gold species.^{38a, 40} We speculated that Au NPs activated by partial oxidation could be more tolerant towards bases. Au NPs based catalysts are softer and weaker Lewis acids and they may be less affected by the presence of bases, although, on the other hand, their electrophilic activation ability may be weaker than that of homogeneous cationic gold catalysts because of their weaker cationic character. Thus, a

combination of supported Au NPs and a suitable basic co-catalyst could work well for substrates containing acid-sensitive functional groups.

For a proof of concept we chose the hydration of alkynes, which is a straightforward and atom economical way to prepare carbonyl compounds.⁴¹ Many homogeneous catalysts like Hg,⁴² Pd,⁴³ Pt,⁴⁴ Fe,⁴⁵ Ag,⁴⁶ Co,⁴⁷ Ir,⁴⁸ Ru⁴⁹ and Brønsted acids⁵⁰ can catalyze this reaction. Homogeneous gold catalysts are particularly effective.^{11b, 14, 51} Notable examples include the [(PPh₃)AuMe]/H₂SO₄ system reported by Hayashi and coworkers,^{51d, 52} the IPrAuCl/AgSbF₆ system reported by Nolan and coworkers,⁵³ and the small gold clusters/HCl system reported by Corma and coworkers.⁵⁴ Although the above systems are efficient, they do have the following shortcomings: 1) they are not compatible with substrates containing acid-sensitive functional groups; 2) they are not suitable for use with strongly coordinating groups like pyridine because of the strong affinity between the cationic gold and bases; and 3) they cannot be easily recycled. Even the silver free gold (L-Au-NTf₂) catalyzed hydration of alkynes described by Corma and coworkers⁵⁵ performed at room temperature in the absence of other acid promoters-led to non-negligible amounts of decomposed products (from 15% to 100%) when acid sensitive groups such as silyl ethers and triphenylmethyl (Tr) were present in the starting materials. This phenomenon could be attributed to the Lewis acidity of the cationic gold itself.

2.1.2 Screening of reaction conditions

We chose the hydration of phenylacetylene **2-1a** as our model reaction together with the commercially available AUROLite® series (Au NPs supported by TiO₂, ZnO or Al₂O₃, 1% wt/wt loading, average size of Au NPs 2-3 nm). Au/TiO₂ itself performed poorly at 120 °C for 1 hour under microwave conditions (Table 1, entry 1). A strong inorganic base like NaOH (20 mol %) (Table 1, entry 2) did not fare better. Tertiary amines (triethylamine and DMAP, Table 1, entries 3-4) inhibited the reaction, however, primary and secondary amine

bases (*p*-toluenesulfonamide, 4-chloroaniline, benzylamine, diphenylamine, piperazine, piperidine, *N*-methylaniline and morpholine) accelerated the hydration, affording the product in yields ranging from 17% to 76% (Table 1, entries 5-12). Morpholine proved to be the best co-catalyst in the lot (Table 1, entry 12) although morpholine itself did not

Table 1. Screening of conditions for Au/TiO₂ catalyzed alkynes hydration^a

entry	base (mol %)	Au/TiO ₂ (mol %)	solvent	yield (%)
1	-	0.5	dioxane	6
2	NaOH (20)	0.5	dioxane	2
3	Et ₃ N (20)	0.5	dioxane	4
4	DMAP (20)	0.5	dioxane	0
5	TsNH ₂ (20)	0.5	dioxane	20
6	4-chloroaniline (20)	0.5	dioxane	57
7	benzylamine (20)	0.5	dioxane	30
8	diphenylamine (20)	0.5	dioxane	17
9	piperazine (20)	0.5	dioxane	33
10	piperidine (20)	0.5	dioxane	29
11	<i>N</i> -methylaniline (20)	0.5	dioxane	30
12	morpholine (20)	0.5	dioxane	76
13	morpholine (20)	-	dioxane	0
14	morpholine (20)	1	dioxane	88
15	morpholine (5)	1	dioxane	90
16	morpholine (5)	1	toluene	18
17	morpholine (5)	1	MeNO ₂	0
18 ^b	morpholine (5)	1	dioxane	85
19 ^c	morpholine (5)	1	dioxane	81
20 ^d	morpholine (5)	1	dioxane	- ^e

^a Reaction condition: concentration of phenylacetylene is 1 M, microwave at 120 °C for 1 h, yields were determined by ¹H NMR. ^b H₂O (1 equiv.) was used. ^c H₂O (5 equiv.) was used. ^d Au/ZnO or Au/Al₂O₃ was used. ^e A relative complex mixture.

catalyze the hydration (Table 1, entry 13). Using a higher loading of Au/TiO₂ (1 mol %) (Table 1, entry 14) and reducing the amount of morpholine (5%) (Table 1, entry 15) further improved the yield of the reaction. Toluene and nitromethane were not as good solvents as dioxane (Table 1, entries 16-17). The amount of water had minor influence on the reaction (Table 1, entries 18-19). We also tested other gold supports (Au/ZnO or Au/Al₂O₃), but they produced complex mixtures (Table 1, entry 20).

2.1.3 Substrates scope and discussion

With optimized conditions in hand, we investigated the substrates scope (Table 2). Phenylacetylenes substituted with electron-donating or electron-withdrawing groups gave good yields of hydration product **2-2** (Table 2, entries 1-4). Terminal aliphatic alkynes also worked well if higher gold catalyst loading (4 mol %) and lower temperature (110 °C) were used (Table 2, entries 5 and 6). Common functional groups such as nitrile, ester or alkene groups were well tolerated in this hydration protocol (Table 2, entries 7, 8 and 17). We were pleased to find that our catalyst system was compatible with a wide range of acid-sensitive functional groups. Alkynes containing triisopropylsilyl (TIPS), *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyldiphenylsilyl (TBDPS) ethers gave the desired hydration products with excellent yields (Table 2, entries 9-11). No deprotection products were detected. Two other acid labile functional groups, triphenylmethyl (Tr) and allyl ether, were compatible with our reaction conditions (entries 12 and 13). Acetals or ketals are usually more acid sensitive than silyl ethers or Tr but, to our delight, they withstood the reaction conditions. Indeed, alkynes containing a cyclic tetrahydropyranyl ether (THP) moiety (**2-1n**), a noncyclic acetal group (**2-1o**) or a structurally complex glycoside (**2-1p**) yielded the corresponding hydration products in excellent yields (Table 2, entries 14-16). Most of these acid sensitive groups could not have withstood the strong Lewis acidic catalysts reported in the literature.⁴¹ 2-Ethynylpyridine (**2-1r**) was also a challenging substrate because the nitrogen in pyridine strongly binds to most metal catalysts used in hydration.⁴¹ However, **2-1r** gave a very good yield of the hydration product using our methodology (Table 2, entry 18). The internal alkyne diphenylacetylene (**2-1s**) gave the corresponding hydration product (**2-2s**) in 80% yield (Table 2, entry 19) and so did a diyne such as 1,4-diethynylbenzene (**2-1t**) although higher temperatures were needed in the reaction (Table 2, entry 20).

Table 2. Substrate scope of alkyne hydration catalyzed by Au/TiO₂ and morpholine^a

^a Yields were determined by ¹H NMR. ^b Condition A: Au/TiO₂ (1 mol %), morpholine (5 mol %), H₂O (2 equiv.), MW 120 °C for 1 h. ^c Condition B: Au/TiO₂ (4 mol %), morpholine (10 mol %), H₂O (2 equiv.), MW 110 °C for 2 h. ^d Condition A with Au/TiO₂ (2 mol %). ^e Condition B except reaction time is 1 h. ^f Au/TiO₂ (4 mol %), morpholine (20 mol %), H₂O (4 equiv.), MW 140 °C for 2 h.

The pH of the reaction mixture remained weakly basic (pH 8-9) throughout the reaction. This could explain why acid sensitive compounds were well tolerated. To learn whether the leaching of gold species from the TiO₂ support promoted the reactivity of our system, we filtered off the solid Au/TiO₂ after the reaction, added more **2-1a** (1 equiv) and morpholine (5 mol %) to the filtrate, and subjected the resulting mixture to our standard reaction conditions (Scheme 5). We found that no conversion took place in this manner, an indication that the catalysis was heterogeneous in nature.

To support our earlier assertion that a homogenous cationic gold catalyst is usually incompatible with basic additives we decided to investigate the effect of morpholine on the

Scheme 5. Leaching experiment for Au/TiO₂ catalyzed alkynes hydration

reactivity of a gold catalyst (Scheme 6). A homogeneous gold catalyst such as PPh₃AuNTf₂ catalyzed the hydration of alkyne **2-1a** efficiently at room temperature (Scheme 6a), but it became inactive in the presence of morpholine, either at room temperature (Scheme 6b) or under microwave conditions (Scheme 6c). This experiment proved that morpholine could deactivate a homogeneous gold catalyst but not Au NPs based catalyst.

Scheme 6. Effect of base on the reactivity homogeneous gold catalysis

We also investigated the role of morpholine in the reaction. To this end we conducted the hydration of phenylacetylene **2-1a** in dry dioxane and found significant amounts of the hydroamination product (scheme 7).^{16b-d, 56} This result indicated that enamines are plausible intermediates in the hydration of alkynes.⁵⁷

Scheme 7. Possible intermediate for hydration of alkynes under basic condition

2.1.4 Conclusion

In summary, we have developed an efficient alkyne hydration catalyzed by heterogeneous gold under basic conditions. Our method worked well for various alkynes bearing different functional groups, and it was especially useful with substrates bearing acid-sensitive functionalities. High yields (up to 93%) were also observed. This commercially available gold catalyst was easy to handle and fairly air-stable. The work described in this chapter was published in *Org. Lett.* **2015**, 17, 162-165 and highlighted in *Synfacts* **2015**, 11(04), 0439 and *Organic Chemistry Portal*.

2.1.5 Experimental

General procedure for the hydration of alkynes

Method A: Au/TiO₂ (1 mol %) was added to a solution of alkyne **2-1** (0.25 mmol, 1 equiv.), morpholine (5 mol %) and H₂O (0.5 mmol, 2 equiv.) in dioxane (0.25 mL) in a microwave reactor tube. The microwave tube containing the reaction mixture was allowed to react under microwave conditions at 120 °C for 1 h and then cooled down to room temperature followed by filtration of Au/TiO₂. The reaction mixture was concentrated and isolated through silica gel chromatography.

Method B: Au/TiO₂ (4 mol %) was added to a solution of alkyne **1** (0.25 mmol, 1 equiv.), morpholine (10 mol %) and H₂O (0.5 mmol, 2 equiv.) in dioxane (0.25 mL) in a microwave reactor tube. The mixture was allowed to react in the microwave at 110 °C for 2 h and then cooled down to room temperature followed by filtration of Au/TiO₂. The reaction mixture was concentrated and isolated through silica gel chromatography.

Spectroscopic data

acetophenone (**2-2a**)

^1H NMR (400 MHz, CDCl_3) δ 8.00 – 7.93 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 2.61 (s, 3H). Colorless oil, 26.1 mg, 87% isolated yield.

1-(4-methoxyphenyl)ethanone (**2-2b**)

^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H). Colorless oil, 33.3 mg, 89% isolated yield.

1-(4-fluorophenyl)ethanone (**2-2c**)

^1H NMR (400 MHz, CDCl_3) δ 7.98 (dd, J = 8.7, 5.6 Hz, 2H), 7.12 (t, J = 8.6 Hz, 2H), 2.58 (s, 3H). Colorless oil, 27.5 mg, 80% isolated yield.

1-(o-tolyl)ethanone (**2-2d**)

^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.25 (dd, J = 10.8, 8.2 Hz, 2H), 2.58 (s, 3H), 2.53 (s, 3H). Colorless oil, 30.0 mg, 90% isolated yield.

2-octanone (**2-2e**)

¹H NMR (400 MHz, CDCl₃) δ 2.41 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H), 1.54 – 1.44 (m, 2H), 1.37 – 1.15 (m, 6H), 0.87 (t, *J* = 6.4 Hz, 3H). Colorless oil, 29.4 mg, 92% isolated yield.

5-phenylpentan-2-one (**2-2f**)

¹H NMR (400 MHz, CDCl₃) δ 7.27 (m, 2H), 7.18 (m, 3H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.11 (s, 3H), 1.91 (p, *J* = 7.5 Hz, 2H). Colorless oil, 36.3 mg, 90% isolated yield.

5-oxohexanenitrile (2-2g)

¹H NMR (400 MHz, CDCl₃) δ 2.64 (t, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.17 (s, 3H), 1.91 (p, *J* = 7.0 Hz, 2H). Colorless oil, 21.0 mg, 76% isolated yield.

5-oxohexyl benzoate (2-2h)

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.15 (s, 3H), 1.89 – 1.61 (m, 4H). Colorless oil, 46.2 mg, 84% isolated yield.

6-[(triisopropylsilyl)oxy]hexan-2-one (**2-2i**)

¹H NMR (400 MHz, CDCl₃) δ 3.68 (t, *J* = 6.1 Hz, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.59 (m, 4H), 1.17 – 0.85 (m, 21H). Light yellow oil, 66.1 mg, 97% isolated yield.

6-[(tert-butyldimethylsilyl)oxy]hexan-2-one (**2-2j**)

^1H NMR (400 MHz, CDCl_3) δ 3.59 (t, J = 6.2 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 2.12 (s, 3H), 1.77 – 1.35 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H). Light yellow oil, 54.6 mg, 95% isolated yield.

6-(tert-butyldiphenylsilyl)hexan-2-one (**2-2k**)

^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.56 (m, 4H), 7.46 – 7.29 (m, 6H), 3.65 (t, J = 6.2 Hz, 2H), 2.40 (t, J = 7.3 Hz, 2H), 2.10 (s, 3H), 1.60 (m, 4H), 1.04 (s, 9H). Light yellow oil, 82.2 mg, 93% isolated yield.

6-(trityloxy)hexan-2-one (**2-2l**)

^1H NMR (400 MHz, CDCl_3) δ 7.43 (d, J = 7.7 Hz, 6H), 7.36 – 7.13 (m, 9H), 3.06 (t, J = 5.9 Hz, 2H), 2.38 (t, J = 6.9 Hz, 2H), 2.10 (s, 3H), 1.64 (m, 4H). Colorless oil, 79.6 mg, 89% isolated yield.

6-(allyloxy)hexan-2-one (**2-2m**)

^1H NMR (400 MHz, CDCl_3) δ 6.02 – 5.73 (m, 1H), 5.25 (d, J = 17.3 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.11 – 3.78 (m, 2H), 3.42 (t, J = 5.5 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.12 (s, 3H), 1.73 – 1.42 (m, 4H). Colorless oil, 35.8 mg, 92% isolated yield.

6-[(tetrahydro-2H-pyran-2-yl)oxy]hexan-2-one (**2-2n**)

^1H NMR (400 MHz, CDCl_3) δ 4.56 (t, $J = 3.3$ Hz, 1H), 3.99 – 3.62 (m, 2H), 3.58 – 3.20 (m, 2H), 2.46 (t, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 1.91 – 1.37 (m, 10H). Colorless oil, 45.1 mg, 90% isolated yield.

11,11-dimethoxyundecan-2-one (**2-2o**)

^1H NMR (400 MHz, CDCl_3) δ 4.34 (t, $J = 5.7$ Hz, 1H), 3.30 (s, 6H), 2.40 (t, $J = 7.5$ Hz, 2H), 2.12 (s, 3H), 1.64 – 1.42 (m, 4H), 1.51 – 1.07 (m, 10H). Colorless oil, 50.6 mg, 88% isolated yield.

6-[(3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]tetrahydro-2H-pyran-2-yl]oxyhexan-2-one (**2-2p**)

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.19 (m, 18H), 7.15 (m, 2H), 5.16 – 4.24 (m, 9H), 4.03 – 3.18 (m, 8H), 2.43 (m, 2H), 2.09 (s, 3H), 1.72 – 1.57 (m, 4H). HRMS (ESI) calcd for $[\text{C}_{40}\text{H}_{46}\text{O}_7\text{NH}_4^+]$ ($[\text{MNH}_4^+]$) 656.3587; found 656.3590. Colorless oil, 145.1 mg, 91% isolated yield.

1-(cyclohex-1-en-1-yl)ethanone (**2-2q**)

^1H NMR (400 MHz, CDCl_3) δ 6.89 (s, 1H), 2.38 – 2.13 (m, 7H), 1.73 – 1.44 (m, 4H).

Colorless oil, 27.6 mg, 89% isolated yield.

1-(pyridin-2-yl)ethanone (**2-2r**)

^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 7.59 – 7.38 (m, 1H), 2.72 (s, 3H). Light yellow oil, 22.5 mg, 75% isolated yield.

1,2-diphenylethanone (**2-2s**)

^1H NMR (400 MHz, CDCl_3) δ 8.01 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 6.8 Hz, 1H), 7.46 (t, J = 6.8 Hz, 2H), 7.36 – 7.05 (m, 5H), 4.29 (d, J = 1.3 Hz, 2H). Light yellow solid, 39.1 mg, 80% isolated yield.

1,1'-(1,4-phenylene)diethanone (**2-2t**)

^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 4H), 2.64 (s, 6H). White solid, 26.3mg, 65% isolated yield.

2.2 Hydration of alkynes through acid-assisted brønsted acid catalysis

2.2.1 Background

Based on the experience we gained for alkynes hydration using base as co-catalyst, we also wanted to further explore the potential of Au/TiO₂ to catalyze alkyne hydration in the absence of base. Because our former group member Junbin has found that the bigger counterion such as Tf₃C⁻ could accelerate the homogeneous gold catalyzed reactions such as hydration and hydroamination of alkynes much faster than relative smaller counterions including Tf₂N⁻ and TfO⁻,^{4a, 58} so we assumed that Tf₃C⁻ might also help heterogeneous gold catalysis. However, through screening we didn't find the corresponding proofs (Table 3, entries 1-5). But an interesting outcome was observed that when only catalytic amount of Brønsted acid HCTf₃ and HOAc as solvent were subjected into the reaction almost quantitative yield of ketone product was formed (Table 3, entry 6). In addition, when another gold nanoparticle Au/ZnO was, by mistake, applied into the reaction using HOAc as solvent, unfortunately, ZnO support completely reacted with HOAc to generate a Lewis acid Zn(OAc)₂, but to our delight, the hydration product

Table 3. Screening of Au/TiO₂ catalyzed alkynes hydration without base

entry	Au NPs (mol %)	solvent	additive (mol %)	yield (%)
1	Au/TiO ₂ (0.2)	dioxane	HCTf ₃ (0.5)	59
2	Au/TiO ₂ (0.2)	Tol	HCTf ₃ (0.5)	messy
3	Au/TiO ₂ (0.2)	MeOH	HCTf ₃ (0.5)	0
4	Au/TiO ₂ (0.2)	HOAc	HCTf ₃ (0.5)	99
5	Au/TiO ₂ (0.2)	HOAc	-	7
6	-	HOAc	HCTf ₃ (0.5)	99
7	Au/Al ₂ O ₃ (0.2)	HOAc	-	5
8	Au/ZnO (0.2)	HOAc	-	8 (ZnO dissolved)
9	-	HOAc	-	3

was also found in very high yield (88%) (Table 3, entry 8). Therefore, these two exciting results lead us to seek for a rational explanation.

The concept of combined acid catalysis was first proposed by Yamamoto and coworkers, which included Brønsted acid-assisted Brønsted acid (BBA) catalysis and Lewis acid-assisted Brønsted acid (LBA) catalysis.⁵⁹ Based on this concept, we proposed that the acidity of a weak Brønsted acid like acetic acid can be enhanced significantly by combining it with a Brønsted acid such as HCTf₃ or Lewis acid such as Zn(OAc)₂ (Scheme 8). This enhanced acidity could greatly speed up the hydration of alkynes which was obviously observed in aforementioned screening. What's more, there are many readily available Brønsted acids and Lewis acids to choose and each of them has different acid strength and counterions, so we can fine tune the reactivity of the combined acid system to achieve the best efficiency.

Scheme 8. Concept of combined acid catalysis

2.2.2 Screening of reaction conditions

We used the hydration of phenyl acetylene **2'-1a** as our model reaction (Table 4). As expected, the weak Brønsted acid acetic acid itself did not promote the hydration of **2'-1a** (Table 4, entry 1) even at 120 °C, but the combination of acetic acid with only a very mild Lewis acid (KCl) gave a 16% conversion under the same conditions (Table 4, entry 2). The combination of acetic acid with a slightly stronger Lewis acid (LiNTf₂) gave a good yield of the hydration product **2'-2a** (Table 4, entry 3). We also tried to lower the loading of the acid co-catalyst and reduce the temperature: the combination of AcOH with a strong

Brønsted acid TfOH (0.5 mol %) was very efficient at 100 °C (Table 4, entry 4). TsOH, HBF₄·Et₂O, and Tf₂NH were less efficient (Table 4, entries 5-7). Super acid Tf₃CH⁶⁰ also gave a very good yield of product (Table 4, entry 8). These results indicated that a Brønsted acid-assisted Brønsted acid (BBA) combination was able to catalyze the hydration of **2'-1a** at low catalyst loadings (0.5 mol %). Then, we explored the viability of using a Lewis acid-assisted Brønsted acid (LBA) system because there are more choices of available Lewis acids. Most of the AcOH/Lewis acid combinations tested were effective (Table 4, entries 9-12). Among them, Ga(OTf)₃ (Table 4, entry 12) gave the best reactivity. We could further lower the catalyst loading down to 0.2 mol % by increasing the concentration of **2'-1a** (Table 4, entry 13). The combination of AcOH and Ga(OTf)₃ is important; without AcOH Ga(OTf)₃ is not a good catalyst for the hydration reaction (Table 4, entry 14).

Table 4. Screening of conditions for alkynes hydration through combined acid catalysis

entry	co-catalyst (mol %)	condition	yield ^b (%)
1	-	Mw, ^a 120 °C, 1 h	trace
2	KCl (4)	Mw, ^a 120 °C, 1 h	16
3	LiNTf ₂ (4)	Mw, ^a 120 °C, 1 h	93
4	TfOH (0.5)	100 °C, 10 h	99
5	TsOH (0.5)	100 °C, 24 h	Trace
6	HBF ₄ ·Et ₂ O (0.5)	100 °C, 24 h	4
7	Tf ₂ NH (0.5)	100 °C, 24 h	56
8	Tf ₃ CH (0.5)	100 °C, 10 h	99
9	Yb(OTf) ₃ (0.5)	100 °C, 14 h	99
10	Sc(OTf) ₃ (0.5)	100 °C, 12 h	99
11	In(OTf) ₃ (0.5)	100 °C, 10 h	99
12	Ga(OTf) ₃ (0.5)	100 °C, 8 h	99
13 ^c	Ga(OTf) ₃ (0.2)	100 °C, 6 h	99
14 ^d	Ga(OTf) ₃ (0.5)	120 °C, 1 h	trace

^a Mw = Microwave. ^b ¹H NMR Yield. ^c [**2'-1a**] = 2.5 M. ^d The reaction was conducted in dioxane.

2.2.3 Substrates scope and discussion

With the optimized conditions in hand (AcOH/TfOH or AcOH/Ga(OTf)₃), we explored

Table 5. Substrate scope of the LBA alkynes hydration

$$\text{R}-\text{C}\equiv\text{C}-\text{R}' \xrightarrow[\text{HOAc, 100 } ^\circ\text{C}]{\text{H}_2\text{O (1 equiv.)}, \text{Ga(OTf)}_3 \text{ (0.2 mol \%)}} \text{R}-\text{C}(=\text{O})-\text{CH}_2-\text{R}'$$

2'-1 **2'-2**

entry	2'-1	2'-2	time (h)	yield (%) ^a
1 ^b	2'-1a	2'-2a	6	99
2 ^b	2'-1b	2'-2b	3	96
3 ^b	2'-1c	2'-2c	5	99
4 ^b	2'-1d	2'-2d	2	99
5 ^e	2'-1e	2'-2e	3	91
6 ^c	2'-1f	2'-2f	1	92
7 ^c	2'-1g	2'-2g	1	99
8 ^d	2'-1h	2'-2h	12	85
9 ^b	2'-1i	2'-2i	2	99
10 ^b	2'-1j	2'-2i	20	97
11 ^b	2'-1k	2'-2k	20	99
12 ^c	2'-1l	2'-2a	1	70
13 ^d	2'-1m	2'-2m	12	96
14 ^f	2'-1n	2'-2n	1	78

^a Yields were determined by ¹H NMR. ^b Condition A: [2'-1] = 2.5 M in HOAc, H₂O (1 equiv.), Ga(OTf)₃ (0.2 mol %), 100 °C using oil bath. ^c Condition B: [2'-1] = 2.5 M in HOAc, H₂O (1 equiv.), Ga(OTf)₃ (1 mol %), 100 °C using microwave. ^d Condition A with Ga(OTf)₃ (1 mol %). ^e Condition B with Ga(OTf)₃ (1 mol %) at 90 °C. ^f Condition A with H₂O (2 equiv.) and microwave was used.

the substrate scope of this new methodology (Table 5). Substituted phenyl acetylenes with either electron-donating or electron-withdrawing groups all gave close to quantitative yields of hydration products **2'-2** (Table 5, entries 2-4). Terminal aliphatic alkyne also worked well (Table 5, entry 5). The hydration of internal alkynes was slower than that of terminal alkynes, and a slightly higher catalyst loading (1 mol %) was needed to achieve good yields (Table 5, entries 6-8). Alkenes and carboxylic acids were well tolerated (Table 5, entries 9 and 11), but the -OH group in 1-ethynylcyclohexanol (**2'-1j**) did not survive the hydration condition (Table 5, entry 10). Hydration of ethyl phenylpropiolate (**2'-1l**) gave the decarboxylation product **2'-2a** in 70% yield (Table 5, entry 12). An anti-Markovnikov product cinnamaldehyde (**2'-2m**) was formed in the hydration of propargyl acetate (**2'-1m**) (Table 5, entry 13). Finally, hydration of diyne (**2'-1n**) also gave the expected di-hydration product **2'-2n** in good yield (Table 5, entry 14).

Considering the use of relative inconvenient solvent HOAc, we furthermore tested the hydration reaction in dioxane in the presence of catalytic amount of combined acid (Scheme 9). It turned out that 90% of the hydrolysis product was obtained with 10% of unreacted **2'-1a** left after 70 minutes under microwave condition. Therefore, compared with the two control experiments (Table 4, entries 1 and 14), this result clearly showed that the LBA system is highly efficient for hydration of alkynes.

Scheme 9. Hydration of phenylacetylene with catalytic amount of combined acid

It should be noted that our combined acid catalysis sometimes had higher or different regioselectivities compared to transition metals (e.g., Au) catalyzed counterparts due to different reaction mechanisms. For example, the hydration of phenyl substituted internal

alkyne **2'-1h** (Table 5, entry 8) produced the aryl ketone isomer (**2'-2h**), but the gold catalyzed hydration of **2'-1h** gave a mixture of two isomers.⁵³ In a more extreme case, the gold catalyzed hydration of propargyl acetate gave the Markovnikov product **2'-3m** (Scheme 10b).⁶¹ However, our system furnished the anti-Markovnikov product **2'-2m** exclusively (Scheme 10a). The regioselectivity of our system can be rationalized by relative stability of the corresponding carbocation intermediates.

Scheme 10. Different selectivity of alkyne hydration between LBA and gold catalysis

We also examined the feasibility of using solid acids in our LBA or BBA strategy for alkyne hydration because heterogeneous solid acids can be easily recycled and less corrosive than acids in solution phase. We investigated common solid acids catalysts such as Zeolite (ZSM-5) and Nafion. It turns out that ZSM-5 showed relatively slow reaction on the hydration of phenylacetylene **2'-1a** (71% after 24 hours). Nafion gave much better result and it can be easily reused and did not lose its reactivity after 3 reaction cycles (Scheme 11a). We also tested other two alkyne substrates **2'-1b** and **2'-1g**, similar high efficiency as $\text{Ga}(\text{OTf})_3$ were observed as well (Scheme 11b and 11c). Nafion is a tetrafluoroethylene-based copolymer with perfluoroalkanesulfonic acid functionality; its excellent performance could be due to its higher acidity (compared to Zeolite).

The possible reaction pathway of this transformation was also investigated. Although acetic acid is a weak nucleophile compared to water, due to its high concentration (as solvent) it is possible that hydroacetoxylation reaction takes place first followed by

Scheme 11. Examples of BBA alkyne hydration using recyclable Nafion NR50

hydrolysis of the enol acetate intermediate to give ketone product **2'-2**. In this process, the acidity of either $\text{Ga}(\text{OTf})_3$ or HOAc was not strong enough to activate the triple bond of alkyne, but the combined system of them (LBA) provided much stronger acidity than when one of them was used. To capture the possible enol acetate intermediate we conducted the hydration of **2'-1a** under anhydrous condition. We found that even in the absence of water we can still obtain hydration product **2'-2a** in 92% yield along with acetic acid anhydride (Scheme 12), but no enol acetate was observed. It has been reported that acid can catalyze the acetoxylysis of enol acetate to give corresponding ketone and acid anhydride (Scheme 12).⁶² So one plausible explanation for formation of acid anhydride is that the reaction went through our proposed enol acetate intermediate **2'-4**.

Scheme 12. Hydration of phenylacetylene using anhydrous acetic acid

2.2.4 Conclusion

In summary, we have developed a highly efficient acid-assisted Brønsted acid catalysis system for alkyne hydration. This methodology worked well for various alkyne substrates using very low catalyst loading. Furthermore, solid acids like Nafion were also efficient and could be recycled easily multiple times without loss of reactivity. The work described in this chapter was published in *Chem. Commun.* **2015**, 51, 903-906.

2.2.5 Experimental

Preparation of Ga(OTf)₃ stock solution in HOAc (0.05 M)

In a glass vial with a screw cap, Ga(OTf)₃ (129.5 mg) was dissolved in HOAc (5 mL).

General procedure for hydration of alkynes **2'-1**

Method A: To a mixture of alkyne **2'-1** (1.25 mmol), H₂O (1.25 mmol, 1 equiv.) in HOAc (0.45 mL), Ga(OTf)₃ stock solution (50 µL) was added. The mixture was stirred in an oil bath at 100 °C for 1-20 h and then cooled down to room temperature.

Method B: To a mixture of alkyne **2'-1** (1.25 mmol), H₂O (1.25 mmol, 1 equiv.) in HOAc (0.25 mL), Ga(OTf)₃ stock solution (250 µL) was added. The mixture was stirred in a microwave reactor at 100 °C for 1 h and then cooled down to room temperature.

Spectroscopic data

acetophenone (**2'-2a**)

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 2.60 (s, 3H).

4-methoxyacetophenon (**2'-2b**)

^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.55 (s, 3H).

4-fluoroacetophenon (**2'-2c**)

^1H NMR (400 MHz, CDCl_3) δ 7.97 (m, 2H), 7.12 (m, 2H), 2.58 (s, 3H).

2-methylacetophenone (**2'-2d**)

^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, J = 7.7 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.26 (m, 2H), 2.58 (s, 3H), 2.53 (s, 3H).

2-octanone (**2'-2e**)

^1H NMR (400 MHz, CDCl_3) δ 2.39 (t, J = 7.5 Hz, 2H), 2.11 (s, 3H), 1.56 – 1.50 (m, 2H), 1.30 – 1.20 (m, 6H), 0.85 (t, J = 6.5 Hz, 3H).

4-octanone (**2'-2f**)

^1H NMR (400 MHz, CDCl_3) δ 2.37 (dd, J = 12.7, 7.3 Hz, 4H), 1.64 – 1.47 (m, 4H), 1.30 (dd, J = 15.0, 7.5 Hz, 2H), 0.90 (td, J = 7.3, 2.5 Hz, 6H).

1,2-diphenylethanone (**2'-2g**)

^1H NMR (400 MHz, CDCl_3) δ 8.05 – 7.97 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.36 – 7.21 (m, 5H), 4.29 (s, 2H).

propiophenone (**2'-2h**)

^1H NMR (400 MHz, CDCl_3) δ 8.02 – 7.86 (m, 2H), 7.53 (m, 1H), 7.46 – 7.41 (m, 2H), 2.99 (q, J = 7.3 Hz, 2H), 1.21 (t, J = 7.3 Hz, 3H).

1-acetylcyclohexene (**2'-2i**)

^1H NMR (400 MHz, CDCl_3) δ 6.98 – 6.82 (m, 1H), 2.26 (s, 3H), 2.25 – 2.21 (m, 2H), 2.20 – 2.17 (m, 2H), 1.68 – 1.52 (m, 4H).

4-oxopentanoic acid (**2'-2k**)

^1H NMR (400 MHz, CDCl_3) δ 2.74 (t, J = 6.4 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 2.19 (s, 3H).

cinnamaldehyde (**2'-2m**)

^1H NMR (400 MHz, CDCl_3) δ 9.68 (d, J = 7.7 Hz, 1H), 7.57-7.54 (m, 2H), 7.48 (d, J = 16.0 Hz, 1H), 7.44 – 7.39 (m, 3H), 6.73 (dd, J = 15.9, 7.7 Hz, 1H).

1,4-diacetylbenzene (**2'-2n**)

^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 4H), 2.62 (s, 6H).

3. Au/TiO₂ CATALYZED ALKYNES HYDROAMINATION AND INDOLE SYNTHESIS

3.1 Background

Nitrogen containing compounds such as amines and N-heterocycles are widely encountered in the scaffolds of various bioactive natural products, pharmaceuticals, and materials.⁶³ Therefore, many methods such as reductive amination⁶⁴ and C–N cross-coupling⁶⁵ have emerged for their construction.⁶⁶ Among these methods, hydroamination represents an atom-economical strategy because of the direct addition of amines to readily accessible alkenes, alkynes and allenes.⁶⁷ On the one hand, intermolecular hydroamination affords structurally complex amines; on the other hand, intramolecular hydroamination provides access to a wide range of N-containing cyclic compounds. Various transition metal catalysts have proven their value in the hydroamination of alkynes,⁶⁸ of which homogeneous cationic gold catalysis has attracted significant attention because of its excellent activity under mild reaction conditions.^{16, 69} However, as mentioned before, the non-recyclability of homogeneous gold catalysts and the decay of cationic gold greatly limited their application in organic synthesis.⁸ In this regard, heterogeneous gold catalysts, especially gold nanoparticles, are highly desirable in such transformation due to their stability and ease of manipulation.⁷⁰ Gold nanoparticles (Au NPs) have been successfully applied in many organic reactions such as oxidation,⁷¹ reduction,^{31-32, 72} hydrosilylation,^{29c, 73} and cross-coupling,^{30a, 74} but reports of Au NPs mediated hydroamination, through π bond activation, are scarce.^{57, 75} Herein in this chapter we studied an alkyne hydroamination catalyzed by commercially available

3.2 Screening of reaction conditions

Table 6. Screening of Au/TiO₂ catalyzed intermolecular hydroamination

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used as catalyst, no imine product was observed, underscoring the crucial role of gold nanoparticles (Table 6, entry 9 and 10).

3.3 Substrates scope and discussion

With optimized conditions in hand, the substrate scope of intermolecular hydroamination was next evaluated (Table 7). Due to the instability of the resulting imines, they were immediately reduced to amines after the reaction was completed. Both electron donating and electron withdrawing substituents on aniline were well tolerated (Table 7, **3a-3f**). Anilines with substituents on sterically hindered positions (*o*-methyl and phenyl) could also provide the desired amines in high yields, although more catalyst and longer

Table 7. Scope of Au/TiO₂ catalyzed intermolecular hydroamination of terminal alkynes^a

^a Reaction conditions: **3-1** (1 mmol), **3-2** (1.2 mmol), Au/TiO₂ (0.2 mol % Au), H₃PO₄·12WO₃ (0.1 mol %), neat at 80 °C. Isolated yields were showed in parentheses. ^b Au/TiO₂ (0.5 mol % Au), H₃PO₄·12WO₃ (0.5 mol %) were used in 24 h.

reaction time were required (Table 7, **3-(3g-3h)**). The functional groups on phenylacetylene didn't affect the efficiency of the hydroamination (Table 7, **3-(3i-3l)**). Harsher conditions were needed to achieve good yields when aliphatic alkynes were examined (Table 7, **3-(3m-3p)**). Indole rings are one of the most ubiquitous and important heterocycles in nature.⁷⁶ A plethora of methodologies exist for indole ring synthesis,⁷⁷ but among them, the cycloisomerization of 2-alkynylanilines is the most straightforward and atom-economical. However, this straightforward synthesis of indoles hasn't received much attention using recyclable heterogeneous gold catalysts. The only reported work by Helaja and coworkers used home-made gold nanoparticles, which limits its application.⁷⁸ Capitalizing on our success with intermolecular hydroamination of alkynes, we envisioned that commercially available Au/TiO₂ would enable the intramolecular version. Indeed, when microwave was applied, various 2-alkynylanilines were easily converted to the corresponding indole derivatives. As shown in Table 3, different substituted 2-alkynylanilines furnished the corresponding indole products in very good to excellent yields (Table 8, **3-(5a-5d)**). The halogens (F and Cl) and methyl group at the 4- or 5-position of aniline proved beneficial, allowing indole products to be obtained in excellent

Table 8. Au/TiO₂ catalyzed indole synthesis through intramolecular hydroamination^a

^a Reaction conditions: **3-4** (0.1 mmol), Au/TiO₂ (5 mol % Au), in toluene (1 mL) at 120 °C for 1 h; Isolated yields. ^b 140 °C. ^c H₃PO₄·12WO₃ (5 mol %) was used.

yields (Table 8, **3-(5e-5i)**). When R² was replaced by an aliphatic group, an acid promoter was required (Table 8, **3-5j**).

The hydroamination of basic amines catalyzed by cationic gold is a challenge. This is because basic amine (e.g., morpholine) has much stronger affinity towards cationic gold than towards the alkyne substrate, thus, impairing the cationic gold.⁷ This is one reason why most homogeneous gold catalysts cannot work in the strong basic environment created by basic amines.^{16a, d} We speculated that the cationic gold species present in Au/NPs might be more tolerant towards bases, and consequently, they could efficiently activate alkynes in the presence of basic amines. To examine this assumption, the hydroamination of phenylacetylene with morpholine was carried out using Au/TiO₂ as catalyst. To our delight, after reduction, the desired amine product was obtained in 76% yield. In contrast, a commonly used L-AuCl/AgOTf or an otherwise efficient imido gold pre-catalyst completely lost their activities in the presence of morpholine (Scheme 13).^{4a} However, when thiomorpholine and pyrrolidine were used as basic amine partners, the hydroamination reaction didn't occur; Piperidine gave low yield (25%) of imine product according to ¹H NMR. This result indicated that gold nanoparticles might be a better activator for triple bonds in the presence of some specific strong bases such as morpholine.

Scheme 13. Comparison of homogeneous gold and Au/TiO₂ in the hydroamination of basic amine

The scalability of the present method was also investigated through a gram-scale experiment (Scheme 14). The hydroamination proceeded smoothly, giving the corresponding imine product **3-3a'** in 89% yield.

Scheme 14. Gram-scale intermolecular hydroamination of **3-1a** and **3-2a**

A leaching experiment was also carried out (Scheme 15). The hydroamination of **3-1a** and **3-2a** provided the desired imine **3-3a'** in 43% yield after 4 hours under the optimized conditions; then a portion of the supernatant (150 μL) was transferred to another vial. Both the reaction mixture with Au/TiO₂ and the supernatant without Au/TiO₂ were allowed to react for another 2 hours. We found that the mixture containing Au/TiO₂ afforded **3-3a'** in 85% yield; In contrast, the supernatant without Au/TiO₂ didn't produce additional **3-3a'**. These results demonstrated that the hydroamination was catalyzed by gold species present in gold nanoparticles rather than species leached into solution.

Scheme 15. Leaching experiment of hydroamination with Au/TiO₂

3.4 Conclusion

In conclusion, we have developed a highly efficient hydroamination protocol using commercially available gold nanoparticles (Au/TiO₂). Compared with commonly used homogeneous gold catalyst, this heterogeneous gold catalyst is cost-effective, easy-to-

manipulate. Au/TiO₂ catalyzed intermolecular hydroamination of terminal alkynes affording amines under solvent-free condition. What's more, a series of indole derivatives were synthesized through intramolecular hydroamination under microwave. The work described in this chapter was published in *Adv. Synth. Catal.*, **2016**, 358, 3313-3318 and Highlighted in *Synfacts* **2017**, 13 (01), 0113.

3.5 Experimental

General procedure for hydroamination of terminal alkynes **3-1** and anilines **3-2**

Au/TiO₂ (39.4 mg, 0.2 mol % Au) and H₃PO₄·12WO₃ (2.88 mg, 0.1 mol %) were placed in a dry and clean vial which was then vacuumed and purged with argon three times. Then a mixture of alkyne **3-1** (1 mmol) and aniline **3-2** (1.2 mmol) was added into the vial. The reaction mixture was stirred in oil bath at 80 °C for the designated time and cooled down to room temperature. Then Au/TiO₂ was filtered, the residual was dissolved in DCM (6 mL). NaBH(OAc)₃ (424 mg, 2 equiv.) and AcOH (114 µL, 2 equiv.) were then added into the solution. The mixture was allowed to stir at room temperature for 24 h. The reaction was quenched with 1M NaOH aqueous solution, extracted with DCM (5 mL × 2), combined organic phase was dried over Na₂SO₄, and after filtration of Na₂SO₄ the filtrate was concentrated to dryness and it was subjected to flash chromatography (silica gel; EA/hexane).

General procedure for indole **3-5** synthesis through cycloisomerization of 2-alkynylanilines **3-4**

2-alkynylaniline **3-4** (0.1 mmol) was placed in a clean and dry microwave vial and dissolved in toluene (1 mL). Au/TiO₂ (98.5 mg, 5 mol % Au) was then added into the solution. The mixture reacted in microwave reactor for 1 h at 120 °C and cooled down to

room temperature. Then Au/TiO₂ was filtered, the filtrate was concentrated to dryness and subjected to flash chromatography (silica gel; EA/hexane).

Spectroscopic data

N-(1-phenylethyl)aniline (**3-3a**)

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.29 (m, 4H), 7.25 – 7.20 (m, 1H), 7.08 (t, *J* = 7.9 Hz, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 2H), 4.48 (q, *J* = 6.7 Hz, 1H), 4.01 (s, 1H), 1.51 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 147.30, 145.24, 129.11, 128.64, 126.87, 125.85, 117.23, 113.29, 53.45, 25.03.

4-methoxy-N-(1-phenylethyl)aniline (**3-3b**)

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.32 (m, 4H), 7.26 – 7.23 (m, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 8.9 Hz, 2H), 4.44 (q, *J* = 6.7 Hz, 1H), 3.71 (s, 3H), 1.52 (d, *J* = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 151.88, 145.48, 141.56, 128.61, 126.82, 125.89, 114.75, 114.55, 55.73 (d, *J* = 2.0 Hz), 54.26 (d, *J* = 2.0 Hz), 25.14.

4-fluoro-N-(1-phenylethyl)aniline (**3-3c**)

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 6.81 – 6.76 (m, 2H), 6.44 – 6.41 (m, 2H), 4.41 (q, *J* = 6.7 Hz, 1H), 3.91 (s, 1H), 1.50 (d, *J* = 6.7 Hz, 3H).

¹⁹F NMR (376 MHz, CDCl₃) δ -128.38. ¹³C NMR (100 MHz, CDCl₃) δ 155.63 (d, *J*_{C-F} =

234.0 Hz), 145.01, 143.59, 128.65, 126.93, 125.78, 115.47 (d, $J_{\text{C-F}} = 22.0$ Hz), 114.04 (d, $J_{\text{C-F}} = 8.0$ Hz), 54.05, 25.07.

4-methyl-N-(1-phenylethyl)aniline (**3-3d**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.29 (m, 4H), 7.23 – 7.20 (m, 1H), 6.90 (d, $J = 8.3$ Hz, 2H), 6.43 (d, $J = 8.4$ Hz, 2H), 4.45 (q, $J = 6.7$ Hz, 1H), 3.90 (s, 3H), 2.18 (s, 3H), 1.50 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.39, 144.99, 129.56, 128.58, 126.76, 126.33, 125.82, 113.37, 53.66, 25.05, 20.30.

4-chloro-N-(1-phenylethyl)aniline (**3-3e**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.31 (m, 4H), 7.27 – 7.24 (m, 1H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.43 (d, $J = 8.6$ Hz, 2H), 4.44 (q, $J = 6.7$ Hz, 1H), 4.04 (s, 1H), 1.52 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.73, 144.66, 128.90, 128.71, 127.02, 125.74, 121.78, 114.33, 53.57, 25.01.

3-methoxy-N-(1-phenylethyl)aniline (**3-3f**)

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.28 (m, 4H), 7.22 – 7.19 (m, 1H), 6.98 (t, $J = 8.1$ Hz, 1H), 6.20 (d, $J = 8.3$ Hz, 1H), 6.13 (d, $J = 8.1$ Hz, 1H), 6.05 (s, 1H), 4.46 (q, $J = 6.6$ Hz, 1H), 4.12 (s, 1H), 3.67 (s, 3H), 1.50 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ

160.60, 148.61, 145.10, 129.78, 128.62, 126.86, 125.78, 106.43, 102.44, 99.31, 54.93, 53.50, 24.90.

2,4,6-trimethyl-N-(1-phenylethyl)aniline (**3-3g**)

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.26 (m, 4H), 7.24 – 7.22 (m, 1H), 6.77 (s, 2H), 4.24 (q, J = 6.8 Hz, 1H), 3.08 (s, 1H), 2.21 (s, 3H), 2.13 (s, 6H), 1.49 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.38, 142.24, 130.88, 129.66, 129.40, 128.35, 126.89, 126.14, 56.97, 22.50, 20.53, 18.72.

N-(1-phenylethyl)-[1,1'-biphenyl]-2-amine (**3-3h**)

^1H NMR (400 MHz, CDCl_3) δ 7.55 – 7.49 (m, 4H), 7.43 – 7.39 (m, 1H), 7.37 – 7.32 (m, 4H), 7.27 – 7.22 (m, 1H), 7.12 – 7.07 (m, 2H), 6.74 (td, J = 7.4, 0.9 Hz, 1H), 6.48 (d, J = 8.1 Hz, 1H), 4.55–4.46 (m, 1H), 4.33 (s, 1H), 1.42 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 145.25, 144.01, 139.63, 130.13, 129.37, 128.98, 128.63, 128.53, 127.49, 127.25, 126.82, 125.74, 116.92, 111.71, 53.55, 25.10.

N-(1-(4-fluorophenyl)ethyl)aniline (**3-3i**)

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.31 (m, 2H), 7.12– 7.08 (m, 2H), 7.02– 6.98 (m, 2H), 6.66 (td, J = 7.4, 0.9 Hz, 1H), 6.49 (dd, J = 7.7, 0.9 Hz, 2H), 4.47 (q, J = 6.7 Hz, 1H), 4.00

(s, 1H), 1.50 (dd, $J = 6.7, 0.7$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -116.37. ^{13}C NMR (100 MHz, CDCl_3) δ 145.38, 142.24, 130.88, 129.66, 129.40, 128.35, 126.89, 126.14, 56.97, 22.50, 20.53, 18.72.

N-(1-(*m*-tolyl)ethyl)aniline (**3-3j**)

^1H NMR (400 MHz, CDCl_3) δ 7.24 – 7.15 (m, 3H), 7.13 – 7.08 (m, 2H), 7.05 (d, $J = 7.1$ Hz, 1H), 6.65 (t, $J = 7.3$ Hz, 1H), 6.53 (dd, $J = 8.5, 0.9$ Hz, 2H), 4.45 (q, $J = 6.7$ Hz, 1H), 4.01 (s, 1H), 2.35 (s, 3H), 1.51 (d, $J = 6.7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.37, 145.23, 138.18, 129.08, 128.50, 127.65, 126.53, 122.85, 117.14, 113.25, 53.48, 25.01, 21.52.

N-(1-(*o*-tolyl)ethyl)aniline (**3-3k**)

^1H NMR (400 MHz, CDCl_3) δ 7.45 – 7.43 (m, 1H), 7.20 – 7.15 (m, 3H), 7.13 – 7.09 (m, 2H), 6.66 (td, $J = 7.4, 0.8$ Hz, 1H), 6.47 (d, $J = 7.9$ Hz, 2H), 4.69 (q, $J = 6.6$ Hz, 1H), 4.02 (s, 1H), 2.46 (s, 3H), 1.50 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.25, 142.74, 134.57, 130.59, 129.14, 126.67, 126.58, 124.64, 117.13, 113.00, 49.78, 22.98, 18.98.

3-methoxy-N-(1-(4-methoxyphenyl)ethyl)aniline (**3-3l**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.12 (m, 2H), 7.00 (t, $J = 8.1$ Hz, 1H), 6.89 – 6.75 (m, 2H), 6.21 (dd, $J = 8.0, 2.2$ Hz, 1H), 6.15 (dd, $J = 8.0, 1.8$ Hz, 1H), 6.07 (t, $J = 2.3$ Hz, 1H), 4.43 (q, $J = 6.7$ Hz, 1H), 4.03 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 1.48 (d, $J = 6.7$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3) δ 160.64, 158.48, 148.77, 137.24, 129.80, 126.86, 114.01, 106.46, 102.31, 99.33, 55.22, 54.95, 52.85, 24.92.

N-(octan-2-yl)aniline (**3-3m**)

^1H NMR (400 MHz, CDCl_3) δ 7.17 – 7.13 (m, 2H), 6.68 – 6.56 (m, 3H), 3.47 – 3.42 (m, 2H), 1.63 – 1.50 (m, 2H), 1.49 – 1.25 (m, 8H), 1.16 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 147.69, 129.23, 116.68, 113.03, 48.44, 37.23, 31.82, 29.35, 26.11, 22.61, 20.77, 14.07.

4-fluoro-N-(octan-2-yl)aniline (**3-3n**)

^1H NMR (400 MHz, CDCl_3) δ 6.89 – 6.84 (m, 2H), 6.53 – 6.49 (m, 2H), 3.46 – 3.32 (m, 2H), 1.60 – 1.20 (m, 10H), 1.15 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -128.70. ^{13}C NMR (100 MHz, CDCl_3) δ 155.52 (d, $J_{\text{C-F}}$ = 233.0 Hz), 143.87, 115.62 (d, $J_{\text{C-F}}$ = 23.0 Hz), 114.10, 49.37, 37.09, 31.80, 29.33, 26.08, 22.59, 20.62, 14.06.

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

^1H NMR (400 MHz, CDCl_3) δ 6.75 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H), 3.36 – 3.32 (m, 1H), 2.96 (s, 1H), 1.59 – 1.18 (m, 10H), 1.13 (d, J = 6.3 Hz, 3H), 0.86 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 151.76, 141.91, 114.91, 114.66, 55.82, 55.78, 49.53, 37.23, 29.36, 26.11, 22.59, 20.77, 14.05.

N-(5-phenylpentan-2-yl)aniline (**3-3p**)

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.26 (m, 2H), 7.21 – 7.14 (m, 5H), 6.67 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 8.2 Hz, 2H), 3.53 – 3.42 (m, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.83 – 1.43 (m, 4H), 1.17 (d, J = 6.3 Hz, 3H).

4-(1-phenylethyl)morpholine (**3-3q**)

^1H NMR (400 MHz, CDCl_3) δ 7.31– 7.21 (m, 5H), 3.69 – 3.66 (m, 4H), 3.29 (q, J = 6.7 Hz, 1H), 2.49 – 2.32 (m, 4H), 1.34 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.76, 128.28, 127.63, 126.99, 67.16, 65.40, 51.26, 19.76.

2-phenyl-1H-indole (**3-5a**)

^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.67 – 7.61 (m, 3H), 7.47 – 7.36 (m, 3H), 7.31 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.82 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 137.83, 136.77, 132.35, 129.23, 128.99, 127.68, 125.12, 122.32, 120.63, 120.24, 110.83, 99.98.

2-(4-methoxyphenyl)-1H-indole (**3-5b**)

^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H), 7.60 – 7.57 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.12 (dt, J = 24.5, 7.1 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.70 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.34, 137.91, 136.61, 129.40, 126.49, 125.17, 121.88, 120.28, 120.14, 114.44, 110.67, 98.82 (d, $J_{\text{C-H}}$ = 9.0 Hz), 55.36 (d, $J_{\text{C-H}}$ = 9.0 Hz).

2-(4-fluorophenyl)-1H-indole (**3-5c**)

^1H NMR (400 MHz, CDCl_3) δ 8.26 (s, 1H), 7.64 – 7.61 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.23 – 7.09 (m, 4H), 6.76 (s, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -113.99. ^{13}C NMR (100 MHz, CDCl_3) δ 162.39 (d, $J_{\text{C-F}}$ = 246.0 Hz), 136.99, 136.80, 129.22, 128.73, 126.86 (d, $J_{\text{C-F}}$ = 7.0 Hz), 122.40, 120.62, 120.37, 116.04 (d, $J_{\text{C-F}}$ = 22.0 Hz), 110.85, 99.94 (d, $J_{\text{C-F}}$ = 5.0 Hz).

2-(o-tolyl)-1H-indole (**3-5d**)

^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.17 (dt, J = 27.5, 7.1 Hz, 2H), 6.61 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 137.38, 136.11, 136.04, 132.59, 131.03, 128.93, 128.81, 127.92, 126.05, 122.01, 120.49, 120.01, 110.69, 102.95 (d, $J_{\text{C-H}}$ = 7.0 Hz), 21.05.

5-fluoro-2-phenyl-1H-indole (**3-5e**)

^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.65 (d, $J = 7.8$ Hz, 2H), 7.46 (t, $J = 7.7$ Hz, 2H), 7.37 – 7.26 (m, 3H), 6.94 (td, $J = 9.1, 2.4$ Hz, 1H), 6.79 (d, $J = 1.3$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -124.0. ^{13}C NMR (100 MHz, CDCl_3) δ 158.18 (d, $J_{\text{C-F}} = 233.0$ Hz), 139.64, 133.29, 132.02, 129.60 (d, $J_{\text{C-F}} = 10.0$ Hz), 129.07, 128.01, 125.18, 111.44, (d, $J_{\text{C-F}} = 9.0$ Hz), 110.62 (d, $J_{\text{C-F}} = 26.0$ Hz), 105.38, (d, $J_{\text{C-F}} = 23.0$ Hz), 100.06.

6-fluoro-2-phenyl-1H-indole (**3-5f**)

^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.64 (d, $J = 7.4$ Hz, 2H), 7.53 (dd, $J = 8.6, 5.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.33 (t, $J = 7.4$ Hz, 1H), 7.09 (dd, $J = 9.5, 1.6$ Hz, 1H), 6.90 (td, $J = 9.7, 2.3$ Hz, 1H), 6.80 (d, $J = 1.3$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -120.32. ^{13}C NMR (100 MHz, CDCl_3) δ 160.02 (d, $J_{\text{C-F}} = 237.0$ Hz), 138.36, 136.71 (d, $J_{\text{C-F}} = 12.0$ Hz), 132.10, 129.05, 127.75, 125.76, 124.95, 121.34 (d, $J_{\text{C-F}} = 10.0$ Hz), 109.00 (d, $J_{\text{C-F}} = 25.0$ Hz), 99.82, 97.28 (d, $J_{\text{C-F}} = 26.0$ Hz).

5-chloro-2-phenyl-1H-indole (**3-5g**)

^1H NMR (400 MHz, CDCl_3) δ 8.34 (s, 1H), 7.65 (d, $J = 7.4$ Hz, 2H), 7.59 (s, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.40 – 7.27 (m, 2H), 7.14 (dd, $J = 8.6, 1.8$ Hz, 1H), 6.76 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 139.27, 135.09, 131.84, 130.31, 129.09, 128.11, 125.84, 125.21, 122.56, 119.96, 111.82, 99.55 (d, $J_{\text{C-H}} = 4.0$ Hz).

6-chloro-2-phenyl-1H-indole (**3-5h**)

^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 7.70 – 7.61 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 9.9 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 6.80 (d, J = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 138.61, 137.09, 131.89, 129.08, 127.99, 127.81, 127.67, 125.12, 121.43, 121.02, 110.80, 99.91.

5-methyl-2-phenyl-1H-indole (**3-5i**)

^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.54 – 7.36 (m, 3H), 7.36 – 7.24 (m, 2H), 7.03 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 1.3 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 137.92, 135.14, 132.50, 129.53, 129.46, 128.97, 127.55, 125.04, 123.96, 120.28, 110.51, 99.55 (d, $J_{\text{C-H}}$ = 4.0 Hz), 21.44.

2-butyl-1H-indole (**3-5j**)

^1H NMR (400 MHz, CDCl_3) δ 7.84 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.07 (dt, J = 14.6, 7.0 Hz, 2H), 6.22 (s, 1H), 2.75 (t, J = 7.6 Hz, 2H), 1.73 – 1.66 (m, 2H), 1.46 – 1.36 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 139.90, 135.76, 128.82, 120.86, 119.68, 119.52, 110.18, 99.46, 31.27, 27.94, 22.36, 13.83.

4. Au/TiO₂ CATALYZED REGIOSELECTIVE HYDROCHLORINATION OF ALKYNES WITH HCl/DMPU

4.1 Background

Chlorination is one of the fundamental and important transformation in organic synthesis due to the biological activities and synthetic value of the chlorinated products.⁷⁹ On the one hand, the chlorine containing compounds are widely found in natural products, pharmaceuticals and agrochemicals.⁸⁰ On the other hand, the development of coupling reaction such as Buchwald-Hartwig amination^{65a, 81} and Suzuki-Miyaura coupling⁸² made the chlorinated building blocks highly desirable. Among various chlorinated compounds, vinylchloride is one of the most important groups. Compared to the traditional way for synthesis of vinylchlorides from carbonyl compounds,⁸³ the direct hydrochlorination of alkynes from HCl was a more straightforward and higher atom-efficiency method. In the last decades, some groups have made improvement on indirect hydrochlorination strategies for preactivated alkynes,⁸⁴ in which the metal chloride such as LiCl, MgCl₂, TMSCl were mostly used as chlorine sources (Scheme 16a). In addition, the transition metals catalyzed dual functionalization of alkynes to construct functionalized vinylchlorides was also developed (Scheme 16b).⁸⁵ However, the direct hydrochlorination of unactivated alkynes using HCl as chlorine source was rarely reported. Dai's group found that HCl gas could hydrochlorinate electron-rich phenylacetylenes albeit more or less hydrated products formed (Scheme 16c).⁸⁶ One remarkable hydrochlorination of alkyne was recently reported by Derien's group. They developed a highly efficient ruthenium catalyzed hydrochlorination of alkynes, both good yield and selectivity were

achieved although strict oxygen and water free operation was needed in this strategy (Scheme 16d).⁸⁷

a indirect hydrochlorination of preactivated alkynes

b dual chlorination and functionalization of alkynes

c hydrochlorination of electron-rich phenylacetylenes with HCl gas

d ruthenium catalyzed hydrochlorination of unactivated alkynes

Scheme 16. Synthetic methods for chlorination of alkynes to synthesize vinylchlorides

Searching for appropriate HCl based chlorinating reagent is crucial for such direct hydrochlorination reaction. Several aqueous or organic solutions of HCl have been commercialized (Table 9, entries 1-5), however they are not very effective chlorinating reagents due to the low activity caused by relative low concentration of HCl. Moreover, the nucleophilicity of chloride in protic medium is greatly reduced.⁸⁸ Our group has previously developed a novel nucleophilic fluoronating reagent HCl/DMPU based on the concept of hydrogen bond basicity (pK_{BHX}).^{15a, 89} Considering that DMPU is non-basic, non-nucleophilic, and strong hydrogen-bond acceptor, we assumed that it would be also an ideal chlorinating reagent carrier for organic reactions. To our delight, the synthesized HCl/DMPU presents a much higher mole ratio between HCl and DMPU than other

commercially available HCl solutions, which indicated that it might have higher activity for nucleophilic chlorination reactions. In addition, the bigger hydrogen bond basicity (pK_{BHX}) of DMPU would also increase the nucleophilicity of chloride and meanwhile form more stable complexes with HCl (Table 9, entry 6).

Table 9. Comparison of different formulation of HCl solutions

entry	formulation	mole ratio (HCl:solvent)	pK_{BHX} of stabilizer
1	HCl/water, 37% (w/w)	0.21	0.65
2	HCl/ether, 2 M	0.22	1.01
3	HCl/dioxane, 4 M	0.34	0.73
4	HCl/ <i>i</i> PrOH, 5.5 M	0.42	1.06
5	HCl/AcOH, 1 M	0.06	-
6	HCl/DMPU, 43% (w/w)	2.65	2.79

Gold catalysis is well known for its excellent ability to activate C-C unsaturated bonds, thus allowing the generation of heteroatom-carbon bond via the nucleophilic addition on alkenyl gold intermediates.^{5c, 90} The commercially available gold catalysts such as PPh_3AuCl were usually stabilized through formation of Au-Cl complexes due to relatively strong bond energy between gold and chlorine.⁹¹ Thus silver salts were usually needed to break the strong Au-Cl bond to release active cationic gold species. So from this point of view, gold catalyzed hydrochlorination reaction of alkyne to generate vinylchloride is not practical because the presence of chloride as reactant is deleterious for cationic gold catalysts. In our reserach studies, gold nanoparticles have been successfully used as catalysts for various organic transformations,^{64a, 92} especially the weaker cationic character of gold nanoparticles was able to tolerate strong basic enviroment, which led to the hydration of alkynes occur under basic condition without influence the acid-sensitive fuctionalities.^{92c} Therefore, we hypothesized that this character may also enable the gold nanoparticles compatible with chloride using newly designed HCl/DMPU reagent.

4.2 Screening of reaction conditions

To test the feasibility of our hypothesis, we chose hydrochlorination of 1-octyne as model reaction with Au/TiO₂ (2 mol %) as catalyst. Not surprisingly, three commercially available HCl solutions were not effective for this transformation because of the low concentration of HCl (Table 10, entries 1-3). However, when our designed HCl/DMPU was applied, very high yield of hydrochlorinated product (90%) was observed, and good regioselectivity was also achieved (Table 10, entry 4). To further increase the

Table 10. Screening of hydrochlorination of 1-octyne^a

entry	HCl (equiv.)	sol.	T (°C)	t (h)	4-2a/4-2a'	yield (%)
1	HCl/Et ₂ O (2)	DCE	80	5	100/0	8
2	HCl/ <i>i</i> PrOH (2)	DCE	80	5	100/0	15
3	HCl/H ₂ O (2)	DCE	80	5	100/0	4
4	HCl/DMPU (2)	DCE	80	5	90/10	90
5	HCl/DMPU (2)	tol	80	5	88/12	67
6	HCl/DMPU (2)	dioxane	80	5	87/13	93
7	HCl/DMPU (2)	MeCN	80	5	92/8	80
8	HCl/DMPU (2)	<i>t</i> -BuOH	80	5	99/1	23
9	HCl/DMPU (2)	DMF	80	5	98/2	55
10	HCl/DMPU (4)	DMF	80	14	98/2	66
11 ^b	HCl/DMPU (4)	DMF	80	14	98/2	83
12	HCl/DMPU (4)	DMF	100	14	98/2	85
13	HCl/DMPU (4)	DMA	100	14	98/2	77
14	HCl/DMPU (4)	NMP	100	14	99/1	45
15 ^c	HCl/DMPU (4)	DMF	100	14	98/2	68
16 ^d	HCl/DMPU (4)	DMF	100	14	98/2	57
17 ^e	HCl/DMPU (4)	DMF	100	7	98/2	91
18 ^f	HCl/DMPU (4)	DMF	100	14	98/2	71
19 ^g	HCl/DMPU (4)	DMF	100	14	100/0	9
20 ^h	HCl/DMPU (4)	DMF	100	14	100/0	10
21 ⁱ	HCl/DMPU (4)	DMF	100	14	99/1	46

^a Both regioselectivity and yield were determined by ¹H NMR. ^b Au/TiO₂ (4 mol %) was used. ^c [4-1a] = 0.5M. ^d [4-1a] = 0.2M. ^e [4-1a] = 2M. ^f Au/Al₂O₃ (2 mol %) was used. ^g No Au/TiO₂ was used. ^h TiO₂ (1 eq) was used. ⁱ PPh₃AuCl (2 mol %) and AgOTf (2 mol %) were used.

regioselectivity, we screened different solvents. Non-polar or less polar solvents such as toluene, dioxane and acetonitrile didn't improve the selectivity (Table 10, entries 5-7). *t*-BuOH provided the desired product with better selectivity yet much poorer yield (Table 10, entry 8). DMF was ultimately considered as the best solvent because of its moderate yield and higher regioselectivity (Table 10, entry 9). More HCl/DMPU (4 eq) could increase the yield to 66% (Table 10, entry 10). And with more Au/TiO₂ (4 mol %) the yield could be further enhanced to 83% (Table 10, entry 11). Then it was found that higher reaction temperature works equally well to obtain good yield (85 %) (Table 10, entry 12). Then we also tested other amide-type of solvent such as DMA and NMP, but they were not efficient (Table 10, entries 13 and 14). Different reaction concentrations were also screened (Table 10, entries 15-17), and higher concentration (2 M) gave a 91% yield. Au/Al₂O₃ was also used in this hydrochlorination reaction, but its efficiency was not as good as Au/TiO₂ (Table 10, entry 18). Au/TiO₂ was essential for this transformation because when no Au/TiO₂ was used or just the support TiO₂ was used, only 9% and 10% of products were observed respectively (Table 10, entries 19 and 20). Finally, it was found that homogeneous gold catalyst was much less effective than heterogeneous gold nanoparticles, which further testified our hypothesis (Table 10, entry 21).

4.3 Substrates scope and discussion

With the optimized condition in hand, we evaluated the substrate scopes. The vinylchlorides derived from aliphatic terminal alkynes were obtained in both good yields and regioselectivities (Table 11, **4-(2a-2c)**). Our hydrochlorination method also exhibited excellent functional groups tolerance. Both cyano and carboxylic acid groups could be tolerated (Table 11, **4-2d** and **4-2e**). Chloro-containing alkyne also provided corresponding Markovnikov vinylchloride product in good yield (Table 11, **4-2f**). Both benzyl ether and allyl ether substrates worked very well under standard condition (Table

11, **4-2g** and **4-2h**). Both ester and imide groups remained intact during the hydrochlorination process (Table 11, **4-2i** and **4-2j**). Sulfane and sulfone substrates also gave good yield and selectivity without influence on functional groups (Table 11, **4-2k** and **4-2l**). Aromatic terminal alkynes were also examined, however, more anti-Markovnikov products were formed (Table 11, **4-2m** and **4-2n**). To test the potential of this strategy in the late-stage hydrochlorination of complex molecules, the terminal alkynes attached to biomolecular scaffolds were then examined. A structurally complex glycoside could give corresponding vinylchloride **4-2o** without loss of the glycosyl linkage (Table 11, **4-2o**). The protected amino acids such as a phenylalanine derivative was also able to undergo

Table 11. Au/TiO₂ catalyzed hydrochlorination of alkynes with HCl/DMPU^{a,b}

hydrochlorination with moderate yield (Table 11, **4-2p**). An estrone derivative bearing alkyne moiety was also suitable substrate for such transformation (Table 11, **4-2q**). Lastly, a cholesterol ester derivative could smoothly provided desired vinylchloride **4-2r** with excellent yield and selectivity as well (Table 11, **4-2r**). In addition, we also tried 1,6-heptadiyne, which led to the formation of a divinylchloride product (Table 11, **4-2s**). Finally, internal alkynes were also examined. 4-Octyne was capable of generate vinylchloride in *trans* manner (Table 11, **4-2t**), while diphenylacetylene gave *cis*-vinylchloride with 33% yield (Table 11, **4-2u**).

To examine the synthetic value of synthesized vinylchloride, we applied 2-chloro-1-octene **4-2a** for typical cross coupling reactions. For instance, 4-methoxyaniline **4-3** could easily undergo Buchwald–Hartwig amination with **4-2a**, and after reduction 67% of desired amination product was formed (Scheme 17a). In addition, a Suzuki-Miyaura coupling was also tested between **4-2a** and 3,4-(Methylenedioxy)phenylboronic acid **4-5**, corresponding coupling product was observed in 75% yield (Scheme 17b).

Scheme 17. Synthetic utility of vinylchlorides from hydrochlorination of alkynes

Finally, to demonstrate the applicability of our strategy to gram-scale synthesis, we conducted the hydrochlorination of 10 mmol of **4-1a** under standard condition, after 7 hours same yield as reaction in small scale was observed and the regioselectivity was also not influenced (Scheme 18).

Scheme 18. Gram-scale synthesis for hydrochlorination of **4-1a** with HCl/DMPU

4.4 Conclusion

In conclusion, we have designed a highly efficient chlorinating reagent HCl/DMPU. Compared with conventional HCl sources, HCl/DMPU used a non-protic, non-basic and non-nucleophilic medium DMPU. HCl/DMPU has a higher concentration of HCl and stronger binding energy between HCl and DMPU due to the strong hydrogen bonding basicity of DMPU. These features ensured a good potential for various chlorine involved organic transformations. In addition, gold nanoparticles were creatively utilized in the hydrochlorination of alkynes for synthesis of vinylchlorides with HCl/DMPU, both good yields and regioselectivity were observed and a variety of functionalities were compatible in this hydrochlorination process. Moreover, this method was easily scaled up and no strict oxygen and water free operation was needed. The work described in this chapter was submitted to *Angew. Chem. Int. Ed.* **2017**.

4.5 Experimental

Procedure for generation of HCl/DMPU

To a 500 mL of Two-neck round-bottom flask, a pressure-equalizing dropping funnel and inlet of a drying tube packed with CaCl_2 are attached. The outlet of the drying tube is attached to one joint of 100 mL Two-neck round-bottom flask through tubing, the end of the tubing was placed a 5" pipette. The other joint of the same flask is attached to the second drying tube connected to a base bath.

After flushing the whole system by argon for 10 minutes, sodium chloride and a stirring bar are added to the 500 mL Two-neck flask, concentrated sulfuric acid is added to

dropping funnel, DMPU and a small stirring bar are added to the 100 mL receiving flask. Both two flasks are cooled in ice-water bathes.

Concentrated sulfuric acid is then gradually dropped onto sodium chloride at a rate of one drop per second, and an extremely exothermic reaction takes place. During absorption of HCl, colorless DMPU turns into a viscous yellowish liquid.

Yielded HCl/DMPU solution is 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 bench.

General procedure for Au/TiO₂ catalyzed hydrochlorination of alkynes using HCl/DMPU

Au/TiO₂ (158 mg, 2 mol %) was added to a solution of alkyne **4-1** (0.4 mmol) and DMPU/HCl (4 equiv.) in DMF (0.2 mL). The mixture was allowed to stir in an oil bath at 100 °C for designated time. After cooling down to room temperature, the reaction mixture was diluted with Et₂O (2 mL) and the solid residue was filtered off, the filtrate was washed with water and brine solution. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography on silica gel (n-hexane/ethyl acetate).

Procedure for synthesis of 4-4

4-3 (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. **4-2a** (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 $\text{NaBH}(\text{OAc})_3$ (0.4 mmol, 42.4 mg) and AcOH (0.4 mmol, 11.4 μL) were added. The reaction mixture 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 H_2O and brine, dried over Na_2SO_4 . Na_2SO_4 was then filtered off, the solvent was evaporated and the residue was purified by flash chromatography on silica gel to obtain **4-4** (EA:*n*-Hex=1:8).

Procedure for synthesis of 6

4-5 (0.3 mmol, 49.8 mg), $\text{Pd}(\text{dppf})\text{Cl}_2$ (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. **4-2a** (0.2 mmol, 29.3 mg), EtOH (0.3 mL), toluene (0.3 mL) and H_2O (0.3 mL) were injected into the vial through syringe. The vial was placed into a preheated oil bath at 100 $^\circ\text{C}$. The mixture was allowed to stir for overnight. The reaction mixture was cooled down to room temperature and dilute with EA (2 mL). Then the solution was washed with NaHCO_3 (aq.). The organic phase was dried over Na_2SO_4 . Then Na_2SO_4 was filtered off. After evaporation of solvent, the residue was purified by flash chromatography on silica gel to obtain **4-6** (EA:*n*-Hex=1:15).

Spectroscopic data

2-chlorooct-1-ene (**4-2a**)

^1H NMR (400 MHz, CDCl_3) δ = 5.12 (d, J =8.1 Hz, 2H), 2.32 (t, J =7.4 Hz, 2H), 1.57-1.52 (m, 2H), 1.28 (m, 6H), 0.91-0.87 (t, J =6.7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 143.15, 111.6 (t, J =29.0 Hz), 39.14 (t, J =18.0 Hz), 31.51, 28.20, 27.12, 22.54, 14.03 (d, J =13.0 Hz).

(4-chloropent-4-en-1-yl)benzene (**4-2b**)

^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, J = 9.6, 5.3 Hz, 2H), 7.21 (t, J = 6.6 Hz, 3H), 5.15 (d, J = 16.0 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H), 2.38 (t, J = 7.4 Hz, 2H), 1.96-1.88 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 142.59, 141.69, 128.42, 125.87, 112.27 (t, J =23.0 Hz), 38.53, 34.60, 28.76 (t, J =10.0 Hz).

(1-chlorovinyl)cyclohexane (**4-2c**)

^1H NMR (400 MHz, CDCl_3) δ 5.10 (s, 2H), 2.17 (m, 1H), 1.92 (m, 2H), 1.79 (m, 2H), 1.68 (m, 1H), 1.34-1.23 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ = 148.42, 109.58 (t, J =25.0 Hz), 46.79, 46.66, 31.39, 25.98.

5-chlorohex-5-enenitrile (**4-2d**)

^1H NMR (400 MHz, CDCl_3) δ 5.24 (s, 2H), 2.53 (t, J =8.0 Hz, 2H), 2.37 (t, J =8.0 Hz, 2H), 1.97-1.90 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 139.98, 118.98, 114.31 (t, J =21.0 Hz), 37.48 (t, J =13.0 Hz), 22.65 15.76.

5-chlorohex-5-enoic acid (**4-2e**)

^1H NMR (400 MHz, CDCl_3) δ 5.17 (d, J =16.0 Hz, 2H), 2.42-2.37 (m, 4H), 1.91 (t, J =8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 179.53, 141.48, 113.04 (t, J =10.0 Hz), 38.08, 32.43, 21.94.

2,8-dichlorooct-1-ene (**4-2f**)

^1H NMR (400 MHz, CDCl_3) δ = 5.13 (d, $J=8.0$ Hz, 2H), 3.53 (t, $J=8.0$ Hz, 2H), 2.34 (t, $J=8.0$ Hz, 2H), 1.81-1.74 (m, 2H), 1.62-1.53 (m, 2H), 1.50-1.42 (m, 2H), 1.37-1.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 142.81, 111.94 (t, $J=24.0$ Hz), 44.97, 38.95, 32.44, 27.71, 26.91, 26.52.

(((10-chloroundec-10-en-1-yl)oxy)methyl)benzene (**4-2g**)

^1H NMR (400 MHz, CDCl_3) δ = 7.35-7.26 (m, 5H), 5.13 (d, $J=12.0$ Hz, 2H), 4.51 (s, 2H), 3.47 (t, $J=8.0$ Hz, 2H), 2.33 (t, $J=8.0$ Hz, 2H), 1.64-1.55 (m, 4H), 1.36-1.27 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ = 143.14, 138.70, 128.32 (d, $J=32.0$ Hz), 127.60 (d, $J=27.0$ Hz), 127.44 (d, $J=27.0$ Hz), 111.94 (t, $J=33.0$ Hz), 72.85, 70.49 (t, $J=20.0$ Hz), 39.14, 29.76, 29.42, 29.24, 28.51, 27.15, 26.16. HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{27}\text{ClONa}^+]$ ($[\text{MNa}^+]$) 317.1648; found 317.1642.

11-(allyloxy)-2-chloroundec-1-ene (**4-2h**)

^1H NMR (400 MHz, CDCl_3) δ = 5.95-5.86 (m, 1H), 5.26 (d, $J=16.0$ Hz, 1H), 5.17-5.10 (m, 3H), 3.96 (d, $J=4.0$ Hz, 2H), 3.41 (t, $J=8.0$ Hz, 2H), 2.31 (t, $J=8.0$ Hz, 2H), 1.59-1.54 (m, 4H), 1.29 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ = 143.12, 135.09, 116.63, 111.68, 71.76, 70.46, 39.11, 29.73, 29.41, 29.21, 28.49, 27.13, 26.14.

10-chloroundec-10-en-1-yl benzoate (**4-2i**)

^1H NMR (400 MHz, CDCl_3) δ = 8.05-8.03 (m, 2H), 7.56-7.53 (m, 1H), 7.45-7.41 (m, 2H), 5.11 (d, $J=8.0$ Hz, 2H), 4.31 (t, $J=8.0$ Hz, 2H), 2.31 (t, $J=8.0$ Hz, 2H), 1.78-1.72 (m, 2H), 1.58-1.31 (m, 12H). ^{13}C NMR (100 MHz, CDCl_3) δ = 166.64, 143.09, 132.75, 130.51, 129.50, 128.28, 111.67 (d, $J=7.0$ Hz), 65.07, 39.11, 29.35, 29.19, 28.69, 28.47, 27.12, 25.99. HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{25}\text{ClOH}^+]$ ($[\text{MH}^+]$) 309.1621; found 309.1667.

2-(10-chloroundec-10-en-1-yl)isoindoline-1,3-dione (**4-2j**)

^1H NMR (400 MHz, CDCl_3) δ = 7.84-7.81 (m, 2H), 7.70-7.68 (m, 2H), 5.10 (d, $J=8.0$ Hz, 2H), 3.66 (t, $J=8.0$ Hz, 2H), 2.30 (t, $J=8.0$ Hz, 2H), 1.66 (m, 2H), 1.52 (m, 2H), 1.58-1.31 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ = 168.41, 143.09, 133.79, 132.16, 123.10, 111.69, 39.10, 38.02, 29.29, 29.16, 29.08, 28.54, 28.45, 27.10, 26.79. HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{24}\text{NClONa}^+]$ ($[\text{MNa}^+]$) 356.1393; found 356.1385.

(7-chlorooct-7-en-1-yl)(phenyl)sulfane (**4-2k**)

^1H NMR (400 MHz, CDCl_3) δ = 7.34-7.25 (m, 4H), 7.66-7.62 (m, 1H), 5.11 (d, $J=12.0$ Hz, 2H), 2.92 (t, $J=8.0$ Hz, 2H), 2.32 (t, $J=8.0$ Hz, 2H), 1.70-1.62 (m, 2H), 1.58-1.52 (m, 2H), 1.47-1.42 (m, 2H), 1.36-1.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 142.90, 136.89, 128.90, 128.82, 125.68, 111.90 (t, $J=14.0$ Hz), 39.01, 33.51, 28.98, 28.43, 28.02, 26.97.

((7-chlorooct-7-en-1-yl)sulfonyl)benzene (**4-2l**)

^1H NMR (400 MHz, CDCl_3) δ = 7.90-7.88 (m, 4H), 7.18-7.15 (m, 1H), 7.57-7.54 (m, 1H), 5.09 (d, $J=12.0$ Hz, 2H), 3.07 (t, $J=8.0$ Hz, 2H), 2.27 (t, $J=8.0$ Hz, 2H), 1.74-1.66 (m, 2H), 1.52-1.46 (m, 2H), 1.40-1.24 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ = 142.57, 139.13, 133.61, 129.25, 128.00 (d, $J=8.0$ Hz), 112.09, 56.16, 38.82, 27.92, 27.80, 26.63, 22.50. HRMS (ESI) calcd for $[\text{C}_{14}\text{H}_{19}\text{ClO}_2\text{SNa}^+]$ ($[\text{MNa}^+]$) 309.0692; found 309.0691.

(2R,3R,4S,5R)-3,4,5-tris(benzyloxy)-2-((benzyloxy)methyl)-6-((5-chlorohex-5-en-1-yl)oxy)tetrahydro-2H-pyran (**4-2o** ($\alpha + \beta$))

^1H NMR (400 MHz, CDCl_3) δ 7.34-7.25 (m, 18H), 7.16 – 7.13 (m, 2H), 5.14-4.38 (m, 19H), 2.36-2.19 (m, 2H), 1.77-1.57 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ = 142.57, 138.87, 138.60, 138.45, 138.22, 138.08, 137.92, 128.35, 127.95, 127.91, 127.74, 127.66, 127.58, 112.26, 112.15, 103.60, 97.06, 96.93, 84.70, 82.11, 80.09, 77.80, 75.67, 74.83, 73.47, 73.40, 70.21, 69.49, 68.98, 68.53, 67.78, 38.80, 29.69, 28.64, 28.25, 23.81. HRMS (ESI) calcd for $[\text{C}_{40}\text{H}_{45}\text{ClO}_6\text{Na}^+]$ ($[\text{MNa}^+]$) 679.2802; found 679.2786.

(S)-methyl 2-(5-chlorohex-5-enamido)-3-phenylpropanoate (**4-2p**)

^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (100 MHz, CDCl_3) δ = 172.08, 171.80, 141.77, 135.74, 129.17, 128.59, 127.16, 112.92, 52.89 (d,

$J=11$ Hz), 52.34 (d, $J=10$ Hz), 38.06, 37.84, 34.61, 22.68. HRMS (ESI) calcd for $[C_{16}H_{20}NCIO_3Na^+]$ ($[MNa^+]$) 332.1029; found 332.1031.

(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 (**4-2q**)

1H NMR (400 MHz, $CDCl_3$) δ = 7.18 (d, $J=8.0$ Hz, 1H), 6.71-6.69 (m, 1H), 6.64 (s, 1H), 5.12 (d, $J=8.0$ Hz, 2H), 3.92 (t, $J=8.0$ Hz, 2H), 2.89-2.87 (m, 2H), 2.53-2.46 (m, 2H), 2.40-2.32 (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). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 220.87, 157.08, 142.94, 137.66, 131.85, 126.26, 114.52 (d, $J=10$ Hz), 114.47, 112.06, 111.86, 67.72, 50.40, 47.99, 43.97, 39.04, 38.37, 25.86, 31.58, 29.64, 29.19, 28.24, 27.06, 26.56, 25.92, 25.77, 21.58, 13.84. HRMS (ESI) calcd for $[C_{26}H_{35}ClO_2Na^+]$ ($[MNa^+]$) 437.2223; found 437.2213.

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 5-chlorohex-5-enoate (**4-2r**)

1H NMR (400 MHz, $CDCl_3$) δ 5.37-5.36 (m, 1H), 5.14 (d, $J=12$ Hz, 2H), 4.62-4.57 (m, 1H), 2.41-2.25 (m, 6H), 1.98-1.80 (m, 8H), 1.56-0.84 (m, 32H), 0.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.45, 141.79, 139.57, 122.65, 112.79, 73.98, 73.89, 56.66, 56.11, 50.00, 42.28, 39.70, 39.49, 38.25, 38.12, 36.96, 36.57, 36.16, 35.77, 33.09, 31.83, 28.21,

27.99, 27.79, 24.26, 23.81, 22.80, 22.54, 22.39, 21.01, 19.31, 18.70, 11.85. HRMS (ESI) calcd for $[C_{33}H_{53}ClO_2Na^+]$ ($[MNa^+]$) 539.3632; found 539.3622.

2,6-dichlorohepta-1,6-diene (**4-2s**)

1H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, J = 16.0 Hz, 4H), 2.36 (t, J = 8.0 Hz, 4H), 1.88-1.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.99, 112.65 (t, J = 10 Hz), 37.69, 24.43.

(Z)-4-chlorooct-4-ene (**4-2q**)

1H NMR (400 MHz, $CDCl_3$) δ 5.43 (t, J = 8.0 Hz, 1H), 2.27 (t, J = 8.0 Hz, 2H), 2.16-2.11 (m, 2H), 1.61-1.53 (m, 2H), 1.45-1.37 (m, 2H), 0.93-0.82 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.50, 125.38 (d, J = 6 Hz), 41.39, 39.68, 21.94, 20.55, 13.69, 12.95.

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

1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.78, 141.91, 114.89, 114.60, 55.89, 49.60, 37.24, 31.82, 29.36, 26.12, 22.60, 20.81, 14.02.

5-(oct-1-en-2-yl)benzo[d][1,3]dioxole (**4-6**)

^1H NMR (400 MHz, CDCl_3) 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).
 ^{13}C NMR (100 MHz, CDCl_3) δ = 148.21, 147.56, 146.76, 135.75, 119.48, 111.07, 107.89, 106.68, 100.92, 35.58, 31.65, 28.98, 28.25, 22.60, 14.05.

5. Au/TiO₂ CATALYZED STEREOSELECTIVE SEMIHYDROGENATION OF ALKYNES USING AMMONIUM FORMATE AS REDUCTANT

5.1 Background

Numerous natural products, pharmaceuticals, dyes, agrochemicals contain C=C double bonds with well-defined *Z* or *E* configuration, so their efficient and selective synthesis is highly desirable.⁹³ Among various synthesis of alkenes, the semihydrogenation of internal alkynes is one of the most straightforward methods. Lindlar's catalyst is commonly used for *cis*-alkene construction. However, it usually suffers from *E/Z* isomerization and over-hydrogenation;⁹⁴ in addition, the use of toxic lead and flammable H₂ gas as reductant would cause environmental and safety issue. To overcome these drawbacks, many attempts to conduct *Z*-selective semireduction of alkynes, mediated by homogeneous transition metal catalysts, have been reported,⁹⁵ and many transfer hydrogenation reagents have replaced H₂.⁹⁶ These strategies rely on costly and specially designed metal catalysts,⁹⁷ or toxic and inconvenient transfer hydrogen reagents such as organosilanes and Zn.⁹⁸ More often than not, these expensive metal catalysts can't be reused. Indeed, none of the aforementioned homogeneous catalysts provide a more practical alternative to the traditional Lindlar's catalyst.

In the pursuit of sustainable and environmentally friendly catalysis, highly selective and easily recyclable heterogeneous catalysts, especially metal nanoparticles, have attracted increased attention.^{70a, c, d, 92c, 99} Pd nanoparticles (Pd NPs) are very efficient

heterogeneous catalysts for the *cis*-selective semihydrogenation of alkynes, but over-reduction has hindered its wider use. Furthermore, H₂ gas was always used as the hydrogen source.¹⁰⁰ Compared with Pd, which does not differentially adsorb C=C and C≡C bonds, gold nanoparticles (Au NPs) are well known alkynophiles,^{90a, 101} and also possess better selectivity.¹⁰² From this perspective, Au NPs would be the perfect catalyst for alkyne semireduction. However, this application is still underdeveloped and challenging.¹⁰³ Costly and unsafe hydrogen sources such as silane, CO, and amine borane are usually used.^{72a, c, 104} For example, very recently, Kaneda and coworkers reported a core-gold/shell-ceria nanomaterial catalyzed semihydrogenation of alkynes using hydrogen gas as reductant.¹⁰⁵ Although both, good yields and *cis*-selectivity, were obtained, the inconvenience of preparing specialized nanomaterials and carrying these reactions under H₂ atmosphere will limit their wider application in organic synthetic laboratories. Herein, we are pleased to find a highly *cis*-selective alkyne semihydrogenation protocol using commercially available and recyclable Au/TiO₂, and easily handled and inexpensive ammonium formate as reductant. This reaction is eco-friendly because of the formation of easily reused gaseous byproducts, CO₂ and NH₃.¹⁰⁶

5.2 Screening of reaction conditions

We chose the semihydrogenation of diphenylacetylene as our model reaction (Table 12). After testing different hydrogen sources, we found that the combination of Au/TiO₂ (1 mol %) and HCOONH₄ (1.5 equiv.) gave *cis*-diphenylethene **5-2a** (70%) exclusively (no *trans*-isomer or over-reduction product) (Table 12, entries 1-5). Enhancing the reductant loading to 2.5 equiv. led to a dramatic increment on the yield (Table 12, entry 6). The catalyst loading of Au/TiO₂ could be reduced to 0.5 mol % by further increasing the use of HCOONH₄ (4 equiv.) without reduction of yield and *cis*-selectivity (Table 12, entry 7). In addition, water was well tolerated (Table 12, entry 8). The commonly used HCOOH and

Et₃N system, as hydrogen donor, was also tested, but only 46% of product was obtained (Table 12, entry 9). Other solvents such as dioxane, MeCN and *n*-BuOH were also screened in order to further reduce the use of catalyst. No reaction was observed with dioxane (Table 12, entry 10) and poor stereoselectivity was observed with MeCN and *n*-BuOH, (Table 12, entries 11-13). In addition, a different support (Au/Al₂O₃) also afforded the desired *cis*-diphenylethylene **5-2a** in both, good yield and selectivity, indicating that the support played a less important role in this semihydrogenation process (Table 12, entry 14).

Table 12. Semihydrogenation of diphenylacetylene with Au/TiO₂

entry	Au/TiO ₂ (mol %)	[H] (equiv.)	solvent	yield ^a (%)	Z/E
1	1	H ₂	DMF	12	100:0
2	1	Et ₃ SiH & H ₂ O (1.5)	DMF	35	100:0
3	1	Et ₃ SiH & iPrOH (1.5)	DMF	17	100:0
4	1	N ₂ H ₄ ·H ₂ O (1.5)	DMF	7	100:0
5	1	HCOONH ₄ (1.5)	DMF	70	100:0
6	1	HCOONH ₄ (2.5)	DMF	93	100:0
7	0.5	HCOONH ₄ (4)	DMF	94	100:0
8 ^b	0.5	HCOONH ₄ (4)	DMF	93	100:0
9	0.5	HCOOH & Et ₃ N (4)	DMF	46	100:0
10	0.2	HCOONH ₄ (4)	dioxane	0	-
11	0.2	HCOONH ₄ (4)	MeCN	62	85:15
12	0.2	HCOONH ₄ (4)	DMF	54	100:0
13	0.2	HCOONH ₄ (4)	<i>n</i> -BuOH	46	87:13
14 ^c	0.5	HCOONH ₄ (4)	DMF	91	100:0

^a Yields were determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. ^b V_{DMF}/V_{H₂O}=9:1. ^c Au/Al₂O₃ was used as catalyst.

5.3 Substrates scope and discussion

To demonstrate the general scope of our alkyne semireduction methodology, we examined various terminal and internal alkynes using our optimized conditions: Au/TiO₂

(0.5 mol %), HCOONH₄ (4 equiv) in DMF at 80 °C. Substituted diphenylacetylenes bearing either electron-withdrawing or electron-donating groups furnished *cis*-alkenes in excellent yield and selectivity (Table 13, **5-(2a-2d)**). Ester groups were well tolerated in this semireduction (Table 13, **5-(2e-2f)**). Phenylpropyne also worked well albeit the minor *E*-isomer was observed (Table 13, **5-2g**). The hydroxyl group in the propargylic position of phenylpropyne helped to increase both, the yield and *cis*-selectivity (Table 13, **5-2h**). This catalyst system was also very efficient with aliphatic internal alkynes, which are usually difficult substrates for semireductions, although longer reaction time (20 h) and more catalyst loading (2 mol %) were needed (Table 13, **5-2i**). Various terminal alkynes were also examined. Substituted phenyl acetylenes with either electron-withdrawing or

Table 13. Au/TiO₂ catalyzed semihydrogenation of alkynes with HCOONH₄^a

$$\begin{array}{ccc}
 \text{R}^1\text{---}\text{C}\equiv\text{C}\text{---}\text{R}^2 & \xrightarrow[\text{DMF, 80 }^\circ\text{C}]{\text{Au/TiO}_2 \text{ (0.5 mol \%)} \\ \text{HCOONH}_4 \text{ (4 equiv.)}} & \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{R}^2 \\
 \mathbf{5-1} & & \mathbf{5-2}
 \end{array}$$

<p>5-2a, 92%, (Z/E:100/0)</p>	<p>5-2b, 87%, (Z/E:100/0)</p>	<p>5-2c, 92%, (Z/E:100/0)</p>	<p>5-2d, 91%, (Z/E:98/2)</p>
<p>5-2e^d, 94%, (Z/E:94/6)</p>	<p>5-2f^d, 96%, (Z/E:99/1)</p>	<p>5-2g^d, 88%, (Z/E:94/6)</p>	<p>5-2h, 93%, (Z/E:99/1)</p>
<p>5-2i^e, 90%, (Z/E:100/0)</p>	<p>5-2j^f, 90%</p>	<p>5-2k^f, 91%</p>	<p>5-2l^f, 95%</p>
	<p>5-2m^f, 94%</p>
<p>5-2n^f, 91%</p>	<p>5-2o^f, 76%</p>	<p>5-2p^f, 93%</p>	<p>5-2q^g, 85%</p>

^a Reaction condition: **5-1** (0.25 mmol), Au/TiO₂ (0.5 mol %), HCOONH₄ (1 mmol) in DMF (0.25 mL) at 80 °C. ^b Isolated yields. ^c Z/E ratio was determined by GCMS and ¹H NMR. ^d Au/TiO₂ (1 mol %) was used. ^e Au/TiO₂ (2 mol %) was used, H₂O (0.025 mL) was added. ^f DMF (1 mL) was used. ^g H₂O (0.025 mL) and DMF (1 mL) was used.

The basic 2-ethynylpyridine was also compatible with our nanogold catalyst (Table 13, **5-2o**). Lastly, two aliphatic terminal alkynes were also tested, and good yields 93% and 85% were obtained with them (Table 13, **5-(2p-2q)**).

It is well known that the introduction of fluorine in molecules bring about important changes in physicochemical and physiological properties.¹⁰⁷ Among these fluorinated molecules, *gem*-difluoromethylene containing compounds have attracted growing interest due to their potential biological activities, such as anticancer agents,¹⁰⁸ HIV-1 protease inhibitors,¹⁰⁹ phosphotyrosine (pTyr) mimetics,¹¹⁰ and fluorinated sugars.¹¹¹ Compared with monofluoro and trifluoromethyl compounds, the introduction of difluoro groups can be defiant. In years past, our group reported the synthesis of *gem*-difluoromethylene containing building blocks.¹¹² We found that *gem*-difluorohomopropargyl alcohols could also be efficiently reduced to alkenes with high *cis*-selectivity using Au-nanoparticles (Table 14). Furthermore, the resulting difluorinated alkenes could serve as building blocks to provide an easy way for accesing difluoro-substituted dihydropyrans and α,β -unsaturated δ -lactones, which are important pharmacophores in bioactive molecules.¹¹³ Various difluorinated terminal alkynes bearing either electron-withdrawing or electron-donating groups on the phenyl ring were examined, and all of them furnished the corresponding homoallylic alcohol products in excellent yields (Table 14, **5-(4a-4h)**). Furthermore, both, excellent stereoselectivities and yields were obtained using internal difluorohomopropargyl alcohols (Table 14, **5-(4i-4l)**).

The success gotten with the semireduction of *gem*-difluorohomopropargyl alcohols strengthened the outreach of our protocol. The *gem*-difluorohomoallylic alcohols obtained in Table 14 are useful difluoro-building blocks. For example, **5-4e** was easily converted into the difluoro-substituted dihydropyran **5-6**, an important precursor of fluorinated sugar mimetics.¹¹⁴ Using the same metathesis strategy, *gem*-difluorinated unsaturated lactone

Table 14. Semihydrogenation of *gem*-difluorohomopropargyl alcohols with HCOONH₄^a

^a Isolated yields; Reaction condition: **4-3** (0.25 mmol), Au/TiO₂ (0.5 mol %), HCOONH₄ (1 mmol) in DMF (1 mL) at 80 °C. ^b Au/TiO₂ (2 mol %), DMF (0.25 mL) and H₂O (0.025 mL) were used and 7 h was needed.

5-8 was easily obtained. The introduction of two electronegative fluorine atoms would produce a more active Michael acceptor towards nucleophilic amino acid residues in certain target proteins, while at the same time increasing its lipophilicity (Scheme 19).¹¹⁵

Scheme 19. Preparation of fluorinated dihydropyran and α,β -unsaturated δ -lactone from

5-4e. i: allyl bromide, NaH, THF/DMF; ii: Grubbs' 2nd Cat., DCM; iii: *i*Pr₂EtN, DMAP, acryloyl chloride, DCM; iv: Ti(O*i*Pr)₄, Grubbs' 2nd Cat., Tol.

In addition, a leaching experiment was conducted to determine whether gold species leached into the reaction mixture (Scheme 20). The semihydrogenation of diphenylacetylene **5-1a** was selected as a test reaction. After 3 h *cis*-diphenylethylene **5-**

2a (66%) was formed; then, an aliquot of the supernatant (125 μ L) was transferred to another vial containing additional 2 equiv. of HCOONH_4 . Both, the reaction residue with Au/TiO_2 and the supernatant without Au/TiO_2 were allowed to react for another 2 hours. We found that the residual containing Au/TiO_2 afforded **5-2a** in 85% yield; in contrast, the supernatant without Au/TiO_2 didn't produce any further **5-2a**. Based on these results, we concluded that the semireduction of alkynes was not catalyzed by leaching gold species.

Scheme 20. Leaching experiment of semireduction of diphenylacetylene with Au/TiO_2

5.4 Conclusion

In conclusion, we have developed a highly efficient *cis*-selective alkyne semihydrogenation protocol that is a good alternative to the conventional Lindlar's catalyst. Au/TiO_2 enabled the semihydrogenation using environmentally friendly conditions. Cost-effective and easy-to-handle ammonium formate was used as reductant, and only two gaseous by-products (NH_3 and CO_2) were formed. In addition, no over-reduced alkane by-products were formed. A diverse set of *gem*-difluorohomoallylic alcohol building blocks was synthesized using this strategy, which led to the construction of potentially bioactive difluorinated molecules. The work described in this chapter was published in *Chem. Commun.* **2016**, 52, 6013-6016 and highlighted in *Synfacts* **2016**, 12(07), 0763.

5.5 Experimental

General procedure for Au/TiO₂ semihydrogenation of alkynes using HCOONH₄ as reductant

Au/TiO₂ (24.6 mg, 0.5 mol %) and HCOONH₄ (1 mmol) were added to a solution of alkyne (0.25 mmol) in DMF (0.25 mL). The mixture was allowed to stir in an oil bath at 80 °C for designated time. After cooling down to room temperature, the solid Au/TiO₂ was filtered off, the filtrate was diluted with DCM and washed with water and brine solution. The organic layer was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by flash chromatography on silica gel (n-hexane/ethyl acetate).

Procedure for synthesis of 5-6

5-4e (0.2 mmol, 40.4 mg) was dissolved in dry THF/DMF (1.4 mL / 0.4 mL), then NaH (0.6 mmol, 24 mg) was added into the solution at 0 °C. The mixture was allowed to stir for 15 minutes at room temperature. Then allyl bromide (0.6 mmol, 72.5 mg) was added. The resulting mixture was stirred at room temperature for overnight. Then the reaction mixture was quenched by 2 mL NH₄Cl (aq.), extracted with Et₂O (2 × 2 mL). The combined organic layer was washed with brine and dried over Na₂SO₄. After concentration the residue was purified by flash chromatography on silica gel to obtain **5-5** as colorless oil.

The solution of purified **5-5** (0.14 mmol, 34.4 mg) and Grubbs' catalyst (5 mol %) in DCM were stirred for 24 hours at room temperature. Then after concentration the residue was purified by flash chromatography on silica gel to afford **5-6** as colorless oil.

Procedure for synthesis of 5-8

Acryloyl chloride (0.4 mmol, 28 µL) was added dropwise to the solution of **5-4e** (0.2 mmol, 40.4 mg), DMAP (5 mol %) and N,N-diisopropylethylamine (0.5 mmol, 86.9 µL) in DCM (0.5 mL) at 0 °C. The mixture was stirred at room temperature for overnight. The reaction mixture was quenched with water (1 mL) and extracted with DCM (2 × 1 mL). The

combined organic layer was dried over Na_2SO_4 . After concentration the residue was purified by flash chromatography on silica gel to obtain **5-7** as colorless oil.

The solution of purified **5-7** (0.17 mmol, 44 mg) and $\text{Ti}(\text{O}i\text{Pr})_4$ (0.05 mmol, 15 μL) in toluene (6 mL) were stirred under reflux for 3 h. Then solution of Grubbs' catalyst (7 mol %, 10.1 mg) in toluene (1.5 mL) was added dropwise into the reaction mixture over 30 min. The resulting mixture was stirred for additional 1 h under reflux and then cooled down to room temperature. After concentration the residue was purified by flash chromatography on silica gel to obtain **5-8** as colorless oil.

Spectroscopic data

(*Z*)-1,2-diphenylethene (**5-2a**)

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.12 (m, 10H), 6.61 (s, 2H).

(*Z*)-1-methyl-4-styrylbenzene (**5-2b**)

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.16 (m, 7H), 7.14 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 7.9 Hz, 2H), 6.55 (s, 2H), 2.31 (s, 2H).

(*Z*)-1-fluoro-4-styrylbenzene (**5-2c**)

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.11 (m, 7H), 6.91 (t, J = 8.7 Hz, 2H), 6.57 (q, J = 12.2 Hz, 2H).

(Z)-1-methoxy-4-styrylbenzene (5-2d)

^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.16 (m, 7H), 6.76 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 1.7 Hz, 2H), 3.78 (s, 3H).

(Z)-ethyl 3-phenylacrylate (5-2e)

^1H NMR (400 MHz, CDCl_3) δ 7.57 (dd, J = 7.4, 1.7 Hz, 2H), 7.43 – 7.28 (m, 3H), 6.94 (d, J = 12.6 Hz, 1H), 5.94 (d, J = 12.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H).

(Z)-methyl oct-2-enoate (5-2f)

^1H NMR (400 MHz, CDCl_3) δ 6.22 (dt, J = 11.5, 7.5 Hz, 1H), 5.75 (dt, J = 12, 1.6 Hz, 1H), 3.70 (s, 3H), 2.64 (qd, J = 7.6, 1.6 Hz, 2H), 1.47 – 1.40 (m, 2H), 1.34 – 1.29 (m, 4H), 0.88 (t, J = 8, 3H).

(Z)-prop-1-en-1-ylbenzene (5-2g)

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.20 (m, 5H), 6.48 – 6.40 (dd, J = 12, 1.6 Hz, 1H), 5.86 – 5.72 (dq, J = 11.6, 7.2 Hz, 1H), 1.90 (dd, J = 7.2, 2 Hz, 3H).

(Z)-3-phenylprop-2-en-1-ol (5-2h)

^1H NMR (400 MHz, CDCl_3) δ 7.35 (m, 2H), 7.30 – 7.11 (m, 3H), 6.57 (d, J = 11.7 Hz, 1H), 5.87 (dt, J = 12, 6.4 Hz, 1H), 4.44 (d, J = 6.4 Hz, 2H), 1.66 (s, 1H).

(Z)-[(hex-2-en-1-yloxy)methyl]benzene (**5-2i**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.26 (m, 5H), 5.60 (m, 2H), 4.51 (s, 2H), 4.08 (d, J = 4.6 Hz, 2H), 2.02 (m, 2H), 1.38 (sext, J = 8 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H).

styrene (**5-2j**)

^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.17 (m, 5H), 6.65 (dd, J = 17.6, 10.9 Hz, 1H), 5.69 (d, J = 17.6 Hz, 1H), 5.18 (d, J = 10.9 Hz, 1H).

1-fluoro-4-vinylbenzene (**5-2k**)

^1H NMR (400 MHz, CDCl_3) δ 7.28 – 7.24 (m, 2H), 6.92 – 6.87 (m, 2H), 6.55 (dd, J = 17.6, 10.8 Hz, 1H), 5.53 (d, J = 17.6 Hz, 1H), 5.11 (d, J = 10.8 Hz, 1H).

1-methoxy-4-vinylbenzene (**5-2l**)

^1H NMR (400 MHz, cdcl_3) δ 7.35 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.66 (dd, J = 17.6, 10.9 Hz, 1H), 5.61 (d, J = 17.6 Hz, 1H), 5.12 (d, J = 10.9 Hz, 1H), 3.81 (s, 3H).

1-methyl-2-vinylbenzene (**5-2m**)

^1H NMR (400 MHz, CDCl_3) δ 7.47 – 7.49 (m, 1H), 7.17 (m, 3H), 6.95 (dd, J = 17.4, 11.0 Hz, 1H), 5.64 (d, J = 17.4 Hz, 1H), 5.29 (d, J = 11.0 Hz, 1H), 2.35 (s, 3H).

1-(trifluoromethyl)-4-vinylbenzene (**5-2n**)

^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 6.75 (dd, J = 17.6, 10.9 Hz, 1H), 5.84 (d, J = 17.6 Hz, 1H), 5.38 (d, J = 10.9 Hz, 1H).

2-vinylpyridine (**5-2o**)

^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, J = 4.3 Hz, 1H), 7.64 (td, J = 7.7, 1.6 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.17 – 7.14 (m, 1H), 6.82 (dd, J = 17.5, 10.8 Hz, 1H), 6.20 (d, J = 17.5 Hz, 1H), 5.48 (d, J = 10.8 Hz, 1H).

undec-10-en-1-yl benzoate (**5-2p**)

^1H NMR (400 MHz, CDCl_3) δ 8.05 – 8.03 (m, 2H), 7.56 – 7.52 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 5.86-5.75 (m, 1H), 5.01 – 4.92 (m, 2H), 4.31 (t, J = 6.7 Hz, 2H), 2.03 (q, J = 8 Hz, 2H), 1.79 – 1.72 (m, 2H), 1.47 – 1.29 (m, 12H).

pent-4-en-1-ylbenzene (**5-2q**)

^1H NMR (400 MHz, CDCl_3) δ 7.28 (m, 2H), 7.18 (m, 3H), 5.83 (td, $J = 16.9, 6.7$ Hz, 1H), 5.00 (dd, $J = 20.0, 13.7$ Hz, 2H), 2.62 (t, $J = 7.7$ Hz, 2H), 2.09 (q, $J = 7.2$ Hz, 2H), 1.79 – 1.65 (m, 2H).

2,2-difluoro-1-phenylbut-3-en-1-ol (**5-4a**)

^1H NMR (400 MHz, CDCl_3) δ 7.42 – 7.35 (m, 5H), 5.92 – 5.78 (m, 1H), 5.59 (dd, $J = 17.4, 1.2$ Hz, 1H), 5.46 (d, $J = 11.0$ Hz, 1H), 4.90 (td, $J = 9.6, 2.4$ Hz, 1H), 2.54 (d, $J = 2.5$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.95 (dt, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F), -109.45 (dt, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 135.92, 129.34 (t, $J = 25$ Hz), 128.71, 128.18, 127.59, 121.6 (t, $J = 9$ Hz), 119.57, 75.89 (t, $J = 30$ Hz).

2,2-difluoro-1-(p-tolyl)but-3-en-1-ol (**5-4b**)

^1H NMR (400 MHz, CDCl_3) δ 7.30 (d, $J = 7.8$ Hz, 2H), 7.17 (d, $J = 7.9$ Hz, 2H), 5.92 – 75.79 (d, $J = 11.3$ Hz, 1H), 5.60 (d, $J = 17.4$ Hz, 1H), 5.46 (d, $J = 11.1$ Hz, 1H), 4.86 (td, $J = 9.2, 4$ Hz, 1H), 2.46 (d, $J = 3.8$ Hz, 1H), 2.36 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -108.00 (dt, $J_{\text{F-F}} = 244.4$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F), -109.45 (dt, $J_{\text{F-F}} = 244.4$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 138.54, 133.02, 129.48 (t, $J = 26$ Hz), 128.90, 127.49, 121.47 (t, $J = 9$ Hz), 119.60, 75.78 (t, $J = 30$ Hz), 21.17.

2,2-difluoro-1-(4-methoxyphenyl)but-3-en-1-ol (**5-4c**)

^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.85 (ddd, J = 23.3, 17.4, 11.3 Hz, 1H), 5.59 (d, J = 17.4 Hz, 1H), 5.46 (d, J = 11.1 Hz, 1H), 4.84 (t, J = 9.7 Hz, 1H), 3.81 (s, 3H), 2.51 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.63 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F), -109.67 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 159.85, 129.51 (t, J = 25 Hz), 128.85, 128.12, 121.48 (t, J = 9 Hz), 119.63, 113.61, 75.53 (t, J = 32 Hz), 55.24.

2,2-difluoro-1-(3-methoxyphenyl)but-3-en-1-ol (**5-4d**)

^1H NMR (400 MHz, CDCl_3) δ 7.27 (m, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.90 – 6.87 (m, 1H), 5.85 (ddd, J = 23.4, 17.4, 11.3 Hz, 1H), 5.61 (d, J = 17.4 Hz, 1H), 5.47 (d, J = 11.1 Hz, 1H), 4.88 (t, J = 9.4 Hz, 1H), 3.81 (s, 3H), 2.51 (br, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.87 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F), -109.18 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 159.43, 137.51, 129.34 (t, J = 25 Hz), 129.20, 121.57 (t, J = 10 Hz), 119.96, 119.51, 114.25, 113.14, 75.80 (t, J = 30 Hz), 55.25.

2,2-difluoro-1-(2-fluorophenyl)but-3-en-1-ol (**5-4e**)

^1H NMR (400 MHz, CDCl_3) δ 7.54 (t, J = 7.4 Hz, 1H), 7.33 (tdd, J = 7.3, 5.3, 1.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.07 – 7.03 (m, 1H), 5.93 (dq, J = 17.4, 11.6 Hz, 1H), 5.62 (dt, J = 17.4, 2.4 Hz, 1H), 5.49 (d, J = 11.1 Hz, 1H), 5.27 (td, J = 10.1, 5.0 Hz, 1H), 2.58 (d, J = 5.0 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -110.33 (m, 2F), -117.15 (m, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 161.54, 159.08, 130.34 (d, J = 8 Hz), 129.59, 129.34, 129.08, 124.13 (d, J = 4 Hz), 121.80 (t, J = 9 Hz), 115.28 (d, J = 22 Hz), 66.34 (t, J = 30 Hz).

1-(4-chlorophenyl)-2,2-difluorobut-3-en-1-ol (**5-4f**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.27 (m, 4H), 5.83 (ddd, J = 23.6, 17.4, 11.1 Hz, 1H), 5.58 (dt, J = 17.4, 2.4 Hz, 1H), 5.47 (d, J = 11.1 Hz, 1H), 4.89 (td, J = 9.5, 3.5 Hz, 1H), 2.54 (d, J = 3.5 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.63 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F), -109.68 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 134.62, 134.36, 129.96 (t, J = 26 Hz), 128.93, 128.38, 121.98 (t, J = 9 Hz), 119.40, 75.22 (t, J = 31 Hz).

2,2-difluoro-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (**5-4g**)

^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 5.83 (ddd, J = 23.7, 17.4, 11.0 Hz, 1H), 5.63 – 5.54 (m, 1H), 5.49 (d, J = 11.1 Hz, 1H), 4.98 (td, J = 9.3, 3.3 Hz, 1H), 2.60 (d, J = 3.5 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -62.74 (s, 3F), -107.18 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F), -109.65 (dt, $J_{\text{F-F}}$ = 248.2 Hz, $J_{\text{F-H}}$ = 11.3 Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 139.71, 130.36 (d, J = 33 Hz), 128.76 (t, J = 26 Hz), 127.95, 125.07 (d, J = 4 Hz), 122.21 (t, J = 9 Hz), 119.32, 116.88, 75.27 (t, J = 31 Hz).

1-(benzyloxy)-3,3-difluoropent-4-en-2-ol (**5-4h**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.26 (m, 5H), 6.00 (m, 1H), 5.72 (d, J = 17.4 Hz, 1H), 5.52 (d, J = 11.1 Hz, 1H), 4.58 (s, 2H), 3.98 – 4.08 (m, 1H), 3.76 – 3.50 (m, 2H), 2.71 (br,

1H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.93 (dt, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F), -109.43 (dt, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 137.38, 129.94 (t, $J = 25$ Hz), 128.51, 127.96, 127.76, 126.97, 120.98 (t, $J = 10$ Hz), 73.64, 72.31 (t, $J = 30$ Hz), 68.58.

(Z)-2,2-difluoro-1-phenyldec-3-en-1-ol (**5-4i**)

^1H NMR (400 MHz, CDCl_3) δ 7.45 – 7.42 (m, 2H), 7.39 – 7.33 (m, 3H), 5.80 – 5.72 (m, 1H), 5.43 – 5.32 (m, 1H), 4.89 (td, $J = 10.0, 3.7$ Hz, 1H), 2.55 (d, $J = 3.8$ Hz, 1H), 2.11 – 1.96 (m, 2H), 1.30 – 1.21 (m, 8H), 0.87 (t, $J = 7.0$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -101.20 (ddd, $J_{\text{F-F}} = 251.9$ Hz, $J_{\text{F-H}} = 13.2$ Hz, 11.3 Hz, 1F), -101.99 (dt, $J_{\text{F-F}} = 251.9$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 140.85 (t, $J = 6$ Hz), 136.04, 128.62, 128.10, 127.72, 120.97 (t, $J = 244$ Hz), 120.40 (t, $J = 25$ Hz), 76.28 (t, $J = 30$ Hz), 31.58, 29.19, 28.84, 28.33, 22.54, 14.05.

(Z)-2,2-difluoro-1-(4-methoxyphenyl)dec-3-en-1-ol (**5-4j**)

^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 8.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.79 – 5.72 (m, 1H), 5.37 (dd, $J = 27.5, 15.2$ Hz, 1H), 4.86 – 4.81 (m, 1H), 3.80 (s, 3H), 2.52 (d, $J = 3.4$ Hz, 1H), 2.11 – 2.00 (m, 2H), 1.34 – 1.22 (m, 8H), 0.87 (t, $J = 6.9$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -101.31 (ddd, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 13.2$ Hz, 11.3 Hz, 1F), -102.30 (dt, $J_{\text{F-F}} = 248.2$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 159.82, 140.70 (t, $J = 60$ Hz), 128.94, 128.20, 121.02 (t, $J = 244$ Hz), 120.56 (t, $J = 25$ Hz), 113.53, 75.90 (t,

$J = 30$ Hz), 55.21, 31.59, 29.23, 28.87, 28.36, 22.54, 14.04. HRMS (ESI) calcd. for $[\text{C}_{17}\text{H}_{24}\text{F}_2\text{O}_2]$ ($[\text{Na}^+]$) 321.1642; found 321.2500.

(Z)-2,2-difluoro-1-(4-(trifluoromethyl)phenyl)dec-3-en-1-ol (**5-4k**)

^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 8$ Hz, 2H), 7.57 (d, $J = 8$ Hz, 2H), 5.79 (dt, $J = 12.3, 7.8$ Hz, 1H), 5.35 (dd, $J = 27.9, 15.2$ Hz, 1H), 4.99 – 4.94 (m, 1H), 2.67 (s, 1H), 2.07 – 1.96 (m, 2H), 1.29 – 1.20 (m, 8H), 0.87 (t, $J = 6.9$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -100.85 (dt, $J_{\text{F-F}} = 251.9$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F), -101.82 (ddd, $J_{\text{F-F}} = 251.9$ Hz, $J_{\text{F-H}} = 15.04, 7.52$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 141.42 (t, $J = 5$ Hz), 139.84, 130.78 (d, $J = 32$ Hz), 128.10, 124.96 (d, $J = 4$ Hz), 122.61, 120.71 (t, $J = 244$ Hz), 119.83 (t, $J = 25$ Hz), 75.69 (t, $J = 30$ Hz), 31.52, 29.15, 28.82, 28.37, 22.50, 13.99. HRMS (ESI) calcd for $[\text{C}_{17}\text{H}_{21}\text{F}_5\text{O}]$ ($[\text{Na}^+]$) 359.1410; found 359.2333.

(Z)-1-(benzyloxy)-3,3-difluoroundec-4-en-2-ol (**5-4l**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.26 (m, 5H), 5.93 – 5.75 (m, 1H), 5.55 – 5.45 (m, 1H), 4.58 (dd, $J = 16, 11.6$ Hz, 2H), 4.08 – 3.99 (m, 1H), 3.66 (ddd, $J = 17.3, 10.0, 5.3$ Hz, 2H), 2.68 (d, $J = 4.9$ Hz, 1H), 2.30 – 2.24 (m, 2H), 1.42 – 1.24 (m, 8H), 0.88 (t, $J = 6.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -101.07 (dt, $J_{\text{F-F}} = 255.68$ Hz, $J_{\text{F-H}} = 11.3$ Hz, 1F), -103.91 (dt, $J_{\text{F-F}} = 255.68$ Hz, $J_{\text{F-H}} = 11.03$ Hz, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 140.65 (t, $J = 5$ Hz), 137.45, 128.49, 127.92, 127.76, 121.04 (t, $J = 25$ Hz), 120.40 (t, $J = 242$ Hz), 73.64, 72.95 (t, $J = 29$ Hz), 68.70 (t, $J = 4$ Hz), 31.16, 29.35, 28.88, 28.58, 22.56, 14.05. HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{26}\text{F}_2\text{O}_2]$ ($[\text{Na}^+]$) 335.1799; found 335.2500.

1-(1-(allyloxy)-2,2-difluorobut-3-en-1-yl)-2-fluorobenzene (**5-5**)

^1H NMR (400 MHz, CDCl_3) δ 7.51 (t, $J = 7.2$ Hz, 1H), 7.36 – 7.30 (m, 1H), 7.17 (t, $J = 7.6$ Hz, 1H), 7.08 – 7.02 (m, 1H), 6.01 (ddd, $J = 23.3, 17.4, 11.6$ Hz, 1H), 5.86 (ddt, $J = 22.4, 11.3, 5.7$ Hz, 1H), 5.59 (dt, $J = 17.4, 2.4$ Hz, 1H), 5.47 (d, $J = 11.1$ Hz, 1H), 5.28 – 5.18 (m, 2H), 5.06 – 4.89 (t, $J = 12$ Hz, 1H), 3.98 (ddd, $J = 18.9, 12.8, 5.6$ Hz, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -108.27 (m, 2F), -117.67 (m, 1F).

3,3-difluoro-2-(2-fluorophenyl)-3,6-dihydro-2H-pyran (**5-6**)

^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.58 (m, 1H), 7.38 – 7.32 (m, 1H), 7.23 – 7.14 (td, $J = 8, 0.8$, 1H), 7.08 (ddd, $J = 9.6, 8.3, 1.0$ Hz, 1H), 6.36 – 6.31 (m, 1H), 6.10 – 6.03 (m, 1H), 5.08 (d, $J = 19.1$ Hz, 1H), 4.51 – 4.34 (m, 2H). ^{19}F NMR (376 MHz, CDCl_3) δ -105.1 (m, 2F), -117.90 (m, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 161.55, 159.08, 134.92 (t, $J = 9$ Hz), 130.28 (d, $J = 8$ Hz), 129.85 (t, $J = 3$ Hz), 123.96 (d, $J = 4$ Hz), 122.38 (dd, $J = 31, 26$ Hz), 120.97 (d, $J = 14$ Hz), 115.07 (d, $J = 22$ Hz), 113.53 (dd, $J = 243, 235$ Hz), 77.27 (m), 66.12. MS (m/z): 214.1, 164.0, 133.1, 123.0, 95.0, 90.0, 75.0.

2,2-difluoro-1-phenylbut-3-en-1-yl acrylate (**5-7**)

^1H NMR (400 MHz, CDCl_3) δ 7.48 (t, $J = 7.2$ Hz, 1H), 7.37 – 7.32 (m, 1H), 7.16 (t, $J = 7.6$ Hz, 1H), 7.07 (t, $J = 9.2$ Hz, 1H), 6.53 – 6.40 (m, 2H), 6.20 (dd, $J = 17.3, 10.4$ Hz, 1H),

5.99 – 5.86 (m, 2H), 5.66 (dt, $J = 17.3, 2.3$ Hz, 1H), 5.52 (d, $J = 11.0$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -108.97 (m, 2F), -116.08 (m, 1F).

5,5-difluoro-6-(2-fluorophenyl)-5,6-dihydro-2H-pyran-2-one (**5-8**)

^1H NMR (400 MHz, CDCl_3) δ 7.60 (t, $J = 7.4$ Hz, 1H), 7.44 (dd, $J = 14.2, 6.9$ Hz, 1H), 7.26 (t, $J = 7.6$ Hz, 1H), 7.13 (t, $J = 12$ Hz, 1H), 6.94 (t, $J = 9.1$ Hz, 1H), 6.41 (d, $J = 9.9$ Hz, 1H), 5.98 (dd, $J = 20.7, 3.6$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -105.32 (dd, $J_{\text{F-F}} = 285.8$ Hz, $J_{\text{F-H}} = 22.6$ Hz, 1F), -112.16 (dtt, $J_{\text{F-F}} = 285.8$ Hz, $J_{\text{F-H}} = 11.3, 3.76$ Hz, 1F), -117.42 (m, 1F). ^{13}C NMR (100 MHz, CDCl_3) δ 161.67, 159.18, 138.30 (dd, $J = 34, 25$ Hz), 131.68 (d, $J = 9$ Hz), 130.03 (t, $J = 3$ Hz), 136.33 (dd, $J = 10, 8$ Hz), 124.37 (d, $J = 4$ Hz), 117.49 (d, $J = 8$ Hz), 115.48 (d, $J = 9$ Hz), 111.84 (dd, $J = 247, 238$ Hz), 74.13 (m). MS (m/z): 228.1, 158.0, 123.0, 104.0, 95.0, 76.0.

$5-4i$ (13C)

5-4j (1H)

6. Au/TiO₂ CATALYZED REDUCTIVE AMINATION OF ALDEHYDES AND KETONES USING FORMIC ACID AS REDUCTANT

6.1 Background

As mentioned in chapter 3, The carbon-nitrogen bond formation is one of the most important transformations in organic chemistry because numerous biologically active compounds, dyes, agrochemicals and functionalized materials contain nitrogen.^{63b, 65a, 116} Various methodologies have been established for the construction of nitrogen-containing compounds.^{16d, 31, 56-57, 117} Among these methods, reductive amination of aldehydes and ketones is efficient and straightforward.^{64c, 118} Conventional reductive amination protocols rely for the most part on stoichiometric amounts of boron-,¹¹⁹ tin-¹²⁰ and silane-¹²¹ based reductants, but they are costly and usually give rise to over-alkylation or the formation of toxic byproducts. Some reductive amination methodologies were also reported by using gas reductant such as CO and H₂, but mostly very harsh condition (high pressure and temperature) was needed.¹²² Moreover, few reductive amination of secondary amines in purpose of tertiary amine synthesis was reported because of the steric hindrance for the both formation and reduction of iminium/enamine.¹²³ Reductive amination has also been used in chiral amine synthesis, albeit the unstable imine intermediates may need isolation.¹²⁴ Formic acid has been widely used as reductant in various transfer hydrogen strategies because it is inexpensive and easy to handle. In addition, the by-product is CO₂ gas that can be easily recycled, thus offering a more eco-friendly reaction conditions.^{106a,}

^b Therefore, formic acid is a good alternative transfer hydrogen reagent for reductive amination. However, such formic acid-based reductive amination was rarely reported.

Furthermore, in the few reported examples, the specially designed, costly, and non-recyclable homogeneous transition metal catalysts such as Ru and Ir were usually used.¹²⁵

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Although Au NPs has shown high efficiency in hydride transfer process as described in chapter 5, which allowed the success of N-alkylation of amines using alcohols through a “borrowing hydrogen strategy”,¹²⁶ the use of Au/NPs for amine synthesis through reductive amination strategy was rarely reported.¹²⁷ In addition, the N-alkylation of amines catalyzed by Au NPs through borrowing hydrogen strategy usually needed high pressure and temperature and also only primary amines could be used as substrates, so these drawbacks limited its applications in construction of tertiary amines. Herein, we developed a reductive amination of aldehydes and ketones catalyzed by commercial Au/TiO₂ via introduction of external hydrogen source - inexpensive and environmentally benign formic acid.

6.2 Screening of reaction conditions

Initially, we chose reductive amination of acetophenone **6-1a** and benzylamine **6-2a** as our model reaction (Table 15). Different solvents were first screened; the reaction in *t*-BuOH provided the best yield (68 %) when Au/TiO₂ (1 mol %), **6-2a** (2 equiv.) and HCOOH (4 equiv.) were used at 80 °C (Table 15, entries 1-6). However, it was found that the rest of benzylamine was consumed by formic acid to form N-benzylformamide as byproduct, which inhibited the reaction. And attempt to lower the temperature (60 °C) failed to increase the yield (Table 15, entry 7), but when more benzylamine was used as “sacrifice” (4 equiv.) the desired N-benzyl-1-phenylethanamin was obtained with high yield (91%) (Table 15, entry 8). Increasing the reaction temperature and reducing the amount of formic acid led to reduced yields (Table 15, entries 9 and 10). Au/TiO₂ and HCOOH were indispensable for this reductive amination (Table 15, entries 11 and 12). Moreover, the nanogold

particles with other support (Al_2O_3) was also tested, and the efficiency was almost the same as when Au/TiO_2 was used, so this result proved that the support played less important role in this reductive amination process (Table 15, entry 13).

Table 15. Screening of conditions for reductive amination of **6-1a** catalyzed by Au/TiO_2

entry	solvent	6-1a:6-2a	T (°C)	t (h)	yield (%) ^a
1	dioxane	1:2	80	24	46
2	EtOH	1:2	80	24	62
3	DMF	1:2	80	24	50
4	<i>t</i> -BuOH	1:2	80	24	68
5	Tol	1:2	80	24	56
6	THF	1:2	80	24	42
7	<i>t</i> -BuOH	1:2	60	22	63
8	<i>t</i> -BuOH	1:4	60	22	91
9	<i>t</i> -BuOH	1:4	70	22	77
10 ^b	<i>t</i> -BuOH	1:4	60	22	63
11 ^c	<i>t</i> -BuOH	1:4	60	22	0
12 ^d	<i>t</i> -BuOH	1:4	60	22	0
13 ^e	<i>t</i> -BuOH	1:4	60	22	90

^a Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. ^b HCOOH (2 equiv.) is used. ^c No Au/TiO_2 was used. ^d No HCOOH was used. ^e $\text{Au/Al}_2\text{O}_3$ (1 mol %) was used.

6.3 Substrates scopes and discussion

With the optimized protocol in hand, the Au/TiO_2 catalyzed reductive amination of ketone substrates were explored (Table 16). First, the reductive amination of acetophenone **6-1a** with different primary amines was tested, and good to excellent yields were obtained for all these primary amines (Table 16, entries 1-7). Pyrrolidine also worked well to afford corresponding 1-(1-phenylethyl)pyrrolidine **6-4h** with excellent yield (95%, Table 16, entry 8). Both electron withdrawing and donating groups on acetophenone didn't affect the activity (Table 16, entries 9 and 10) and both cyclic and noncyclic aliphatic

ketones gave the corresponding amine products in high yields (Table 16, entries 11-14). Moreover, a variety of aldehyde substrates were also tested and most of them could be converted into the corresponding amine products in shorter time than ketones (Table 17). Primary amines (Table 17, entries 1-5), cyclic secondary amines (Table 17, entries 6-8) and acyclic secondary amines (Table 17, entries 9-10) worked very well when reacted with benzaldehyde **6-3a**. Less basic amines like N-methylaniline **6-2m** needed longer reaction times (Table 17, entry 10). Electron deficient aldehydes could speed up the reaction with N-methylaniline to some extent due to the enhanced electron-deficiency on the carbonyl carbon (Table 17, entries 11 and 12). Furthermore, a variety of substituted benzaldehydes (Table 17, entries 13-16), 1- naphthaldehyde (Table 17, entry 17), and

Table 16. Scope of reductive amination of ketones catalyzed by Au/TiO₂^{a,b}

^a Reaction conditions: **6-1** (0.25 mmol), **6-2** (1 mmol), Au/TiO₂ (1 mol %), HCOOH (1 mmol) in *t*-BuOH (0.25 mL) at 60 °C.

^b Isolated yields. ^c Au/TiO₂ (2 mol %) was used at 70 °C.

cyclohexanecarbaldehyde (Table 17, entries 18 and 19) were also examined and in all cases excellent reactivity was observed.

Table 17. Scope of reductive amination of aldehydes catalyzed by Au/TiO₂^{a,b}

^a Reaction conditions: **6-3** (0.25 mmol), **6-2** (1 mmol), Au/TiO₂ (1 mol %), HCOOH (1 mmol) in *t*-BuOH (0.25 mL) at 60 °C.

^b Isolated yields.

It was also found that when the amine partners were absent, the tandem reduction/formylation product **6-6** could be obtained in one pot. Because deformylation could be achieved selectively in the presence of other ester groups, this O-formylation method may prove beneficial on those reactions that need to protect alcohol groups in a complex synthetic sequence. Meanwhile, the O-formylation products also testified the excellent activity for hydride transfer of Au NPs. Three substituted benzaldehydes and 1-naphthaldehyde were tested using THF as solvent, all of them provided the desired formates **6-6** in good yields (Scheme 21).

Moreover, in order to clarify whether catalytic gold species leached out from the TiO₂ support into the reaction mixture or not, a leaching experiment was also carried out. The

Scheme 21. One-pot reduction and formylation of aldehydes catalyzed by Au/TiO₂

reductive amination of acetophenone **6-1a** with benzylamine **6-2a** was conducted following the standard condition (Scheme 22). After 7 hours **6-4a** was formed in the yield of 38%, and meanwhile the reaction mixture (150 μL) was transferred to the other reaction vial. Both the residue with Au/TiO₂ and the reaction mixture without Au/TiO₂ were then heated for another 12 hours. It was found that the residual containing Au/TiO₂ catalyst further produced **6-4a** with 88% yield, in contrast, in the absence of Au/TiO₂ the reaction stopped with unchanged 38% yield of **6-4a**. These results indicated that the reductive amination was not catalyzed by leaching catalytic gold species.

Scheme 22. Leaching experiment of reductive amination with Au/TiO₂

6.4 Conclusion

In summary, we have developed an efficient reductive amination methodology, in which commercial available and easily recyclable heterogeneous Au/TiO₂ was used as catalyst, and also cost-effective and environmentally friendly formic acid was used as transfer hydrogen reagent. This combination allowed the formation of various amines from aldehydes and ketones with good reactivity. Our method has a potential of being a good complement for conventional reductive amination. The work described in this chapter was published *Org. Chem. Front.* **2016**, 3, 505-509.

6.5 Experimental

General procedure for reductive amination of ketones and aldehydes

Au/TiO₂ (49.3 mg, 1 mol %) was added to a solution of ketone **6-1** or aldehyde **6-3** (0.25 mmol), amine **6-2** (1.0 mmol, 4 equiv.) in *t*-BuOH (0.25 mL). Then HCOOH (1.0 mmol, 4 equiv.) was also added into the mixture. The reaction mixture was stirred in an oil bath at 60 °C for the designated time and cooled down to room temperature. Then the solid Au/TiO₂ was filtered, the filtrate was concentrated to dryness and it was subjected to flash chromatography.

General one-pot procedure for reduction and formylation of aldehydes

Au/TiO₂ (197 mg, 1 mol %) was added to a mixture of aldehyde **6-3** (1 mmol), and HCOOH (4 mmol, 4 equiv.) in THF (0.25 mL). The mixture was stirred in an oil bath at 80 °C for the designated time and cooled down to room temperature. Then the solid Au/TiO₂ was filtered, the filtrate was concentrated to dryness and it was subjected to flash chromatography.

Spectroscopic data

N-benzyl-1-phenylethanamine (**6-4a**)

^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.16 (m, 10H), 3.81 (d, J = 6.6 Hz, 1H), 3.63 (q, J = 13.2 Hz, 2H), 1.61 – 1.48 (s, 1H), 1.37 (d, J = 6.6 Hz, 3H).

N-(4-methoxybenzyl)-1-phenylethanamine (**6-4b**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.32 (m, 3H), 7.30 – 7.13 (m, 4H), 6.84 (d, J = 8.5 Hz, 2H), 3.80 (m, J = 6.0 Hz, 3H), 3.56 (q, J = 12.9 Hz, 2H), 1.52 (s, 1H), 1.36 (d, J = 6.6 Hz, 1H).

N-phenethyl-1-phenylethanamine (**6-4c**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.10 (m, 10H), 3.77 (q, J = 6.6 Hz, 1H), 2.87 – 2.63 (m, 4H), 1.33 (d, J = 6.6 Hz, 4H).

N-(cyclohexylmethyl)-1-phenylethanamine (**6-4d**)

^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.15 (m, 5H), 3.79 – 3.66 (m, 1H), 2.43 – 2.17 (m, 2H), 1.82 – 1.56 (m, 5H), 1.51 – 1.03 (m, 8H), 0.86 (p, J = 12.0 Hz, 2H).

N-(1-phenylethyl)heptan-1-amine (**6-4e**)

^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.15 (m, 5H), 3.75 (q, J = 6.5 Hz, 1H), 2.44 (ddd, J = 19.0, 11.2, 3.9 Hz, 2H), 1.55 – 1.14 (m, 14H), 0.86 (t, J = 6.2 Hz, 3H).

2-(cyclohex-1-en-1-yl)-N-(1-phenylethyl)ethanamine (**6-4f**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.17 (m, 5H), 5.43 (s, 1H), 3.75 (q, J = 6.5 Hz, 1H), 2.62 – 2.41 (m, 2H), 2.10 (t, J = 6.9 Hz, 2H), 1.97 (m, 2H), 1.82 (m, 2H), 1.66 – 1.47 (m, 4H), 1.34 (d, J = 6.6 Hz, 4H).

2-phenoxy-N-(1-phenylethyl)ethanamine (**6-4g**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.18 (m, 7H), 6.98 – 6.84 (m, 3H), 4.03 (dd, J = 9.9, 5.3 Hz, 2H), 3.85 (q, J = 6.6 Hz, 1H), 2.86 (ddd, J = 17.4, 12.8, 6.8 Hz, 2H), 1.82 (s, 1H), 1.39 (d, J = 6.6 Hz, 3H).

1-(1-phenylethyl)pyrrolidine (**6-4h**)

^1H NMR (400 MHz, CDCl_3) δ 7.28 (m, 5H), 3.18 (q, J = 6.6 Hz, 1H), 2.55 (dd, J = 9.6, 3.7 Hz, 2H), 2.37 (dd, J = 9.6, 4.5 Hz, 2H), 1.75 (m, 5H), 1.40 (d, J = 6.6 Hz, 3H).

N-benzyl-1-(4-fluorophenyl)ethanamine (**6-4i**)

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.18 (m, 7H), 7.02 (m, 2H), 3.80 (q, J = 6.6 Hz, 1H), 3.60 (q, J = 13.2 Hz, 2H), 1.56 (s, 1H), 1.34 (d, J = 6.6 Hz, 3H).

N-benzyl-1-(4-methoxyphenyl)ethanamine (**6-4j**)

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.16 (m, 7H), 6.89 (d, J = 8.5 Hz, 2H), 3.88 – 3.72 (m, 4H), 3.62 (q, J = 13.2 Hz, 2H), 1.35 (d, J = 6.6 Hz, 3H).

N-benzylcyclohexanamine (**6-4k**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.16 (m, 5H), 3.81 (s, 2H), 2.54 – 2.41 (m, 1H), 1.91 (d, J = 12.3 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.61 (d, J = 11.5 Hz, 1H), 1.39 – 1.01 (m, 6H).

N-benzylcycloheptanamine (**6-4l**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.15 (m, 5H), 3.77 (s, 2H), 2.74 – 2.64 (m, 1H), 1.93 – 1.80 (m, 2H), 1.76 – 1.31 (m, 11H).

N-benzylheptan-3-amine (**6-4m**)

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.14 (m, 5H), 3.83 – 3.72 (m, 2H), 2.50 (p, J = 5.8 Hz, 1H), 1.57 – 1.19 (m, 9H), 0.97 – 0.83 (m, 6H).

N-benzylhex-5-en-2-amine (**6-4n**)

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.19 (m, 5H), 5.89 – 5.72 (m, 1H), 5.06 – 4.89 (m, 2H), 3.78 (dd, J = 36.5, 13.0 Hz, 2H), 2.71 (dd, J = 12.5, 6.3 Hz, 1H), 2.15 – 2.01 (m, 2H), 1.64 – 1.34 (m, 3H), 1.08 (dd, J = 11.2, 4.4 Hz, 3H).

dibenzylamine (**6-5a**)

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.28 (m, 8H), 7.25 (dq, J = 5.1, 2.5 Hz, 2H), 3.82 (s, 4H).

N-benzyl-1-cyclohexylmethanamine (**6-5b**)

^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.16 (m, 5H), 3.77 (s, 2H), 2.46 (d, J = 6.7 Hz, 2H), 1.71 (dd, J = 32.7, 14.7 Hz, 5H), 1.54 – 1.08 (m, 5H), 0.91 (dd, J = 22.7, 11.0 Hz, 2H).

N-benzylheptan-1-amine (**6-5c**)

^1H NMR (400 MHz, CDCl_3) δ 7.35 – 7.15 (m, 5H), 3.79 (d, J = 1.7 Hz, 2H), 2.67 – 2.52 (m, 2H), 1.56 – 1.41 (m, 2H), 1.28 (m, 9H), 0.88 (dd, J = 6.7, 5.0 Hz, 3H).

N-benzyl-2-(cyclohex-1-en-1-yl)ethanamine (**6-5d**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.19 (m, 5H), 5.46 (s, 1H), 3.79 (s, 2H), 2.69 (t, J = 6.9 Hz, 2H), 2.16 (t, J = 6.9 Hz, 2H), 1.98 (d, J = 1.7 Hz, 2H), 1.87 (d, J = 4.6 Hz, 2H), 1.64 – 1.50 (m, 4H), 1.41 (s, 1H).

N-benzyl-3-methylbutan-1-amine (**6-5e**)

^1H NMR (400 MHz, CDCl_3) δ 7.28 (dd, J = 27.7, 5.6 Hz, 5H), 3.79 (s, 2H), 2.71 – 2.57 (m, 2H), 1.68 – 1.54 (m, 1H), 1.43-1.38 (m, 3H), 0.89 (d, J = 6.6 Hz, 6H).

1-benzylpyrrolidine (**6-5f**)

^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.15 (m, 5H), 3.61 (s, 2H), 2.50 (m, 4H), 1.78 (m, 4H).

1-benzylpiperidine (**6-5g**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.17 (m, 5H), 3.47 (s, 2H), 2.38 (m, 4H), 1.64 – 1.52 (m, 4H), 1.48 – 1.36 (m, 2H).

4-benzylmorpholine (**6-5h**)

^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.14 (m, 5H), 3.79 – 3.66 (m, 4H), 3.50 (s, 2H), 2.56 – 2.38 (m, 4H).

N,N-dibenzylethanamine (**6-5i**)

^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 7.2$ Hz, 4H), 7.36 (t, $J = 7.6$ Hz, 4H), 7.27 (t, $J = 7.3$ Hz, 2H), 3.63 (s, 4H), 2.56 (q, $J = 7.1$ Hz, 2H), 1.13 (t, $J = 7.1$ Hz, 3H).

N-benzyl-N-methylaniline (**6-5j**)

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.13 (m, 7H), 6.82 – 6.66 (m, 3H), 4.54 (s, 2H), 2.99 (d, $J = 28.5$ Hz, 3H).

N-methyl-N-(pyridin-4-ylmethyl)aniline (**6-5k**)

^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 5.5$ Hz, 2H), 7.31 – 7.12 (m, 4H), 6.79 – 6.64 (m, 3H), 4.52 (s, 2H), 3.05 (s, 3H).

N-methyl-N-(4-(trifluoromethyl)benzyl)aniline (**6-5l**)

^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.25 (dd, $J = 9.9, 5.9$ Hz, 2H), 6.76 (t, $J = 8.7$ Hz, 3H), 4.59 (s, 2H), 3.05 (s, 3H).

1-(4-fluorobenzyl)piperidine (**6-5m**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 6.6 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 9.1 Hz, 1H), 3.55 (s, 2H), 2.42 (m, 4H), 1.64 – 1.50 (m, 4H), 1.44-1.41 (m, 2H)

1-(4-fluorobenzyl)piperidine (**6-5n**)

^1H NMR (400 MHz, CDCl_3) δ 7.26 – 7.17 (m, 2H), 6.84 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.41 (s, 2H), 2.35 (s, 4H), 1.61 – 1.48 (m, 4H), 1.42 (d, J = 5.1 Hz, 2H).

4-(piperidin-1-ylmethyl)benzonitrile (**6-5o**)

^1H NMR (400 MHz, CDCl_3) δ 7.59 (d, J = 7.1 Hz, 2H), 7.43 (d, J = 7.7 Hz, 2H), 3.49 (s, 2H), 2.35 (s, 4H), 1.56 (dd, J = 10.9, 5.5 Hz, 4H), 1.44 (d, J = 5.1 Hz, 2H).

1-(2-fluorobenzyl)piperidine (**6-5p**)

^1H NMR (400 MHz, CDCl_3) δ 7.38 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 6.6 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.01 (t, J = 9.1 Hz, 1H), 3.55 (s, 2H), 2.42 (s, 4H), 1.66 – 1.50 (m, 4H), 1.42 (d, J = 5.0 Hz, 2H).

1-(naphthalen-1-ylmethyl)piperidine (**6-5q**)

^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.55 – 7.37 (m, 4H), 3.88 (s, 2H), 2.48 (s, 4H), 1.65 – 1.53 (m, 4H), 1.47 (d, J = 5.0 Hz, 2H).

bis(cyclohexylmethyl)amine (**6-5r**)

^1H NMR (400 MHz, CDCl_3) δ 2.39 (d, J = 6.7 Hz, 4H), 1.69 (dd, J = 24.2, 13.2 Hz, 10H), 1.57 – 1.38 (m, 2H), 1.20 (dd, J = 24.6, 12.0 Hz, 7H), 0.89 (t, J = 11.5 Hz, 4H).

benzyl formate (**6-6a**)

^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 0.9 Hz, 1H), 7.41 – 7.30 (m, 5H), 5.21 (s, 2H).

4-methylbenzyl formate (**6-6b**)

^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.27 (t, J = 5.7 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.17 (s, 2H), 2.37 (s, 4H).

4-fluorobenzyl formate (**6-6c**)

^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.41 – 7.30 (m, 2H), 7.06 (t, J = 8.6 Hz, 2H), 5.17 (s, 2H).

naphthalen-1-ylmethyl formate (**6-6d**)

^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.89 (t, $J = 8.5$ Hz, 2H), 7.63 – 7.40 (m, 4H), 5.68 (s, 2H).

7. RECYCLABILITY STUDY OF Au/TiO₂ IN VARIOUS ORGANIC TRANSFORMATIONS AND FLOW REACTOR DESIGN

7.1 Recyclability study of Au/TiO₂

As mentioned before, one of the major purpose of this thesis research is to establish “green” gold catalysis using recyclable Au NPs (Au/TiO₂) with contrast to the conventional homogeneous gold catalysis. Therefore, we intensively studied the recyclability of Au/TiO₂ in aforementioned projects (Scheme 23).

Scheme 23. Recyclability study of Au/TiO₂ in various organic transformations

For instance, in alkyne hydration work, we carried out four straight runs of phenylacetylene hydration under the standard conditions (Scheme 23a). After each run, Au/TiO₂ was recovered by simple filtration. The yields after each run decreased only slightly from 90% to 85%. The recyclability of Au/TiO₂ was also investigated for hydroamination of alkynes through five straight runs of intramolecular indole synthesis (Scheme 23b). After each run Au/TiO₂ was filtered out and washed with fresh toluene. We found that gold nanoparticles were efficiently reused without loss of catalytic activity. In addition we also examined the recyclability of gold nanoparticles in semireduction of alkynes. Five straight runs of semihydrogenation of phenylacetylene were conducted (Scheme 23c). The heterogeneous catalyst was easily recovered through simple filtration after each run without significant loss of reactivity. Lastly, The similar excellent recyclability of Au/TiO₂ was also observed in reductive amination project (Scheme 23d).

7.2 Flow reactor design

Flow chemistry has become a popular tool in many organic transformations.¹²⁸ Compared with a conventional start-and-stop batch reaction, it has many advantages like better control of the reaction conditions, faster heat and mass transfer, a better safety profile, and an easier scale up.¹²⁹ Flow reactors are especially suitable for heterogeneous catalysis. Because our Au/TiO₂ could be recycled easily, we took alkynes hydration as example and designed a flow reactor to take full advantage of its recyclability. The components of flow reactor was shown in Figure 1.

Flow reactor setup

One set of close up and endcap was attached to one end of the column and tightened completely, then Au/TiO₂ powder (200 mg) was tightly packed into the empty HPLC column. Before placing the second set of close up and endcap onto the other end of column it is important to make sure that there is no packing material that spills over the

edge of the column because this may cause difficulty in the tightening up step and could cause leaks in the connection. Once the column was set up, all the HPLC loops were attached to both ends of the column to furnish a assembled flow reactor (Figure 2).

Figure 1. Components of flow reactor. a) HPLC LLLA adaptor (for connection between syringe and column). b) Empty HPLC column (50 mm $\times$ 2.1 mm I.D. $\times$ 1/4 in. O.D.). c) HPLC endcaps and close ups. d) HPLC loops

Figure 2. Assembled flow reactor

Experiment setup

Phenylacetylene (2.55 g, 25 mmol), morpholine (107.7 μ L, 5 mol %) and H₂O (0.9 mL, 50

mmol) were dissolved in dioxane (25 mL). The above uniformly mixed solution (10 mL) was transferred to a syringe which was then attached to a syringe pump. After the syringe was connected to the column, the whole flow reactor system was finally set up (Figure 3). The flow rate was fixed at 0.2 mL/h and the column was put into a preheated oil bath (105 °C). The reaction mixture flowed through was collected into glass vials. The glass vials were changed every three hours and conversions were determined by analyzing ^1H NMR spectra.

Figure 3. Complete flow reaction setup

Figure 4. Hydration of phenylacetylene under flow conditions

We found that, in general, our catalyst worked quite well under flow conditions although the yield of hydration product decreased slowly over time, after 4 days the yields decreased from 90% to around 40% (Figure 4), which is a common phenomenon in industrial heterogeneous catalysis because of deactivation of catalysts.

7.3 STEM and XPS study for deactivation of Au/TiO₂

Frequent reasons given for deactivation of heterogeneous metal catalysts include agglomeration of metal nanoparticles, change of oxidation state,¹³⁰ poisoning, or physical loss of metal.¹³¹ To further gain the insight for deactivation of Au/TiO₂, we studied the STEM images of fresh and spent gold catalyst. These images clearly showed that agglomeration of gold nanoparticles took place in the spent catalyst (Figure 5).

Figure 5. STEM images of fresh and spent catalyst

Figure 6. XPS spectrum of fresh and spent catalyst

Furthermore, XPS studies determined that there was no significant change in the oxidation state of Au NPs before or after the reaction (Figure 6). Therefore, we concluded that agglomeration was the major reason for the partial deactivation of Au NPs over time.

8. SUMMARY AND OUTLOOK

In summary, we have successfully demonstrated the feasibility of Au NPs as versatile heterogeneous catalysts towards various organic transformations, which firmly supported our initial hypothesis to make gold catalysis both environmental and economical friendly. To some extent, supported gold nanoparticles can be considered as counterparts of homogeneous ionic gold catalysts and even a good complement for them in certain reactions. First of all, due to the presence of cationic gold species on Au NPs, it was able to function as a soft Lewis acid in the activation of triple bonds, thus different nucleophilic additions could take place easily; on the other hand, the main component-nonionic nanosize gold species can efficiently dissociate transfer hydrogen agents due to its high surface area, the resulting gold hydride species could be utilized for reduction reactions. More importantly, Au NPs can also be easily reused and applied in flow reactor, which is a potential way to reduce the waste of precious gold and make gold chemistry much greener. Therefore, in this sense, Au NPs could be viewed as a “Swiss army knife” multipurpose heterogeneous catalyst. In view of our success obtained on the utilization of gold nanoparticles in a variety of organic reactions, we anticipate that more and more organic reactions could be made compatible with nanogold catalysts. Considering the slow deactivation observed in supported nanogold particles after repetitive use, a future direction of our research may be the design of a new generation of supported nanogold particles that are more robust and have much slower deactivation rate towards organic reactions.

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APPENDIX-LIST OF ABBREVIATIONS

Ac: Acetyl group

Au NPs: Gold nanoparticles

BINAP: 2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl

Bn: Benzyl group

***t*-BuOH:** *tert*-Butanol

Bz: Benzoyl group

COD: 1,5-Cyclooctadiene

Cp: Cyclopentadienyl

dba: Dibenzylideneacetone

DCE: Dichloroethane

DCM: Dichloromethane

DMA: Dimethylacetamide

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

DMPU: 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

FG: Functional group

h: Hour

HRMS: High resolution mass spectroscopy

Hz: Hertz

L: Ligand

M: Molar

mg: Milligram

MHz: Megahertz

mL: Milliliter

Mw: Microwave

m/z: Mass to charge ratio

NHC: N-Heterocyclic carbene

NMP: N-Methyl-2-pyrrolidone

NMR: Nuclear magnetic resonance spectroscopy

NTf₂: Bis(trifluoromethanesulfonyl)imide

Nu: Nucleophile

OTf: Trifluoromethanesulfonate

Pht: Phthalimide

ppm: Parts per million

Py: Pyridine

rt: Room temperature

SbF₆: Hexafluoro antimonate anion

STEM: Scanning transmission electron microscopy

TBDMS: *tert*-Butyldimethylsilyl

TBDPS: *tert*-Butyldiphenylsilyl

THF: Tetrahydrofuran

TIPS: Triisopropylsilyl

Tol: Toluene

Ts: Tosyl group

XPS: X-ray photoelectron spectroscopy

μl: Microliter

α : Alpha

β : Beta

δ : Delta

m : Meta

σ : Ortho

p : para

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Title: Supported Gold Nanoparticle-Catalyzed Hydration of Alkynes under Basic Conditions
Author: Shengzong Liang, Jacek Jasinski, Gerald B. Hammond, et al
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Author: Shengzong Liang,Luisa Hammond,Bo Xu,Gerald B. Hammond

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2. S. Liang, G. B. Hammond, B. Xu, Efficient Hydration of Alkynes through Acid-assisted Brønsted Acid Catalysis, *Chem. Commun.*, **2015**, 51, 903-906.

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3. S. Liang, P. Monsen, G. B. Hammond, B. Xu, Au/TiO₂ Catalyzed Reductive Amination of Aldehydes and Ketones Using Formic Acid as Reductant, *Org. Chem. Front.*, **2016**, 3, 505-509.

<http://pubs.rsc.org/en/content/articlelanding/2016/qo/c5qo00439j#!divAbstract>

CURRICULUM VITAE

Name: Shengzong Liang

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Summary of Achievements

- Published and submitted 12 peer-reviewed scientific articles
- Over 10-year professional background on organic chemistry
- Obtained research experience on design and synthesis bioorganic building blocks and potential drug candidates in pharmaceutical industry (served for Merck and Pfizer companies)
- Obtained research experience on organic synthesis, organometallic chemistry, and nanotechnology in academic environments
- Awarded Doctoral Dissertation Completion Award at University of Louisville
- Highly selective admission for presentation in ACS Division of Organic Chemistry Graduate Research Symposium
- Awarded University Fellowship at University of Louisville
- Awarded Arno Spatola Endowed Graduate Research Fellowship at University of Louisville
- Awarded Outstanding Undergraduate Student Scholarship each academic year

Education

University of Louisville, Department of Chemistry, Louisville, KY, USA 2012-present

Doctor of Philosophy in Organic Chemistry, Advisor: Professor G. B. Hammond

Hunan University, College of Chemistry and Chemical Engineering, Changsha, China 2006-2009

Master of Science in Organic Chemistry, Advisor: Professor Jiannan Xiang

Shanxi University, College of Chemistry and Chemical Engineering, Taiyuan, China 2002-2006

Bachelor of Science in Chemistry, Advisor: Professor Jianguo Ren

Work Experience

Pharmaron Company, Department of Bioorganic chemistry, Beijing, China 2009-2012

Research & Development Scientist

Served for Merck and Pfizer Companies to design and multiple steps synthesize various bioorganic building blocks including amino acids, nucleosides and sugars. Developed methods and multiple steps synthesized potential drug candidates. The scale of synthesis ranged from milligram to kilograms.

Academic Experience

University of Louisville, Department of Chemistry, Louisville, KY, USA

2012-present

Research Assistant

- Developed novel methodologies for recyclable gold nanoparticles catalyzed green organic synthesis such as alkyne hydration under basic condition, hydrochlorination of alkynes, highly stereoselective semi-hydrogenation of alkyne, efficient alkyne hydroamination and reductive amination.
- Designed and synthesized novel difluorinated building blocks, and applied them on difluorination of aromatic molecules mediated by transition metal catalysts or metal-free synthesis of chiral fluorinated amines and alcohols.
- Metal-free photocatalyzed sulfonation and trifluoromethylation of hetero- and aromatic compounds.

Hunan University, College of Chemistry and Chemical Engineering, Changsha, China

2006-2009

Research Assistant

- Explored palladium catalyzed phosphine-free Heck reaction for synthesis of arotinoic acids.
- Designed and synthesized 13-cis-retinoyl ferrocene derivatives, and studied antiproliferative activities of these derivatives.

Teaching Experience

University of Louisville, Department of Chemistry, Louisville, KY, USA

2015-2016

Teaching Assistant

- Prepared teaching materials including problem sets and exams.
- Graded labreports and exams. Addressed individual students' questions and needs.
- Supervised and instructed students with organic laboratory techniques and synthesis of compounds.

Professional Skills

- Well acquainted with these technologies and instruments: schlenk technique, nanotechnology, column chromatography, rotary evaporator, glovebox, solvent purification system, melting point apparatus, IR, Uv-Vis spectrophotometer, fluorescence spectrophotometer, polarimeter, Combi-flash, LCMS, GCMS, HPLC, HRMS, NMR, flow-reactor, photo-reactor, microwave reactor, XPS, STEM
- Proficient in references retrieval, after-treatment, data analysis, spectrum analysis, MS office, Endnote ChemDraw, simple calculation with Gaussian

Honors and Awards

- Graduate Dean's Citation 2017
- Doctoral Dissertation Completion Award, University of Louisville, USA 2016-2017
- Institute for Molecular Diversity & Drug Design Travel Award, University of Louisville, USA 2015
- Arno Spatola Endowed Graduate Research Fellowship, University of Louisville, USA 2014-2015
- University Fellowship, University of Louisville, USA 2012-2014
- Outstanding staff, Pharmaron Company, China 2010
- Tuition waiver for graduate program and financial support by National Science Foundation of China Hunan University, China 2006-2009
- Outstanding Undergraduate Student Scholarship, Shanxi University, China 2002-2005

Presentations

- Shengzong Liang, Gerald B. Hammond and Bo Xu. Recyclable gold nanoparticles as routine benchtop catalysts: efficient hydration, semihydrogenation and reductive amination of alkynes, The 251st ACS

National Meeting, San Diego, March 13-17, **2016**

- Shengzong Liang, Paige Monsen, Jacek Jasinski, Gerald B. Hammond and Bo Xu, Making Supported Nanogold a Routine Benchtop Catalyst for Synthetic Lab, ACS Division of Organic Chemistry Graduate Research Symposium, St. Edward's University, Austin, July 23-26, **2015**

Publications

1. S. Liang, G. B. Hammond, B. Xu, HCl/DMPU: Highly Regioselective Hydrochlorination of Alkynes with A Novel Chlorinating Reagent (Submitted to *Angew. Chem. Int. Ed.*) **2017**
2. R. Ebule, S. Liang, J. Kostyo, Gerald B. Hammond, Bo Xu, Homogeneous Gold Mediated Regioselective Hydrochlorination of Alkynes. (Submitted to *J. Am. Chem. Soc.*) **2017**
3. Z. Li, R. Ebule, S. Liang, J. Kostyo, Gerald B. Hammond, Bo Xu, HBr-DMPU: An Aprotic Organic Solution of Hydrogen Bromide. (Submitted to *Chem. Sci*) **2017**
4. S. Liang, J. Smith, F. Ibrahim, G. B. Hammond, S. Handa, Synthesis of Sulfones in Newly Designed Surfactant through Photoredox Catalysis (in preparation and plan to submit to *Nat. Chem.*) **2017**
5. S. Liang, L. G. B. Hammond, B. Xu, Commercial Supported Gold Nanoparticles Catalyzed Alkyne Hydroamination and Indole Synthesis, *Adv. Synth. Catal.*, **2016**, 358, 3313-3318. (Highlighted in *Synfacts* **2017**, 13 (01), 0113)
6. S. Liang, G. B. Hammond, B. Xu, Supported Gold Nanoparticles Catalyzed *cis*-Selective Semihydrogenation of Alkynes Using Ammonium Formate as Reductant, *Chem. Commun.*, **2016**, 52, 6013-6016. (Highlighted in *Synfacts* **2016**, 12(07), 0763)
7. S. Liang, P. Monsen, G. B. Hammond, B. Xu, Au/TiO₂ Catalyzed Reductive Amination of Aldehydes and Ketones Using Formic Acid as Reductant, *Org. Chem. Front.*, **2016**, 3, 505-509.
8. S. Liang, G. B. Hammond, B. Xu, Efficient Hydration of Alkynes through Acid-assisted Brønsted Acid Catalysis, *Chem. Commun.*, **2015**, 51, 903-906.
9. S. Liang, J. Jasinski, G. B. Hammond, B. Xu, Supported Gold Nanoparticle Catalyzed Hydration of Alkynes under Basic Conditions, *Org. Lett.* **2015**, 17, 162-165. (Highlighted in *Synfacts* **2015**, 11(04), 0439) (Highlighted in *Organic Chemistry Portal*)
10. B. Long, S. Liang, J. Xiang, Synthesis, Characterization and in vitro Antiproliferative Activities of New 13-*cis*-Retinoyl Ferrocene Derivatives. *Eur. J. Med. Chem.*, **2009**, 44, 2572-2576.
11. S. Liang, B. Long, D. Xin, J. Xiang, Synthesis and Cytotoxic Activities of 13-*cis*-Retinoyl Ferrocene Derivatives, *Chinese J. Org. Chem.*, **2009**, 29, 1096-1099.
12. X. Liu, S. Liang, J. Xiang, Phosphine-free Palladium Catalyzed Heck Reaction for the Synthesis of Novel Arotinoic Acids, *Acta Chim. Sin.*, **2008**, 66, 1086-1090.

Book Chapters

1. S. Liang, G. B. Hammond and B. Xu, Functionalization of alkynes for preparing alkenyl fluorides, in *Synthetic Organofluorine Chemistry*, edited by J. Hu and T. Umemoto, Springer-Verlag, **2017** (submitted)
2. S. Liang, G. B. Hammond and B. Xu, Urea-HF complex fluorination for preparing alkyl fluorides, in *Synthetic Organofluorine Chemistry*, edited by J. Hu and T. Umemoto, Springer-Verlag, **2017** (submitted)