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NHC–AuCl/Selectfluor: A Highly Efficient Catalytic System for Carbene-Transfer Reactions

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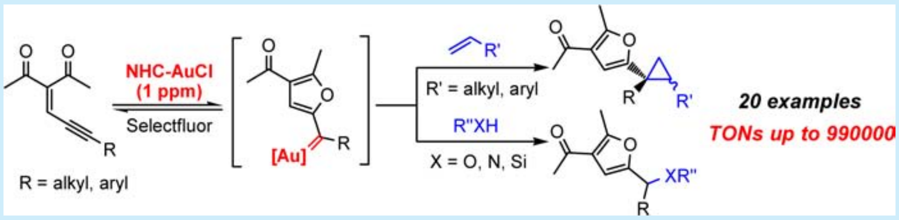
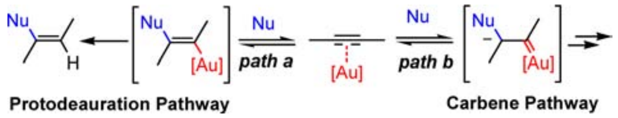
S *Supporting Information*



ABSTRACT: The combination of NHC–gold complex and Selectfluor has been found to be a highly efficient catalyst system for carbene-transfer reactions, with a turnover number (TON) up to 990000 and a turnover frequency (TOF) up to 82500 h^{-1}.

During the past decade, gold catalysis has experienced a period of rapid expansion.[1] Versatile transformation systems have been developed based on the fact that gold catalysts were regarded as the most powerful and efficient π-activators of carbon–carbon multiple bonds.[1,2] For the gold-catalyzed transformations of carbon–carbon triple bonds, the reactions generally fall into two major categories based on the breaking ways of the C–Au bonds: (a) protodeauration pathway[2] and (b) carbene pathway[3] (Scheme 1).

Scheme 1. Two Different Pathways



In most cases, the gold catalyst loadings are typically higher than 1 mol %, which makes such systems impractical due to the high cost of gold.[4] Recently, scientists have made great efforts in enhancing the catalytic efficiency and achieved a significant breakthrough in gold-catalyzed nucleophilic attack of the alkynes.[4,5] For example, Corma and co-workers reported an ester assisted hydration of alkynes catalyzed by small gold clusters with a turnover number (TON) up to 10^7.[5a] Hammond and Xu demonstrated a diverse array of gold-catalyzed reaction including intra- and intermolecular X–H (X = C, N, O) additions to alkynes and cycloisomerizations at low-level catalyst loadings, with TON up to 10^5.[5b] Very recently, Zhang and co-workers designed an elegant ligand-assisted system to achieve highly efficient gold-catalyzed acid addition to alkynes.[5c]

The versatile reactivities of metal carbene make it one of the most useful intermediates. However, the metal carbenes were generally generated in situ from the potential explosive diazo compounds.[6] Recently, the gold carbene generated from the alkyne derivatives has become a safe and reliable carbene sources (Scheme 1, path b).[3] Nevertheless, compared to the catalytic protodeauration reactions (path a), the gold carbene pathway b with low-level catalyst loadings was still highly underexplored. In most cases, the gold catalyst loadings in the carbene process typically ranged from 2 to 5 mol %.[3] Further applications of the gold catalysis in the carbene-transfer process was then limited. Therefore, development of a highly efficient gold–carbene process with high TONs or TOFs (turnover frequencies) would be of great importance.

It is well-known that transition-metal-catalyzed cyclization of enynals/enynones through 5-*exo-dig* nucleophilic attack would form the metal–carbene intermediate efficiently.[7] Therefore, gold-catalyzed cyclization of enynals/enynones would be a good model system to investigate the efficiency of gold catalyst in a carbene-transfer process. Herein, we report a highly efficient NHC–AuCl/Selectfluor-catalyzed carbene-transfer system through the cyclization of enynone **1** with TON value up to 990000.

As an initial examination, enynone **1a** and styrene **2a** were treated with the general gold(I) catalysts, which have even been successfully applied in the protodeauration process with very high TON values.[4,5] As shown in Table 1, both N-heterocyclic carbene (NHC) and phosphine-supported cationic Au^+ complexes (1 mol %) could catalyze the cyclopropanation of **1a** efficiently, giving the desired product **3a** in 85% and 99% yields, respectively (entries 1 and 2). However, the reaction efficiencies dropped down sharply with lower catalyst loadings (entries 3–6). For example, when 0.01 mol % of Ph_3P–AuCl/$AgNTf_2$ or IPr–AuCl/$AgNTf_2$ were used as catalysts, only a trace product **3a** was detected. The gold(III) salts or complexes alone, $KAuCl_4$, IMes–$AuCl_3$, and Pic–$AuCl_2$, were inferior catalysts for this transformation; no reactions occurred or very low yield was

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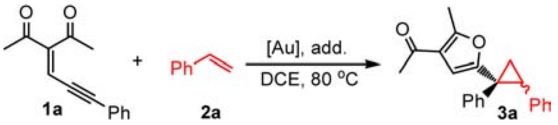
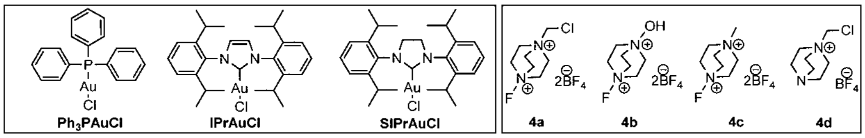
Table 1. Gold-Catalyzed Reaction of **1a** and **2a**[a]



entry	cat.	cat. loading (mol %)	add. (mol %)	time (h)	conv (%)	yield (%)	TON	*cis*/*trans*[b]
1	Ph_3P–AuCl	1	$AgNTf_2$ (1)	12	100	85	85	1.0/1.5
2	IPr–AuCl	1	$AgNTf_2$ (1)	12	100	99	99	1.0/1.2
3	Ph_3P–AuCl	0.1	$AgNTf_2$ (0.1)	12	60	50	500	1.0/1.6
4	IPr–AuCl	0.1	$AgNTf_2$ (0.1)	12	65	52	520	1.0/1.4
5	Ph_3P–AuCl	0.01	$AgNTf_2$ (0.01)	12	trace	trace		
6	IPr–AuCl	0.01	$AgNTf_2$ (0.01)	12	trace	trace		
7	IPr–AuCl	1	**4a** (10)	12	100	99	99	1.0/1.3
8	SIPr–AuCl	1	**4a** (10)	12	100	99	99	1.0/1.3
9	IPr–AuCl	1		12				
10	IPr–AuCl	0.1	**4a** (10)	12	100	96	960	1.0/1.4
11	IPr–AuCl	0.01	**4a** (10)	36	100	86	8600	1.0/1.5
12[c]	IPr–AuCl	0.0001	**4a** (10)	72	100	82[d]	820000	1.0/1.6
13[c]	IPr–AuCl	0.0001	**4b** (10)	72	100	63	630000	1.0/1.5
14[c]	IPr–AuCl	0.0001	**4c** (10)	72	17	15	150000	1.0/1.6
15[c]	IPr–AuCl	0.0001	**4d** (10)	72	trace	trace		
16			**4a** (10)	12				

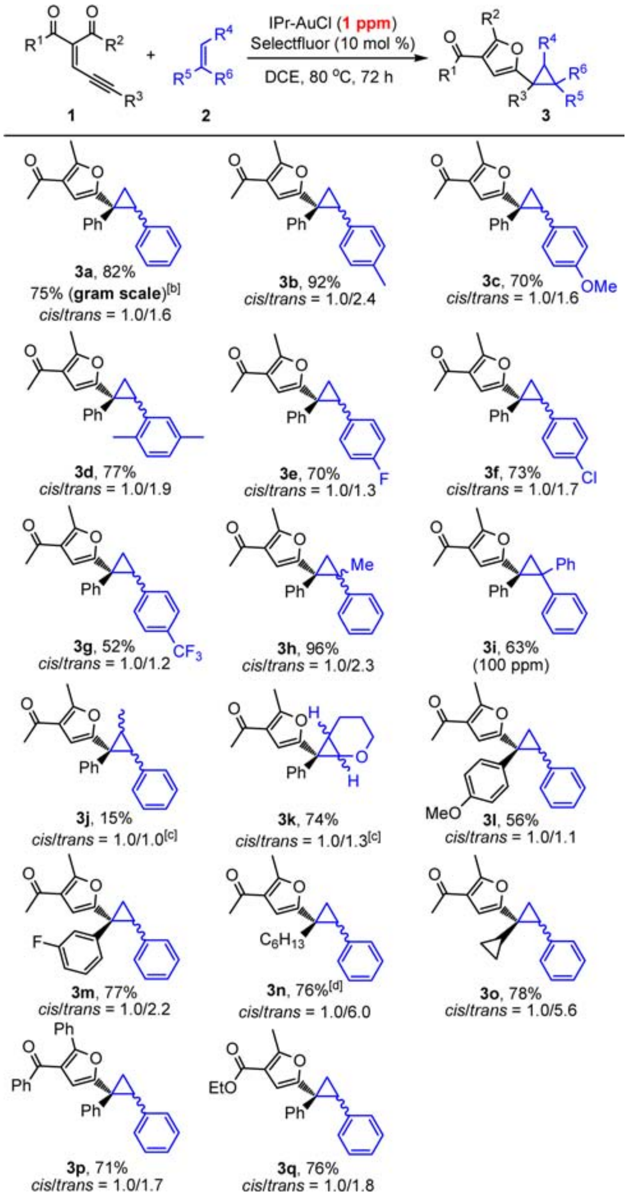
[a] The reaction was conducted with **1a** (0.2 mmol) and **2a** (1.0 mmol) in DCE (0.05 M) at 80 °C; the yield of **3a** was determined by ^1H NMR analysis using CH_3NO_2 as an internal standard. [b] Estimated by ^1H NMR. [c] **1a**/**2a** = 1/10. [d] Isolated yield.



observed (see the Supporting Information). These results could be attributed to the instability of gold(III) sources; such a hypothesis was supported by the observation of gold mirror on the surface of the reaction flask when $KAuCl_4$ was used as catalyst.[8] It seems both gold(I) and gold(III) salts or complexes were not good catalysts for the carbene process because of their inherent instability under such circumstances.[8,9] In seeking to improve the efficiency of the reactions, we were drawn to the observation that Selectfluor (**4a**) has been extensively used as mild organic oxidant in generating L-Au(III)$^+$ in situ from L-Au(I).[10] As an oxidant, we believed that addition of Selectfluor may inhibit the reduction of gold(III). As such, we hypothesized that the combination of NHC–AuCl/Selectfluor as the NHC–Au(III)$^+$ source might show better TON or TOF for carbene transformation reaction. The choice of NHC ligand was made because the strong electron-donating ligands are capable of preventing the reduction of Au(I) or Au(III) to metallic Au(0).[8] With 1.0 mol % of IPr–AuCl and 10 mol % of Selectfluor **4a**, the gold-catalyzed cyclopropanation of **1a** with styrene proceeded with almost quantitative yield (entry 7). The combination of SIPr-AuCl/Selectfluor furnished similar results (entry 8). IPr-AuCl alone was not able to catalyze this transformation (entry 9). Encouraged by these positive results, we then decreased the catalyst loading gradually (the catalyst solutions were prepared by stepwise dilution techniques).[4] With 0.1 and 0.01 mol % of catalyst, complete conversion was obtained in both cases (entries 10 and 11). More intriguingly, the yield was still up to 82% when a lower catalyst loading (0.0001 mol %, 1 ppm) was applied; this corresponds to a TON of 820000 (entry 12). To further prove the positive effects exerted by Selectfluor **4a**, three derivatives **4b–d** were then tested for this transformation as well (entries 13–15). NF-TEDA-OH **4b** and NF-TEDA-Me **4c**, both containing the N–F bond, provided the products **3a** in 63% and 15% yields, respectively (entries 13 and 14). TEDA-CH_2Cl **4d**, an ammonium salt without an N–F bond, was ineffective for this transformation, which strongly indicated that the N–F bond is necessary for this catalytic system (entry 15). The reaction did not occur in the absence of gold catalyst (entry 16).

Having established IPr–AuCl/Selectfluor as a highly efficient catalytic system for the carbene transfer reactions, the generality of this system was then investigated in the presence of 1 ppm of IPr–AuCl and 10 mol % of Selectfluor under N_2 in DCE for 72 h (Scheme 2). First, the reaction could be repeated in gram-scale and gave the product **3a** in similar yield (75%). Second, the catalytic system could be successfully applied to a variety of enynones **1** and alkenes **2** as well. For example, in addition to styrene **2a**, various styrene derivatives could be effectively reacted with enynone **1a** as well (**3a–j**). The electron-rich alkenes were better substrates than the electron-poor ones. The reactions proceeded smoothly for the electron-rich styrene derivatives, with the yields typically higher than 70% (**3a–d**). The bulky 2,5-dimethylstyrene was also found to be a suitable substrate for this catalytic system, giving the product **3d** in 77% yield. Under the same reaction conditions, the electron-deficient styrene derivatives could effectively react with enynone **1a** as well, albeit in relatively lower yields (**3e–g**; 52–73%). Both *α*-methylstyrene and *α*-phenylstyrene could be effectively cyclopropanated with enynone **1a**, affording the products **3h** and **3i** in 96% and 63% yields, respectively. However, higher catalyst loading (100 ppm) was required for full conversion of starting material when bulkier *α*-phenylstyrene was used. *β*-Methylstyrene, an internal alkene, was a much worse substrate for this system, giving the product **3j** only in 15% yield. The reaction proceeded smoothly when 3,4-dihydropyran was used as substrate (**3n**, 74%).

Scheme 2. Reaction Scope for Enyone Derivatives[a]

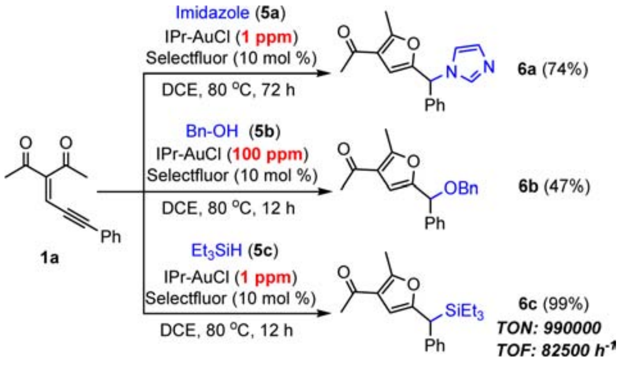


[a] **1a** (0.2 mmol), **2a** (2.0 mmol), DCE (0.05 M); isolated yields; the diastereomeric ratio was determined by ^{1}H NMR. [b] **1a** (5 mmol). [c] The configurations of **3j** and **3k** were assigned by NOE. [d] ~20% [1, 2]-H shift product was formed (see the Supporting Information).

Compared with the alkenes **2**, the reaction was less sensitive to the properties of enynones **1** (**3l**–**q**; 56%–78%). The enynone with an electron-withdrawing group at the phenyl ring (**3m**, 77%) functioned better than the one with an electron-donating group (**3l**, 56%). Intriguingly, much better diastereomeric ratios (cis/trans ≈ 1/6) of products **3n** and **3o** were obtained when alkyl enynones were used as the substrates, with the yields being 76% and 78%, respectively. The reactions for benzoyl- or ethoxycarbonyl-substituted enynones proceeded equally well, leading to the products **3p** and **3q** in 71% and 76% yields, respectively. In most cases, the TON values of the reactions were higher than 700000; in the case of **3h**, the TON value was up to 960000.

In addition to the cyclopropanation reactions, metal carbenes have also proven to be highly versatile for X–H insertion reactions.[7] To further investigate this unique IPr–AuCl/Selectfluor system, we then proceeded to conduct different X–H insertion reactions at the standard reaction conditions. As shown in Scheme 3, imidazole can be used as an efficient substrate, affording to the N–H insertion product **6a** in 74% yield. In the case of O–H insertion of BnOH, however, the catalyst loading has to be improved to 100 ppm to diminish the completing carbene dimerization reaction;[7] it furnished the desired product **6b** in 47% yield. Surprisingly, Si–H insertion reaction of Et_3SiH provided a near-quantitative yield of **6c** in only 12 h, which corresponds to a TON of 990000 and TOF of 82500 h^{-1}. To the best of our knowledge, it is probably one of the most efficient carbene-transfer reaction systems.

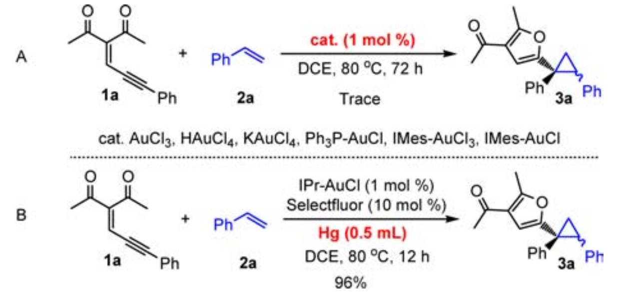
Scheme 3. IPr-AuCl/SelectfluorCatalyzed X–H Insertion Reactions[a]



[a] **1a** (0.2 mmol), **5** (10 equiv), DCE (0.05 M); isolated yields.

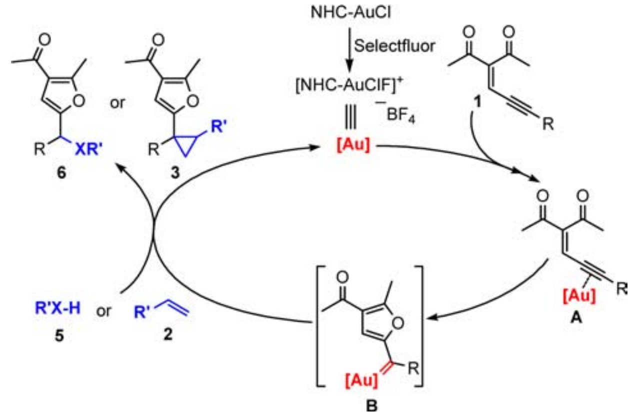
To figure out if the heterogeneous gold species were the true catalyst of our catalytic system, several control reactions were then carried out (Scheme 4). Initially, six common gold salts and complexes, $AuCl_3$, $HAuCl_4$, $KAuCl_4$, Ph_3PAuCl, IMes–$AuCl_3$, and IMes–AuCl, were used. According to Corma's observations, the above six gold sources should decompose into small gold clusters, or at least in part. However, no reactions occurred or only trace product **3a** was detected after 12 h. Therefore, the results of this control reaction indicated that AuNPs may not be the real active catalysts.[5a] Furthermore, we also used the heterogeneous catalyst poisoning technique, by addition of large excess of mercury(0),[11] to exclude the heterogeneous process. The reaction remained almost unaffected in the presence of 0.5 mL of Hg(0).

Scheme 4. Control Reaction



On the basis of the above results, a homogeneous catalytic reaction mechanism involving a cationic $Au(III)^+$ species was then proposed (Scheme 5).[10,11] Initially, $[NHC–AuIIIClF]^+$ (simplified as [Au] in the catalytic cycle) was generated in situ

Scheme 5. Proposed Reaction Mechanism



from the oxidation of NHC−AuCl with Selectfluor. The coordination of the triple bond of enynone **1** to [Au] enhanced the electrophilicity of the alkyne, and the subsequent intramolecular nucleophilic attack of the carbonyl oxygen atom to the electron-deficient alkyne would form the intermediate **B**. In the presence of alkenes or X−H, the carbene intermediate was then trapped to form the cyclopropanes **3** or insertion products **6**.

In conclusion, we have found that the combination of NHC−gold complex and Selectfluor is a highly efficient catalyst system for carbene-transfer reactions, with the TON up to 990000 and the TOF up to 82500 h^{-1}. The reaction probably proceeded through a cationic Au(III)$^+$ species, which was generated in situ from the oxidation of NHC−AuCl with Selectfluor. Further investigations of the detailed reaction mechanism and application of this system are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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