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Gold-Catalyzed [2,3]-Sigmatropic Rearrangement: Reaction of Aryl Allyl Alcohols with Diazo Compounds

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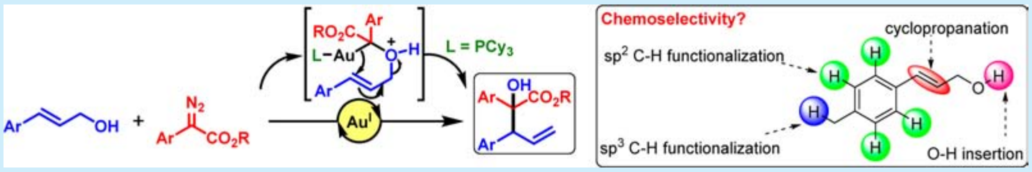
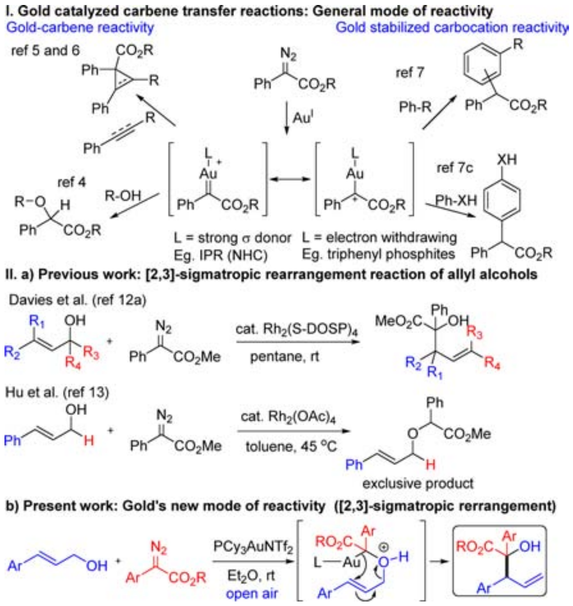
Supporting Information



ABSTRACT: A gold-catalyzed [2,3]-sigmatropic rearrangement reaction has been developed. The intermolecular rearrangement occurs between in situ generated donor−acceptor gold−carbenes and cinnamyl alcohols via tandem oxonium ylide formation. The desired rearranged product has been accomplished selectively over more conventional O−H insertion, cyclopropanation, cycloaddition, and C−H functionalization products under mild, open-air conditions. The scope of the work has been illustrated by synthesizing a new class of substrates that can be used for constructing complex molecular targets.

Gold, once considered as the "lethargic and overweight version of catalytically interesting copper", is today regarded as one of the most versatile metals with rich chemistry.[1] Influenced by relativistic effects,[2] it exhibits increased "π acidity" and "electron delocalization". These two features result in a dual "push−pull" reactivity which has opened exciting new avenues in synthetic organic chemistry.[3] In this direction, gold has been successfully used to catalyze carbene transfer reactions,[3c] such as heteroatom−H (such as O, N) insertion,[4] cyclopropanation[5]/cyclopropenation,[6] C−H functionalization,[4,7] and cycloaddition reactions.[17]

Scheme 1. Gold-Catalyzed [2,3]-Sigmatropic Reaction



The gold-catalyzed carbene transfer reaction is relatively recent, and a seminal report by Nolan and Pérez[4] showed that gold can indeed form gold−carbenes to mediate carbene-transfer reactions (Scheme 1).[8] The ability of carbenes/carbenoids to form ylides with Lewis bases (B:), such as ethers, sulfides, amines, and carbonyls, had a profound influence on the development of diazocarbonyl compounds as synthetic precursors.[9] Ylides, other than simple heteroatom−H insertions, formed during carbene-transfer reactions can also undergo [2,3]-sigmatropic rearrangement, [1,2]-shift (Stevens rearrangement), and related reactions.[8a] Guiding the reaction to the desired [2,3]-sigmatropic rearranged product, selectively, is pertinent and will provide great synthetic advancement by forming C−C or C−heteroatom bonds in a single step (Scheme 1).[10] Generating an oxonium ylide is also challenging, compared to conventional N or S stabilized ylides, due to its inherent instability.[8,10] In this direction, the Rh-catalyzed [2,3]-sigmatropic reaction by Doyle[10] and an intramolecular allylic ether oxonium ylide derived [2,3]-sigmatropic reaction using Rh[11] by Pirrung and Johnson, paved the way forward. An enantioselective [2,3]-sigmatropic reaction between highly substituted allyl alcohols and donor/acceptor carbenoids, developed by Davies, further empowered the synthetic utility of the rearrangement.[12] However, this limits the scope of the reaction to only secondary and tertiary alcohols. More common primary allyl alcohols cannot be used to achieve the desired product. As demonstrated by Hu et al.,[13] a simple cinnamyl alcohol under similar reaction conditions does not lead to the [2,3]-sigmatropic rearranged product but affords the corresponding O−H insertion product. Stringent reaction requirements and competitive O−H/C−H insertions with Rh catalysts further complicate the reaction.[9,13] Recently, Yang and Tang reported

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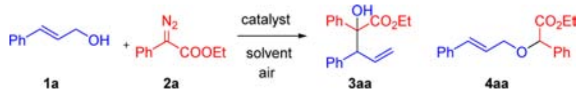
NHC−Au-catalyzed intramolecular [2,3]-rearrangement of allylic oxonium ylides derived from allylic ethers and alkyne as carbene precursors.[14] Allylic sulfides have also been employed for generating corresponding ylides from alkyne precursors to undergo [2,3]-rearrangement.[15] Achieving [2,3]-sigmatropic rearrangement of simple allyl alcohols is challenging and unprecedented due to the instability of corresponding oxonium ylides.

Inspired by the relativistic effect,[2] we envisioned that cationic gold may be used to accomplish the desired [2,3]-sigmatropic reaction. PPh_3AuCl along with $AgSbF_6$ (halide scavenger) was chosen as the initial catalytic system for the following reasons: (i) ability to form electrophilic gold-carbene; (ii) possible stabilization of the cation by backbonding;[2] (iii) controlling the stereoselectivity;[2] and (iv) possible modulation of the nature of gold-carbenes by the ligand variation.[16] Cinnamyl alcohol (**1a**) and ethyl phenyldiazoacetate (**2a**) were chosen as the standard substrates. Under the given conditions, cinnamyl alcohol was an interesting but challenging substrate considering its susceptibility toward probable cyclopropanation,[5,6] O−H insertion,[4,13] C−H functionalization,[7] and cycloaddition reactions.[17] However, after a few initial screening reactions, we were delighted to observe the desired rearranged product **3aa** in a complex crude reaction mixture, albeit in only 22% isolated yield (Table 1, entry 1). The result promised a new class of compounds that can be accessed. The structure of **3aa** was unambiguously confirmed by X-ray crystallography study.[18]

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	**3aa** yield[b] (%)	dr[c]	**4aa** yield[b] (%)
1	$PPh_3AuCl/AgSbF_6$	45 (22)	89:11	35
2	PPh_3AuCl	nr		
3	$AgSbF_6$	nd		
4	$AuCl/AgSbF_6$	nd		67
5[d]	$PPh_3AuCl/AgSbF_6$	15	90:10	27
6	$PPh_3AuCl/AgSbF_6$	58	85:15	18
7[e]	$PPh_3AuCl/AgSbF_6$	41	35:6	19
8	$PPh_3AuCl/AgOAc$	nr		
9	$PPh_3AuCl/AgBF_4$	trace		13
10	$PPh_3AuCl/AgOTf$	60 (48)	95:5	40
11	$PPh_3AuCl/AgNTf_2$	67	96:4	14
12	$IPrAuCl/AgNTf_2$	trace		46
13	$PCy_3AuCl/AgNTf_2$	91	97:3	trace
14[f]	$PCy_3AuCl/AgNTf_2$	93	97:3	trace
15[g]	$PCy_3AuCl/AgNTf_2$	96 (72)	96:4	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (1.5 mol %), solvent (entries 1−5, DCM, 2 mL; entries 6−15, Et_2O, 3 mL), rt, 12 h. [b] Measured by ^1H NMR with terephthalaldehyde as the internal standard, nr = no reaction, nd = not detected. The numbers in parentheses are isolated yields. [c] dr = diastereomeric ratio of **3aa**. [d] catalyst = 5 mol %. [e] catalyst = 1 mol %. [f] catalyst = 2 mol %. [g] catalyst = 3 mol %.

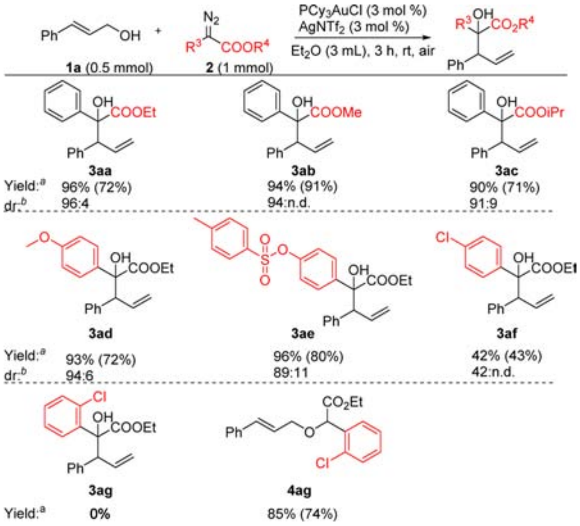
With this promising result (entry 1), we proceeded further with the optimization reactions. Excluding the halide scavenger in the reaction ($AgSbF_6$) did not furnish the expected product, but both the starting materials remained intact. This reaction clearly indicates the necessity of a noncoordinating counterion to activate the cationic gold (Table 1, entry 2). Further, eliminating Au from the reaction system yielded no desired product but a complex crude reaction mixture comprising mainly of diazo dimer byproduct. This disregarded the direct role of Ag, if any, in obtaining the desired rearranged product (Table 1, entry 3).[19] As a consequence of the relativistic effects,[2] the influence of the phosphine ligand in altering the bonding and reactivity of the gold−carbene complex reactivity is relatively more pronounced due to the increased covalent character between Au−P bonds.[2,20] To verify this hypothesis, AuCl, devoid of a ligand (PPh_3), was used, which gave only O−H insertion product in major amount (67%) along with other minor unidentified impurities (Table 1, entry 4). This clearly indicated the necessity of the ligand in guiding the reaction to the [2,3]-sigmatropic rearranged product. Increasing or decreasing the catalyst loading reduced the yield of rearranged product **3aa** to 15 and 41%, respectively (entries 5 and 7). Solvent screening results showed Et_2O as the best solvent (Table 1, entry 6. For more details, see Tables S1 and S3, Supporting Information). A brief screening of Ag salts identified $AgNTf_2$ as the best halide scavenger (Table 1, entries 8−11).

Using IPr as a ligand gave only the O−H insertion product, indicating that the electron-rich strong σ-donor NHC ligand was not suitable for the desired transformation (Table 1, entry 12). Based on the promising outcome shown by PPh_3, we envisaged that having a bulky PCy_3 ligand with a relatively weaker π-acceptor character would greatly facilitate the reaction by inducing the required carbenoid type of reactivity. The reason may be attributed to an increased electron back-donation from Au stabilizing the carbenic carbon as well as the oxonium ylide intermediate for the subsequent rearrangement.[21] Gratifyingly, the desired rearranged product **3aa** was obtained in 91% yield (based on ^1H NMR, entry 13). Further optimization with respect to the catalyst amount and the reaction time (entries 14 and 15) provided the optimal conditions for the present reaction (Table 1, entry 15). It is also noteworthy that PCy_3AuCl was efficient in increasing the diastereoselectivity (96:4) compared to PPh_3AuCl, suggesting a possible association of the catalyst to the ylide in the final product-forming step.

With the optimal conditions established, we studied substrate scope by reacting cinnamyl alcohol with a variety of α-aryl-α-diazoacetates (Scheme 2).[22] As expected, diazo esters comprising ethyl, methyl, and isopropyl groups had no significant effect on the outcome of the reaction and gave **3aa**, **3ab**, and **3ac** in 72, 91, and 71%, respectively (Scheme 2). However, varying substituents on the aromatic group of the diazo compound resulted in a considerable change in the yield of the desired products. Thus, both steric as well as electronic factors played a major role in the reaction outcome as illustrated in the examples (Scheme 2, **3ad−ag**). Substituents such as −OMe and −OTs on the aromatic group of the diazo compound gave excellent yields (**3ad** and **3ae**, 87 and 80%, respectively). Ethyl *p*-chlorophenyldiazoacetate gave 43% of the expected product (**3af**) along with the O−H nsertion product in 56% yield (^1HNMR yield), whereas an *o*-chloro substitution did not give the expected product (Scheme 2, **3ag**) but furnished only the O−H insertion product (74%, Scheme 2, **4ag**), which may be attributed to an unfavorable steric effect (see Scheme 4).

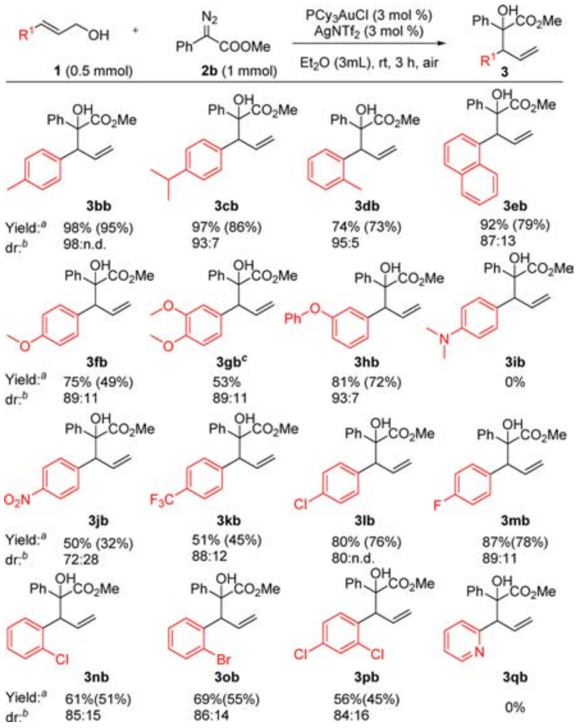
Proceeding further, a variety of cinnamyl alcohols were reacted with methyl phenyldiazoacetate (**2a**, Scheme 3) to afford moderate to excellent yields of the rearranged products in 32−95% yields. As can be seen, alkyl substituents on the aromatic ring resulted in the formation of the required product in excellent yields (Scheme 3, **3bb−db**). The remarkable selectivity observed in these rearrangement reactions is noteworthy, whereas Au-

Scheme 2. Scope of the α-Aryl-α-diazoacetates



[a]Measured by ^{1}H NMR (terephthalaldehyde: internal standard). Numbers in parentheses are isolated yields. [b]dr = diastereomeric ratio.

Scheme 3. Scope of the Allyl Alcohols

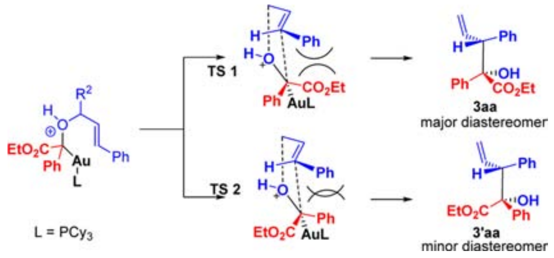


[a]Measured by ^{1}H NMR (terephthalaldehyde: internal standard). Numbers in parentheses are isolated yields. [b]dr = diastereomeric ratio. [c]**3gb** decomposed during isolation.

catalyzed reactions are well-known to provide benzylic CH-functionalized products.[4,7d] An *o*-methyl group on the aryl system, considering the relative proximity to the carbene center, had a negligible effect on the reaction outcome (**3db**, 73%). Similarly, a naphthyl substituent on the allyl alcohol also resulted in 79% of the product (**3eb**). An aryl ring with electronically rich substituents resulted in moderate to excellent yields (Scheme 3, **3fb** and **3hb**, 49 and 72% respectively). The reaction of cinnamyl alcohol derivative containing *p*-NMe$_2$ substitution on the aryl ring was not successful in affording the rearranged product **3ib**, which may be due to the quenching of the gold complex. Substrates with electron-withdrawing groups such as −NO$_2$ and −CF$_3$ reacted well to give moderate yields of the rearranged products, **3jb** and **3kb** in 32 and 45% yield, respectively (Scheme 3). Halide substituents were also found to react smoothly to give the desired product in moderate to excellent yields (Scheme 3, **3lb**−**pb**, 45−78%). The reaction of (*E*)-3-(pyridin-2-yl)prop-2-en-1-ol with **2b** was unsuccessful in furnishing the product **3qb**.

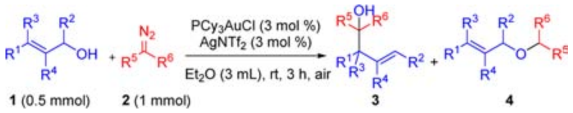
Based on the literature precedence,[8] and the obtained product structure, a generic transition state has been proposed (Scheme 4) as a result of Au associated ylide system. As can be construed, the TS2 is expected to have relatively higher energy than the TS1 due to the potential steric interaction between the adjacent aryl rings resulting in the selective formation of **3aa** as the major diastereomer.

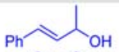
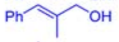
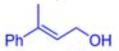
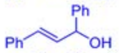
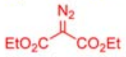
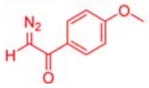
Scheme 4. Generic Transition-State Analysis



To understand the reactivity of gold−carbene complexes, an investigation was performed using electronically dissimilar substrates (Table 2). Effect of the presence of a methyl group at the 1-, 2-, or 3-positions of the 3-phenylallyl alcohols (**1a**) was probed, which has shown a significant change in the outcome of the reaction (entries 1−3, Table 2). Using 1-methyl-3-phenylallyl alcohol gave the desired product **3rb** in moderate yield (31%). Whereas 2-methyl-3-phenylallyl alcohol and 3-methyl-3-phenylallyl alcohol did not furnish the rearranged products but afforded

Table 2. Deviation from the Standard Substrates



entry	substrate[a]	**3** yield[b] (%)	dr[c]	**4** yield[b] (%)
1		**3rb**: 64 (31)	84:16	n.d.
2		n.d.	-	**4sb**: 99 (94)
3		**3tb**: 8	-	**4tb**: 85 (68)
4		**3ub**: 34 (21)	50:50	n.d.
5		**3vb**: 50 (22)	80:20	n.d.
6		n.d.	-	**4wb**: 94 (88)
7		n.r.	-	n.r.
8		n.d.	-	**4ah**: (62)

[a]Entries 1−6: **1** (0.5 mmol), **2a** (1 mmol). Entries 7−8: **1a** (0.5 mmol), **2** (1 mmol). [b]Measured by ^{1}H NMR with terephthalaldehyde as the internal standard. Isolated yields are in parentheses. [c]dr = diastereomeric ratio.

OH insertion products **4sb** and **4tb** in 94 and 68% yields, respectively. Similarly, 1-phenyl-substituted 3-phenylallyl alcohol gave a moderate yield of the expected product (**3ub**, 21%, entry 4). A vinyl extension of the allyl alcohol also gave the expected product **3vb** in moderate yield (22%, entry 5). However, as can be seen in entry 6, lack of an aryl system resulted only in the formation of the O−H insertion product **3wb** in excellent yield (88%). Conversely, employing acceptor−acceptor carbene precursors resulted in no reaction, and both of the starting materials were intact (entry 7). However, using an acceptor carbene gave the O−H insertion product in good yield (**4ah**, 62%, Table 2, entry 8), which emphasizes the requirement of the donor−acceptor nature of the carbene precursor.

In summary, we have developed a homogeneous gold-catalyzed intermolecular [2,3]-sigmatropic rearrangement reaction between in situ generated donor−acceptor gold−carbenes and cinnamyl alcohols. The method generates an oxonium ylide followed by [2,3]-sigmatropic rearrangement, competing favorably with the more conventional O−H insertion, cycloaddition, cyclopropanation, Stevens rearrangement, and C−H functionalization reactions under mild open-air conditions without the need for syringe pumps or related sophisticated delivery methods. We are at present pursuing enantioselective versions of the present method which may be used in building complex molecular targets.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03836.

Experimental procedures, characterization data, and spectra for all compounds (PDF)
Crystal structure of **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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