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Ambient Synthesis of Dienals via Triazole–Gold and Amine Catalysis Relay

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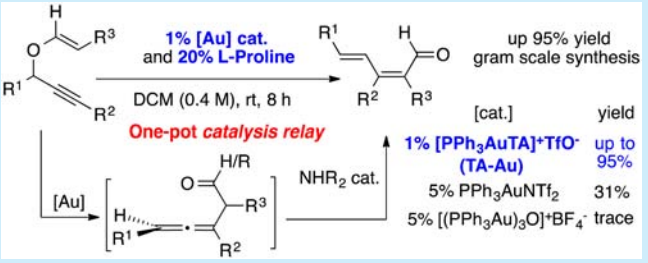
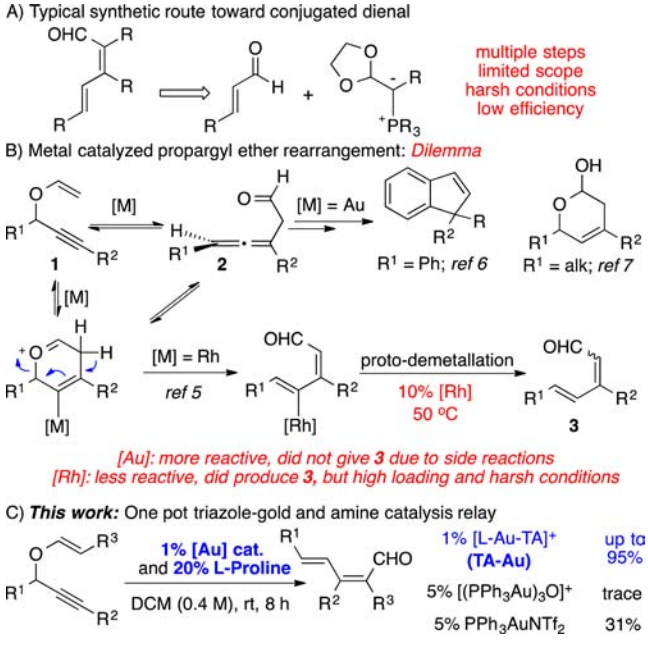
Supporting Information

ABSTRACT: A highly efficient synthesis of substituted conjugated dienals was developed through a triazole–gold (TA–Au)-catalyzed propargyl vinyl ether rearrangement followed by an amine catalyzed allene–aldehyde tautomerization. Various substituted vinylogous aldehydes were prepared in one pot with good to excellent yields (up to 95%) under mild conditions with high atom economy.



Vinylogous aldehydes represent unique and interesting building blocks in organic synthesis.[1] The rich reactivity inherited through diene–aldehyde conjugation provides a synthetic scaffold for a host of transformations. Interesting reactions have been developed using this rather unique synthon, including recent efforts toward asymmetric organocatalysis using trienamine activation.[2,3] However, despite great synthetic versatility, the utilization of diene–aldehydes is far from paradigmatic in complex molecule construction, largely due to the challenges associated with the preparation of these starting materials. As shown in Scheme 1A, typical syntheses of conjugated dienals are achieved through Wittig condensation, often requiring multiple subsequent steps and harsh conditions.[4] In these cases, substrate scope and low atom economy (large amount of byproduct waste generated) are also problematic and synthetically unappealing. Thus, new methods toward dienal synthesis with high efficiency (less steps, high atom economy) are desirable. Herein, we divulge a new strategy to expedite the synthesis of substituted 1,3-dienals from readily available starting materials. This process is initiated by chemoselective triazole gold catalysis and leads to a highly efficient amine tautomerization relay (good to excellent yields and atom economy) under extremely mild conditions.

Scheme 1. Diene Aldehyde: Important but Hard To Prepare



With interest in developing new syntheses of 1,3-dienals, our attention initially turned towards the metal-catalyzed propargyl vinyl ether **1** rearrangement.[5] As shown in Scheme 1B, compound **1** may undergo metal-catalyzed rearrangement to form allene **2**. Alabugin and co-workers recently reported that $[Rh(CO)_2Cl]_2$ could promote the isomerization of **1**, giving dienal **3** through the proposed vinyl-Rh intermediates, though high catalyst loading (10%) and elevated reaction temperature (50 °C) were required.[6]

This transformation was interesting as it offered a new approach to prepare dienals with high efficiency, though the high catalyst loading greatly reduces the viability of applying this method as a practical synthesis. The screening of reaction conditions also revealed an interesting catalyst reactivity dilemma for this transformation. With gold catalysts, good reactivity was observed for both alkyne and allene activation. Thus, even low catalyst loading (usually <1%) and mild conditions (rt) would effectively promote the initial rearrangement. However, no dienal **3** was observed due to the existing side reactions associated with gold-catalyzed allene activation. For example, Nolan and co-workers reported indene formation through phenyl addition to the $[IPrAu]^+$ activated allene.[7]

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Allene−aldehyde cyclization catalyzed by gold−oxonium complex $[(PPh_3Au)_3O]^+$ has also been reported by Toste and co-workers.[8] In contrast, the [Rh] catalyst could transfer vinyl ether **1** to dienal **3**, which was likely associated with lower reactivity of the vinylrhodium toward protodemetalation and lower π-acidity for subsequent allene activation (compared with [Au]). Therefore, high catalyst loading and harsh reaction conditions seem inevitable in these systems.

Recently, our group has developed 1,2,3-triazole−gold complexes (TA−Au) as a new class of gold catalysts in promoting alkyne activation.[9] The interesting new reactivity of this catalyst is evidenced through the observation of true chemoselectivity (activating alkyne over allene), allowing direct access to allene aldehyde **2** in excellent isolated yields.[10] With this information, we postulated that TA−Au catalysts might offer a new opportunity to achieve dienal **3** if a compatible tautomerization condition could be identified. Surely, this new strategy will be more practical with the employment of much more reactive yet chemoselective gold catalysts. To explore the necessary tautomerization step, we prepared allene−aldehyde **2a** and administered various isomerization conditions initially. The reaction conditions are summarized in Figure 1A.

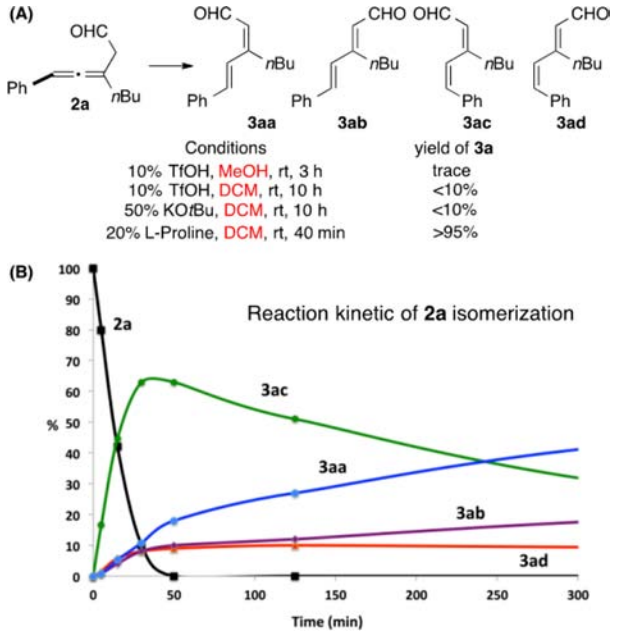
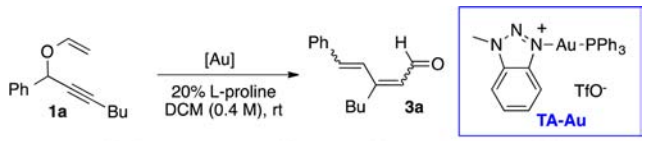


Figure 1. Allene−aldehyde **2a** tautomerization. General reaction conditions: **2a** (0.5 mmol), L-proline (20 mol %) in solvent (0.4 M). Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

As shown in Figure 1A, treating **2a** with TfOH in MeOH gave a trace amount of the desired dienal. Extending the reaction time caused significant decomposition of **2a**. Similar results were observed with strong base (50% KO-*t*-Bu). Fortunately, reacting **2a** with catalytic proline (20%) gave rapid allene isomerization even at room temperature (100% conversion in 40 min), forming the desired dienal **3a** in nearly quantitive yield (>95%, combined all isomers).

With the presence of two conjugated double bonds, one practical issue involved the formation of different isomers. Although Alabugin and co-workers reported excellent double-bond selectivity (only formed **3aa** and **3ab** with >20:1 ratio), we found it was hard to isolate pure stereoisomers since isomerization occurred even upon rotary evaporation (after column). To explore this reaction, we first characterized all four isomers using comprehensive NOE analysis (see the Supporting Information). With the structures of the four isomers identified, we monitored the isomerization process using ^{1}H NMR.

As shown in Figure 1B, monitoring the reaction by NMR indicated the complete conversion of **2a** within 40 min at room temperature. Kinetic isomers **3ac** and **3ad** (*cis*-double bonds at γ/δ positions) were formed initially, similar to the allene iodination reaction we reported previously.[11] These two kinetic isomers further isomerized into the thermodynamic isomers **3aa** and **3ab** (*trans*-double bonds at γ/δ positions) over time (30 h), eventually reaching thermodynamic equilibrium with **3aa**:**3ab** at a 2:1 ratio (overall >95% yields).[12] This result clearly demonstrated the feasibility of amine catalyzed allene−aldehyde tautomerization for the synthesis of substituted dienals as proposed.[13] Moreover, the illustration of the reaction kinetic profile provides valuable mechanistic insight for achieving various dienal isomers selectively. With this crucial mechanistic insight on the tautomerization step, we focused our attention on the catalytic relay with vinyl ether **1** as the starting materials.[14] Again, the key concern is whether gold catalysts work in this one-pot process given the allene-aldehyde intermediate and the other competing side reactions described earlier. To test this hypothesis, we charged various gold catalysts (5%) to **1** in DCM with the presence of 20% L-proline. The results are summarized in Figure 2.



[Au] cat.	condition	time, conv	yield
5% $PPh_3AuCl/AgOTf$	one-pot	2 h, 100%	25%
5% PPh_3AuNTf_2	one-pot	3 h, 100%	31%
5% $[(PPh_3Au)_3O]BF_4$	one-pot	24 h, <5%	trace
1% TA-Au	one-pot	2 h, 55%	90% (brsm)
1% TA-Au	1) [Au] cat. 1 h 2) 20% L-proline, 1 h	100%	95%

Figure 2. TA−Au-promoted catalysis relay. Reaction conditions: **1a** (0.5 mmol), Au catalyst (5 mol %), L-proline (20 mol %) in dichloromethane (0.4 M). Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Other gold catalysts, such as JohnPhosAuCl/AgOTf and XphosAuCl/AgOTf, were also screened in one-pot conditions, giving less than 15% yield of desired product. No desired allene intermediate was observed with 10% TfOH.

With $PPh_3AuCl/AgOTf$ as catalyst, **1a** was completely consumed within 2 h. However, very little dienal **3a** was obtained (<10%). Significant amounts of decomposition were observed as well as the 1,3-rearrangement described in Toste's previous report.[15] Switching the gold catalyst to silver-free PPh_3AuNTf_2 gave slower reaction kinetics, which suggested the coordination of amine significantly decreased gold catalyst reactivity. The combination of gold−oxonium catalysts and proline gave no reaction at all after 24 h, once again demonstrating a competitive binding of the secondary amine toward gold cation. In the case of TA−Au, lower reactivity was observed in the presence of amine catalysts (55% conversion of **1a** after 2 h). However, the reaction was very clean with dienal **3a** being observed as the only product (90% brsm yield,

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3aa:**3ab** = 2:1). Considering that TA−Au could selectively promote the reaction to the allene intermediate, we tested the reaction in a one-pot, two-step fashion: (A) treating **1a** with TA−Au only and monitoring the reaction by TLC and (B) adding proline into the reaction when **1a** was all consumed. With this revised procedure, **3a** was formed in nearly quantitive yield (>95%).

Since allene **2a** was formed during the reaction, good kinetic selectivity can be observed during the tautomerization step. For example, quenching the dienal reaction mixtures **3a** with $NaBH_4$ gave the isomer **4ac** and **4aa** (**dienol products**) as the two major products with 65% and 15% isolated yields correspondingly. Notably, the conjugated dienals **3** can undergo rapid isomerization upon column chromatography. Thus, to isolate pure isomers, reduction of the carbonyl is necessary. With this optimal catalytic relay condition in hand, we explored the reaction substrate scope.

As shown in Figure 3, this reaction tolerates a wide substrate scope, giving the desired dienals (diene alcohols) in excellent

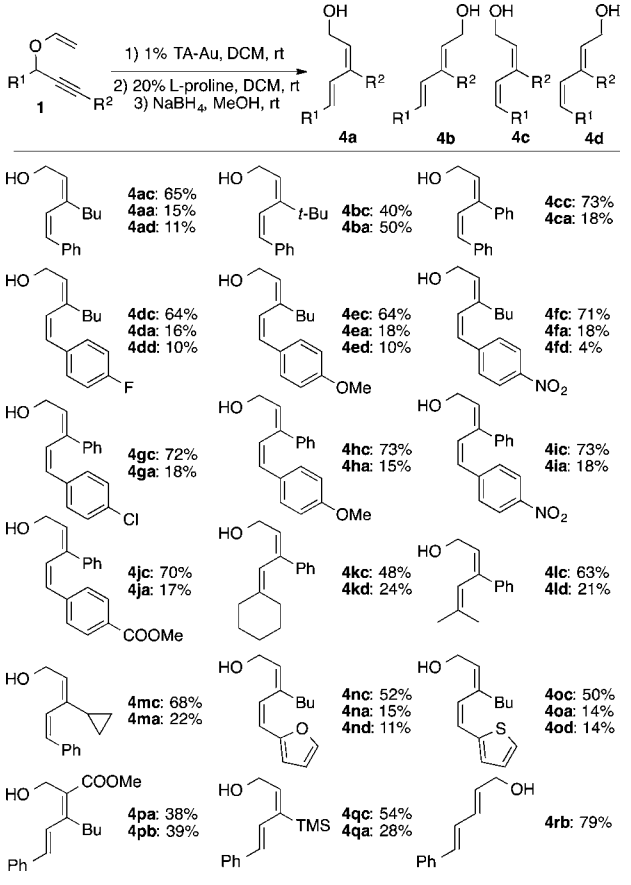

Figure 3. Reaction scope. General reaction conditions: **1** (0.5 mmol), TA−Au catalyst (1 mol %) in dichloromethane (0.4 M) at rt, followed by L-proline (20 mol %). The reaction was then diluted with 2 mL of MeOH and quenched by $NaBH_4$ (0.5 mmol). Isolated yields are shown.

yields (combining all isomers) in almost all cases. The $NaBH_4$ quench at the early stage of isomerization helped to trap the major kinetic isomers, allowing isolation in good yield for most of the cases. Various substituent groups are tolerated at the R^1 position, including alkyl (such as **4k**, **4l**), aryl (such as **4a**−**4j**), and heterocycles (such as **4n**, **4o**). Similarly, aryl and alkyl groups are both suitable for terminal-alkyne R^2 position. Electron-donating and electron-withdrawing groups on both R^1 and R^2 positions do not influence the overall reactivity. Notably, some special substituted groups, such as cyclopropyl (**4m**) and TMS (**4q**), could be easily incorporated into the R^2 position. Finally, terminal alkyne also worked well in this transformation, giving the simple dienal in good overall yield (**4rb**). The broad functional group tolerability highlighted the great advantage of this new method over other literature-reported approaches in preparing substituted dienals.

The stereoselectivity (*Z*/*E* isomers of double bond) is still an important factor for this reaction. As mentioned above, during our investigation, isomerization to thermodynamically stable isomers (or mixtures) occurred even during chromatography and rotary evaporation. Thus, stereoselectivity for the double bond at the 5−6 positions can be easily achieved through isomerization. By simply extending reaction time (12 h), 5,6-trans double-bond products (**a** and **b**) were obtained in all applicable cases, as shown in Figure 3. With substituted groups at the C-4 position (from terminal alkyne R^2 group), the ratio between isomer **a** and **b** will be greatly influenced depending on the size of the R^2 group. As shown in Figure 4A, while R^2 = *n*-

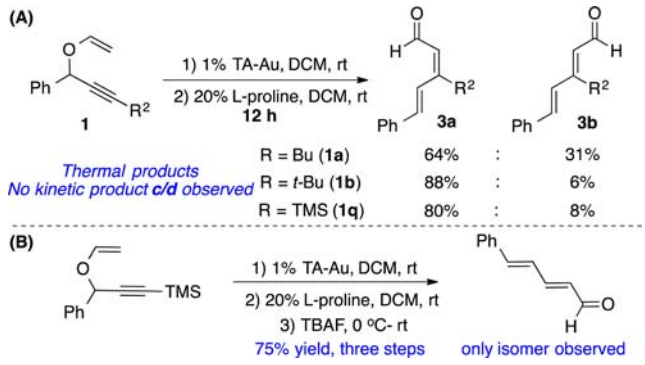

Figure 4. TMS as removable conformational control group.

Bu gave a modest **a**:**b** ratio (2:1), both *t*-Bu and TMS greatly improved the stereoselectivity, giving **a**:**b** >10:1. Notably, the tolerance for TMS-substituted alkynes provides excellent conformational control (12:1 ratio). Removal of the TMS group gave the all *trans*−*trans* dienal as the only isomer observed. Thus, with this removable TMS group, both double-bond conformers **a** and **b** could be achieved with high selectivity.

In conclusion, we report the application of gold catalysis and amine catalysis relay as a new approach to achieve the synthesis of substituted, conjugated-dienals with high efficiency. The chemoselective TA−Au catalyst was identified as the optimal choice while other gold catalyst gave poor to modest yields. The wide substrate tolerance, mild reaction conditions, and high efficiency (1% loading) hold promise for future one-pot designs using readily available propargylvinyl ethers as starting materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR data. 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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