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Gold-Catalyzed 1,3-Transposition of Ynones

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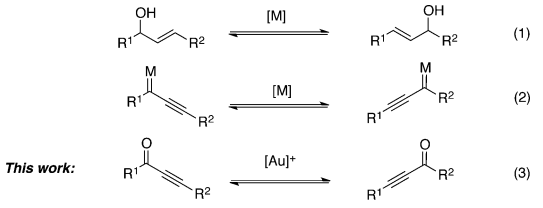
Supporting Information

ABSTRACT: An efficient, regioselective gold-catalyzed 1,3-transposition reaction of ynones and diynones has been developed. It was found that stereoelectronic (interrupted conjugation) and electronic (extended conjugation) factors could efficiently govern the regioselectivity of this thermodynamically controlled transformation. The produced conjugated diynones were efficiently transformed into diverse alkyne-substituted five- and six-membered heterocycles.

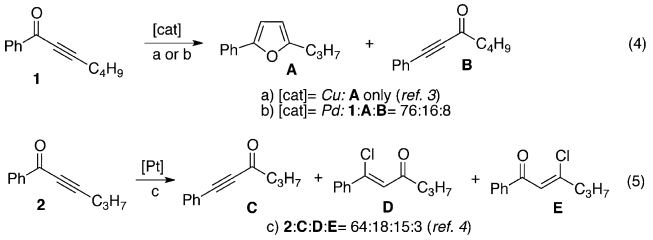
Transition-metal-catalyzed transposition reactions are useful tools in organic synthesis. For instance, the metal-catalyzed 1,3-transposition of allylic alcohols is a well-established method (Scheme 1, eq 1) that has been successfully employed in the synthesis of natural products.[1] Likewise, the metallotropic 1,3-shift has been used for assembly of acyclic, cyclic, and polycyclic compounds (Scheme 1, eq 2).[2] Herein we report an efficient gold-catalyzed 1,3-transposition of ynones (Scheme 1, eq 3).

Scheme 1. Metal-Catalyzed 1,3-Transposition of Functional Groups



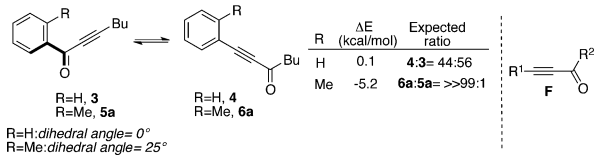
During our ongoing studies of transition-metal-catalyzed cycloisomerization of ynones toward heterocycles,[3] we found an interesting transformation: ynone **1**, which in the presence of a copper catalyst underwent a selective cycloisomerization reaction into furan **A**, under palladium catalysis produced detectable amounts of regioisomeric ynone **B** (Scheme 2, eq 4). In fact, unselective low-yielding transposition reaction of ynones has been reported previously.[4] Thus, in the presence of a Pt catalyst, ynone **2** was transformed into a mixture of transposed ynone **C** and isomeric hydrochlorinated products **D** and **E** (Scheme 2, eq 5). The low efficiency of this reaction was attributed to an equilibrium between **2** and **C**.[4] We thought that the development of regioselective and efficient 1,3-transposition of ynones would be worthwhile[5] since this moiety is widely used as an intermediate in the total synthesis of natural products[6] and in the construction of a variety of heterocyclic scaffolds.[7] First, in order to identify the factors that would allow control of the position of the thermodynamic equilibrium between differently substituted ynones, we computed the ground-state energies of **3** and **4** (Scheme 3).[8] It was found that **3**, in which the phenyl ring is conjugated with the carbonyl group, is nearly as stable as the transposed product **4** (0.1 kcal/mol;[9] Scheme 3), thus predicting a 44:56 product ratio.[10] We also found that steric (small vs big groups) and electronic (electron-withdrawing vs electron-releasing groups) factors at R^1 and R^2 of ynone **F** do not have significant effects on the stability of the isomers and consequently would not control the regioselectivity of this reaction (Scheme 3).[10] Next, we thought that incorporation of an *o*-tolyl group (**5a**, R = Me) would force the carbonyl group out of plane, thus preventing its conjugation with the phenyl moiety and hence destabilizing **5a**. In contrast, there would be conjugation between the phenyl ring and the triple bond in regioisomer **6a**. Therefore, shifting the equilibrium toward the more stable isomer **6a** by engaging this stereoelectronic handle seemed feasible. Indeed, computations validated this hypothesis, showing a dihedral angle of 25° in **5a** and thus predicting the release of ca. 5 kcal/mol upon transposition, which would ensure the full conversion of ynone **5a** to thermodynamically more stable isomer **6a** (Scheme 3).

Scheme 2. Non-regioselective 1,3-Transposition of Ynones[a]



[a]Conditions: (a) CuI (5 mol %), DMA/Et_3N (7:1), 100 °C. (b) $Pd_2(dba)_3$ (5 mol %), TDMPP (20 mol %), PTSA (50 mol %), DMF, 80 °C. (c) $PtCl_4$ (10 mol %), EtOAc, reflux. TDMPP = Tris(2,5-dimethoxyphenyl)phosphine, PTSA = *p*-toluenesulfonic acid.

Scheme 3. Computational Predictions of Regioselectivity in the 1,3-Transposition Reaction of Ynones



Inspired by computational predictions, we examined the transposition reaction of **5a** in the presence of different metals.

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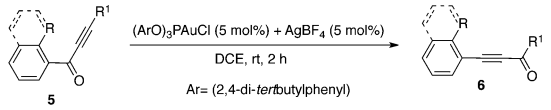
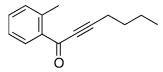
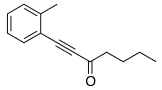
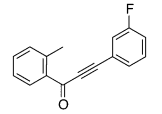
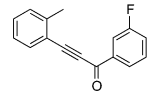
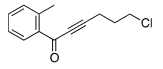
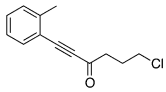
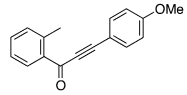
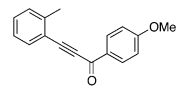
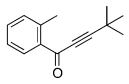
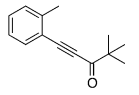
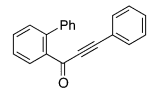
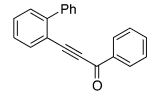
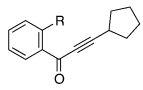
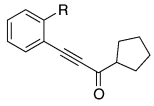
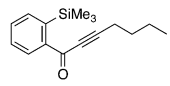
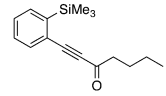
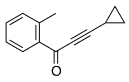
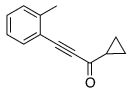
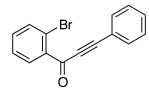
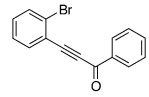
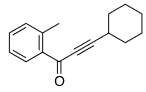
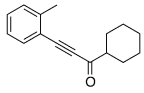
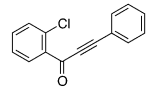
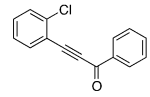
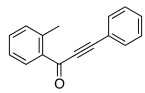
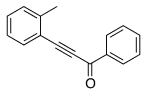
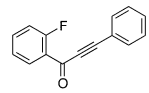
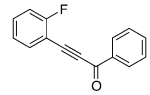
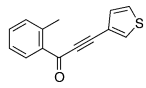
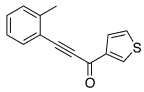
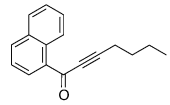
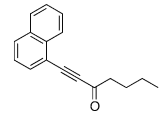
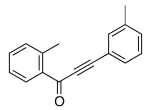
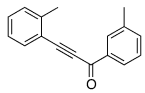
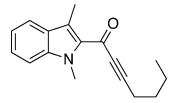
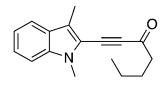
Table 1. Substrate Scope in the Gold-Catalyzed 1,3-Transposition of Ynones



entry	5	6	Yield %[a]	entry	5	6	Yield %[a]
1	 **5a**	 **6a**	95	10	 **5j**	 **6j**	97
2	 **5b**	 **6b**	90	11	 **5k**	 **6k**	81
3	 **5c**	 **6c**	98	12	 **5l**	 **6l**	91
4	 R=H **5d** R=Me **5d'**	 R=H, 89 **6d:5d**=38:62[b,c] R= Me, 91 **6d'** only		13	 **5m**	 **6m**	91[d]
5	 **5e**	 **6e**	90	14	 **5n**	 **6n**	92
6	 **5f**	 **6f**	79	15	 **5o**	 **6o**	89
7	 **5g**	 **6g**	88	16	 **5p**	 **6p**	83
8	 **5h**	 **6h**	88	17	 **5q**	 **6q**	85
9	 **5i**	 **6i**	92	18	 **5r**	 **6r**	90

[a]Isolated yields. [b]Overnight at rt. [c]3 h at 70 °C; **6d:5d** = 51:49. [d]IPrAuCl (5 mol %) + $AgSbF_6$ (5 mol %) was used as the catalyst.

Our optimization study[8] indicated that the use of a cationic gold catalyst such as chloro[tris(2,4-di-*tert*-butylphenyl)phosphite] gold with tetrafluoroborate as the counterion[11] was the best choice for efficient transformation of **5a** into the transposed isomer **6a**. With the optimized conditions in hand, we examined the scope of the *o*-tolyl-type stereoelectronic handle on the transposition of differently substituted 1,3-ynones (Table 1). Thus, ynones **5a**−**c** bearing acyclic substituents reacted smoothly to produce the rearranged products **6a**−**c** (entries 1−3). As expected (vide supra),[10] the reaction of ynone **5d** (R = H) was not regioselective, producing a 36:64 mixture of isomers **6d** and **5d** (entry 4). However, the analogous substrate **5d′** (R = Me) afforded transposed isomer **6d′** exclusively in 91% yield. Likewise, substrates **5e** and **5f** bearing three- and six-membered carbocycles afforded the transposed products in good to excellent yields (entries 5 and 6). Phenyl- and thiophenyl-substituted ynones **5g** and **5h** were also competent reactants in this transformation (entries 7 and 8). As expected, the methyl substituent at the ortho position of the phenyl ring of **5i** governed the regioselectivity of the transposition reaction over the meta-substituted phenyl to produce product **6i** in excellent yield (entry 9). Transposition of F- and OMe-containing ynones proceeded uneventfully as well (entries 10 and 11). As expected, not only a methyl substituent but also a variety of other groups at the ortho position of the ynone phenyl group were effective in imposing the controlling stereoelectronic effect. Thus, aryl ynones **5l**−**q** bearing phenyl (entry 12), trimethylsilyl (entry 13),[12] halogen (entries 14−16), and naphthyl (entry 17) groups showed excellent regioselectivity, affording the rearranged products **6l**−**q** exclusively in high to excellent yields. Notably, 3-methylated indole **5r** could also be efficiently employed in this reaction to produce **6r** (entry 18).[13]

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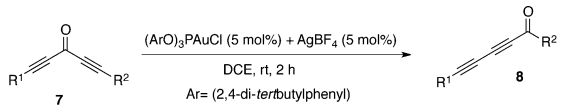
Having established the stereoelectronically controlled transposition of 1,3-ynones, we wondered whether extended conjugation could possibly serve as a regioselectivity-controlling factor in this transformation. If so, then easily accessible skipped diynones **7** could undergo the 1,3-transposition reaction in the presence of a gold catalyst to give valuable conjugated isomers **8** (Table 2). Computations predicted this electronic factor to be overwhelming, as it would release ca. 8 kcal/mol toward the thermodynamically more favored conjugated isomer **8a**.[10] To our delight, **7a** reacted smoothly under the standard conditions to afford **8a** in 88% yield (entry 1). Likewise, diynone **7b** possessing a phenyl group was smoothly transposed into **8b** (entry 2). Naturally, we were next interested in the development of a 1,3-transposition reaction leading toward synthetically more attractive unsymmetrical conjugated diynones. First, we speculated that when diynone **7c** bearing an *o*-tolyl moiety was employed, the stereoelectronic effect (vide supra) would render a selective transposition toward the phenyl group, thus forming **8c** as the sole product (entry 3). However, when this reaction was performed at room temperature, both alkyne moieties of **7c** were involved in the transposition reaction to produce a 58:42 mixture of rearranged products **8c** and **8c′**. Gratifyingly, at elevated temperature the thermodynamically more stable isomer **8c** was obtained exclusively. Next, we speculated that employing a skipped diynone possessing a bulky triisopropylsilyl (TIPS) terminus would impose steric hindrance at the proximal triple bond, and as a result, the distal alkyne would selectively be activated by the gold catalyst toward the 1,3-transposition reaction. Indeed, skipped diynones **7d–h** efficiently afforded the unsymmetrical conjugated diynones **8d–h** bearing a variety of alkyl, aryl, and heteroaryl substituents (entries 4–8).

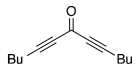
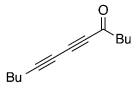
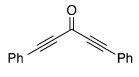
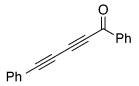
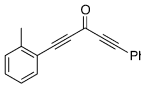
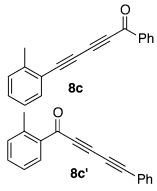
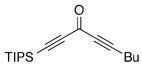
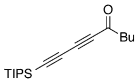
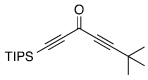
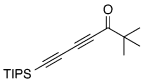
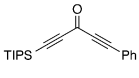
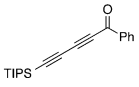
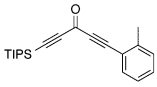
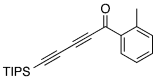
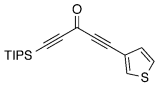
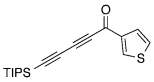
To determine whether this transformation proceeds with skeletal rearrangement, which is often observed in gold-catalyzed transformations,[11d] the C1-labeled ynone **9** was prepared and subjected to the standard reaction conditions (Scheme 4). Thus, the C1-1,3-transposed isomer **10** possessing the labeled carbon at the alkyne moiety was formed. This observation indicates that the ynone transposition reaction does not involve C–C bond disconnection and most likely proceeds through the intermediacy of a four-membered heterocycle ***i***.[4]

Finally, after developing the regioselective gold-catalyzed 1,3-transposition reaction, we examined the possibility of using the obtained conjugated diynones to synthesize heterocyclic scaffolds bearing an alkyne moiety (Scheme 5). Indeed, the addition of hydrazine to diynone **8e** afforded pyrazole **11** in moderate yield,[14] and the cycloaddition reaction of **8f** with sodium azide produced triazole **12** in 71% yield;[7b] also, the reaction of **8f** with benzamidine hydrochloride furnished C4-alkynylated pyrimidine **13**,[7c,d] and the condensation reaction of **8f** with ethyl acetoacetate and ammonium acetate produced alkynylated pyridine **14** in 78% yield.[7c]

In summary, we have developed an efficient thermodynamically controlled 1,3-transposition of ynones and diynones. We found that stereoelectronic (interrupted conjugation) and electronic (extended conjugation) effects can efficiently control the regioselectivity of this reaction. The synthetic usefulness of obtained unsymmetrical diynones was demonstrated by efficient

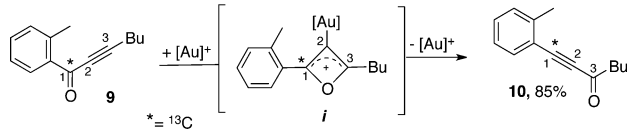
Table 2. Substrate Scope in the Gold-Catalyzed 1,3-Transposition of Skipped Diynones



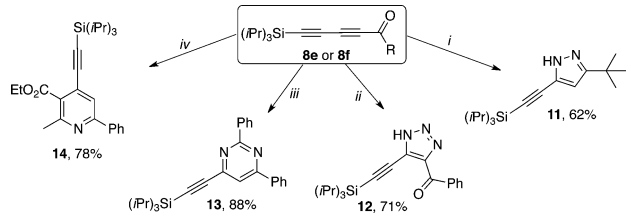
entry	7		8		Yield %[a]
1		**7a**		**8a**	88
2		**7b**		**8b**	91
3		**7c**	 at rt, **8c**:**8c′**= 58:42 at 100 C, **8c**:**8c′**= 100:0	**8c**	79[b]
4[c]		**7d**		**8d**	86
5		**7e**		**8e**	83
6		**7f**		**8f**	93
7		**7g**		**8g**	91
8		**7h**		**8h**	90[b]

[a]Isolated yields. [b]The yield of the reaction performed at 100 °C is shown. [c]Trimethylsilyl and triethylsilyl analogues of the 1,3-ynone did not work under the optimized conditions, and the substrates were recovered intact.

Scheme 4. Isotope-Labeling Experiment



Scheme 5. Synthetic Utility of the Obtained Diynones[a]



[a]Conditions: (*i*) NH_2NH_2 (3.0 equiv), MeCN, rt. (*ii*) NaN_3 (1.1 equiv), DMF, rt. (*iii*) benzamidine hydrochloide (1.2 equiv), Na_2CO_3 (2.4 equiv), MeCN/H_2O = 7:1, 80 °C. (*iv*) Ethyl acetoacetate (1.7 equiv), NH_4OAc (5.0 equiv), EtOH, reflux.

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synthesis of various five- and six-membered heterocyclic scaffolds possessing an alkyne moiety.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization 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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(8) See the Supporting Information for details.

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(10) The experimental ratios were in good accordance with the predicted ratios. See the Supporting Information for details.

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(12) No product was observed under standard reaction conditions.

(13) Simple enonynes did not isomerize to enynones under the reaction conditions even at elevated temperatures.

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