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Expanding the Scope of the Gold(I)-Catalyzed Rautenstrauch Rearrangement: Protic Additives

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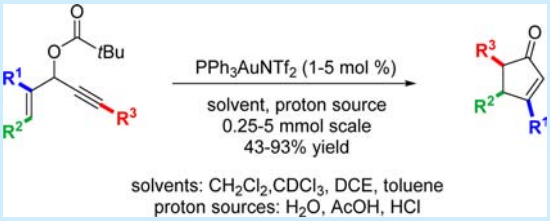
Supporting Information

ABSTRACT: The synthesis of substituted 2-cyclopentenones using a commercially available gold(I) catalyst is described under flexible reaction conditions. During the course of our investigations, we discovered that using a proton source as an additive is required to obtain the desired substituted cyclopentenones in good yields.

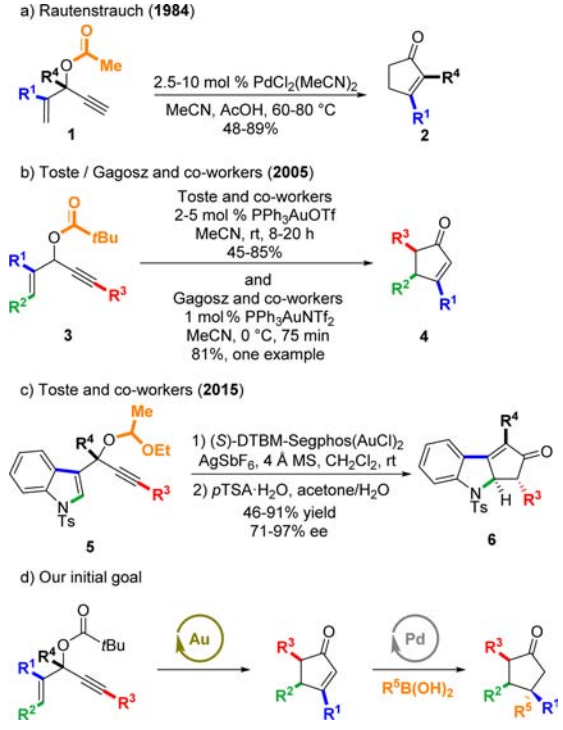


In 2013, we reported a tandem Meyer−Schuster rearrangement/enantioselective conjugate addition for the one-pot asymmetric synthesis of β-disubstituted ketones from racemic propargylic alcohols.[1] With these results in hand, we envisioned extending this concept toward the preparation of enantioenriched 2-cyclopentanones using the Rautenstrauch rearrangement followed by a Pd(II)-catalyzed asymmetric conjugate addition.[2−4]

Synthesis of cyclopentenones from acyclic precursors has been achieved through efficient catalytic processes.[5] A variety of gold catalyzed cyclizations have been reported for the synthesis of cyclopentenones.[6−10] For example, Rautenstrauch pioneered the transformation of 1-ethynyl-2-propargyl acetate derivatives **1** into 2-cyclopentenones **2** mediated by a palladium(II) catalyst in 1984 (Scheme 1a).[11] In 2005, Toste (Scheme 1b)[12] as well as Gagosz[13] reported that gold(I) can catalyze the transformation of similar substrates **3** into the related cyclopentenones **4** in a more efficient manner than when palladium is employed. They demonstrated the tolerance of this reaction to a diverse substitution pattern as well as its sensitivity to the reaction conditions. Indeed, only dilute solutions of substrate in MeCN afforded the desired cyclopentenone products in good yields, while dichloromethane, THF, or methanol afforded lower yields. They also demonstrated that chirality transfer occurred when enantioenriched 1-ethynyl-2-propenyl pivaloates were employed as starting materials. In 2015, Toste disclosed an asymmetric dearomative version of this rearrangement using acetals **5** for the preparation of indole derivatives **6** (Scheme 1c).[14] Very recently, Occhiato and co-workers reported a gold-catalyzed reaction similar to the Rautenstrauch rearrangement generating cyclopenta[*b*]indol-1-ones.[15]

To explore a one-pot Rautenstrauch rearrangement−asymmetric conjugate addition (Scheme 1d), we aimed to use DCE since Stoltz and co-workers showed it to be the optimal solvent for the asymmetric conjugate addition.[2−4] In this regard, our investigations in modifying the parameters of the Rautenstrauch rearrangement in order to suit this goal led to the development of modified conditions for this gold-catalyzed reaction. Herein, we report a versatile set of reaction conditions for the Rautenstrauch rearrangement which allow for the straightforward construction of complex cyclopentenone structures.

Scheme 1. Reported Rautenstrauch Rearrangements



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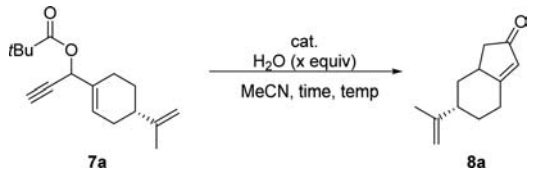
To initiate our investigation, we independently attempted the Rautenstrauch rearrangement under the two sets of conditions reported by Toste[12] and Gagosz[13] and co-workers on the transformation of propargyl pivalate ester **7a** into cyclopentenone derivative **8b**. Toste's group reported a 63% yield with PPh_3AuOTf (Table 1, entry 1) and Gagosz's group reported

Table 1. Reproduction of Gagosz's Results



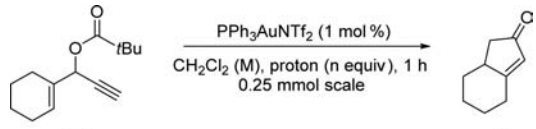
7a 8a

entry	cat. (mol %)	temp (°C)	time (min)	scale (mmol)	water (equiv)	yield (%)
1 (Toste)	PPh_3AuOTf (2 mol %)	rt	600	0.38	nd	82
2 (Gagosz)	PPh_3AuNTf_2 (1 mol %)	5	75	1.0	nd	81
3	PPh_3AuNTf_2 (1 mol %)	rt	60	0.25		48
4	PPh_3AuNTf_2 (1 mol %)	rt	60	0.25	1	74

an 81% yield using PPh_3AuNTf_2 with a notably shorter reaction time (75 min, entry 2). During our early efforts, we noted that previously reported conditions used reagent-grade MeCN. We found that running the reaction in MeCN distilled over CaH_2 afforded **8b** in 48% yield (Table 1, entry 3). We were further inspired by the report of Zhang and Wang which described a closely related Au-mediated Nazarov-type cyclization of enynyl acetates in CH_2Cl_2.[16] They observed that wet solvent was critical to obtain the desired product in good yield. Following this report, we ran the reaction with dry solvent and purposely added a known amount of a proton source to examine its influence on the efficiency. We anticipated that a proton is needed for the proposed hydrolysis of the enol ester intermediate (Scheme 3, **14**).[17,18] Upon addition of 1 equiv of water to the reaction mixture, the product was obtained in 74% yield (Table 1, entry 4).[19] We continued our investigation using anhydrous solvent with a controlled amount of added water in order to quantify the optimal amount of the moisture for the reaction.

In our work, we decided to test water and acetic acid (used by Rautenstrauch) as additives in the transformation of enynyl ester **7b** into cyclopentenones **8b** (Table 2). We optimized these conditions using CH_2Cl_2 or DCE, as they would be suited for the development of the desired tandem reaction involving an asymmetric conjugate addition.[2−4,20] In the absence of water, product **8b** was formed in 44% yield by NMR (Table 2, entry 1), and we observed formation of products of a polymeric nature. Upon the addition of 1 equiv of water, the yield increased to 83% (Table 2, entry 2). We then tested acetic acid as a proton source. The addition of 1 equiv resulted in 59% yield by NMR (Table 2, entry 3), but the yield improved when 2 equiv of acetic acid was added (Table 2, entry 4). In addition, the low concentration required for the reaction hampered its feasibility on a large scale. We observed that a higher concentration negatively influenced the reaction outcome when water was used, giving a 67% NMR yield (Table 2, entry 5). However, we obtained good yields of the desired cyclopentenone when AcOH was used as an additive at 0.25 M on a 5 mmol scale (Table 2, entries 6 and 7), which

Table 2. Reaction Condition Screening



7b 8b

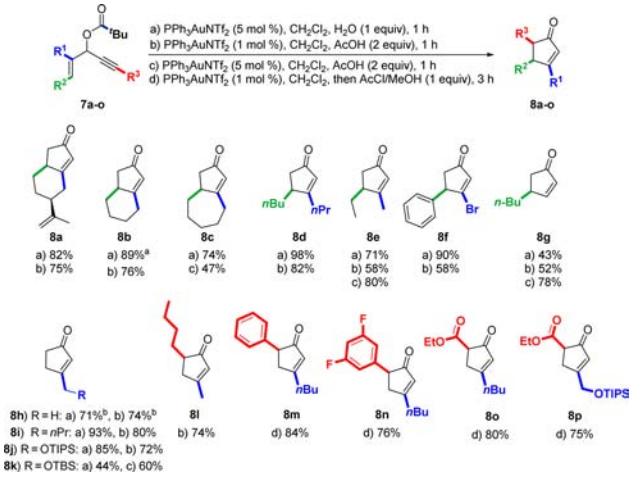
entry	scale (mmol)	C (mol/L)	proton source (equiv)	yield[a,b] (%)
1	0.25	0.063	none	44
2	0.25	0.063	water (1)	83
3	0.25	0.063	AcOH (1)	59
4	0.25	0.063	AcOH (2)	81 (76)
5	0.25	0.25	water (1)	67
6	0.25	0.25	AcOH (2)	77
7	5	0.25	AcOH (2)	(80)

[a]Yields were determined by ^1H NMR spectroscopy analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b]Isolated yields in parentheses.

highlights the scalability of this reaction under relatively concentrated conditions.

Having now developed reaction conditions that would be better suited to the tandem reaction, we investigated the scope and limitations (Scheme 2). The first set of substrates bears alkyl

Scheme 2. Rautenstrauch Rearrangement: Reaction Scope



[a]See the Supporting Information for reaction details. [b]Yields were determined by ^1H NMR spectroscopy analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

groups at R^1 and R^2. Products **8a** and **8b** were afforded in good yields with water (*conditions a*) or acetic acid (*conditions b*) as additives. Employing a cycloheptane ring led to a slight decrease in yield in product **8c** when *conditions a* were used, and the reaction became messy under *conditions b*. When substituents R^1 and R^2 were linear alkyl chains, yields were generally good as exemplified with enones **8d** and **8e**. The yield of **8e** was somewhat lower, potentially due to its high volatility. A halide on substituent R^1 and an aromatic ring as substituent R^2 in **8f** were also tolerated in this reaction and afforded a high yield under *conditions a* and a moderate yield in the presence of acetic acid (*conditions b*). As exemplified by **8g**, omission of substituent R^1 afforded generally lower yield compared to other products. Nevertheless, the yield could be increased by employing a higher catalyst loading in the presence of acetic acid (*conditions c*). Interestingly, omission of the substituent R^2 did not affect the

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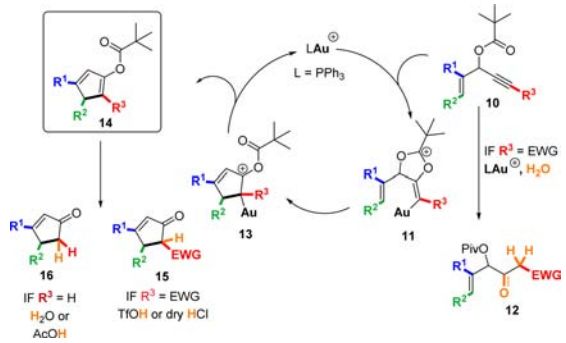
reaction outcome. A methyl (**8h**) or butyl (**8i**) side chain was well tolerated and afforded high yields in the presence of added water (*conditions a*) or acetic acid (*conditions b*). Alternatively, silyl-protected alcohols successfully underwent this transformation under *conditions a*. The increased stability of the TIPS-protected alcohol (**8j**) compared to the TBS protecting group (**8k**) might explain the difference in yield between these reactions.[21] Finally, a substituent could be introduced at the R^3 position. While a simple alkyl chain (**8l**) was successful in the reaction, aromatics (**8m,n**) and ethyl ester (**8o,p**) required a modification of the reaction conditions. Indeed, we observed that the presence of water in the reaction mixture afforded an undesired alkyne hydration product (Scheme 3, **12**) leading to

Scheme 3. Reaction Mechanism

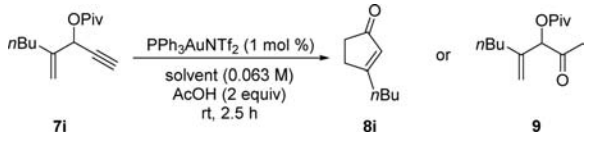


decreased yields. The reaction was then run under anhydrous conditions, and formation of an isolable pivalic enol ester was detected (Scheme 3, **14**). Addition of anhydrous HCl (generated from acetyl chloride and methanol) after consumption of the starting material unveiled the desired product in good yield. This product represents an unprecedented substituted cyclopentenone scaffold.[22]

We decided to explore the tolerance of this reaction to different solvents in order to broaden its utility. Generally, chlorinated solvents (CH_2Cl_2, $CHCl_3$, and DCE) afforded the desired product **8i** in high yield (Table 3, entries 1−3). In turn, ethereal solvents (MTBE, Et_2O, THF, dioxane) proved unsuitable for this reaction since the conversion and the yield were low (entries 4−7). Toluene, acetonitrile, and ethyl acetate led to a decent conversion and reasonable to low yields of product **8i** (entries 8 and 9). Interestingly, polar solvents such as acetone and methanol, where the water content was not controlled, showed good conversion but predominant formation of the undesired hydration product **9** (entries 10 and 11).

After improvement of the reaction conditions and exploration of the reaction scope, our developments can be evaluated in light of the reaction mechanism proposed by Toste and co-workers.[12] In this mechanism, the first event is complexation of the alkyne of **10** by the cationic gold catalyst, which triggers an intramolecular nucleophilic attack of the carbonyl of the pivalic ester to afford the cationic intermediate **11**.[23,24] In the cases where R^3 was an electrophilic group, like an ester or an aromatic ring, hydration afforded the undesired product **12**. The intermediate **11** then undergoes a Nazarov-like rearrangement to form the 5-membered ring **13** followed by elimination to give the substituted cyclopentadiene **14**. We observed that the substituent R^3 modulated the stability of this cyclopentadiene ring, and this determines the conditions necessary to successfully run the Rautenstrauch reaction. When R^3 was an electron-withdrawing group or an aromatic ring, the enol ester **14** was stable

Table 3. Solvent Screening



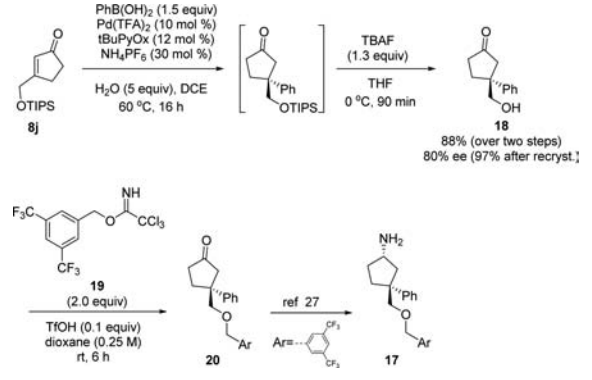
entry	solvent	conv[b] (%)	product **8i** (% yield)[c]	hydration product **9** (% yield)[c]
1	CH_2Cl_2[a]	100	96	0
2	$CDCl_3$[a]	100	87	0
3	DCE[a]	100	94	0
4	MTBE	14	9	4
5	Et_2O	38	14	8
6	THF[a]	18	14	3
7	dioxane[a]	19	0	0
8	toluene[a]	77	57	11
9	MeCN[a]	56	43	0
10	EtOAc	52	36	4
11	acetone	80	10	64
12	MeOH	100	0	>99

[a]Solvent distilled over drying agent. [b]See the Supporting Information for reaction details. [c]Yields were determined by ^1H NMR spectroscopy analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

and the reaction could be run in the absence of water, but a strong acid was required to liberate the desired cyclopentenones **15** at the end of the reaction. When R^3 was a hydrogen, the enol ester was less stable, and a proton source like water or a weak acid was required to afford the cyclopentenones **16** in good yields. The poor yields at the beginning of our investigations were due to unknown side products of polymeric nature and could be avoided by the addition of water from the outset of the reaction.

To demonstrate the usefulness of the revamped conditions for the Rautenstrauch rearrangement, we prepared an intermediate in the synthesis of the cyclopentylamine **17**, a new antidepressant exhibiting dual NK_1R antagonism and SERT inhibition.[25,26] Our synthesis utilized a palladium-mediated asymmetric conjugate addition on the substrate **8j**, forming the quaternary carbon in product **18** with the desired configuration (Scheme 4).[2−4] The

Scheme 4. Formal Synthesis of Cyclopentylamine 17



silyl ether was not isolated, and the TIPS protecting group was removed using tetrabutylammonium fluoride (TBAF). The configuration of the quaternary center in **18** was unambiguously determined by X-ray diffraction analysis. Benzylation with trichloroacetimidate **19**[27] yielded the benzyl ether product **20**, which was a known intermediate toward this cyclopentylamine

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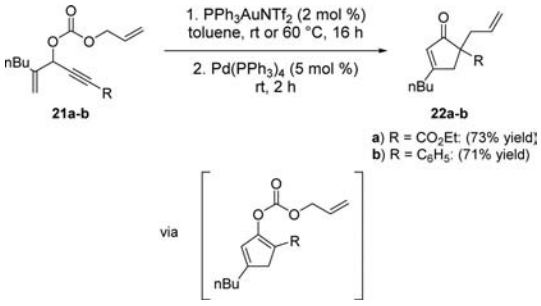
target.[25,26] This reaction sequence would be a novel and flexible enantioselective entry in to this promising class of API allowing a convergent strategy.

Finally, we imagined that the Rautenstrauch rearrangement could be incorporated in a two-step process with a Tsuji–Trost allylation[28,29] to access functionalized chiral cyclopentenones (Scheme 5). Work by Clark and co-workers[30] have already

Scheme 5. Rautenstrauch–Allylation Method



illustrated this step by synthesizing an enantiomeric α-quaternary carbon bearing 2-indanones. This strategy could be applied to the cyclopentenone core structure. According to our preliminatry results, this transformation required ester (**21a**) or aryl (**21b**) substitution on the alkyne to generate a stable enol carbonate intermediate that could be immediately reacted in a one-pot/two-step fashion with $Pd(PPh_3)_4$ to afford racemic allylated cyclopentenones **22a,b** in good yield. The preliminary attempts toward an enantioselective variant resulted in low ee's and required isolation of the enol ester intermediate.[31]

In conclusion, we have developed a set of mild reaction conditions for the Rautenstrauch rearrangement. It represents a versatile route to new cyclopentenone building blocks owing to the addition of a proton source into the reaction mixture. In addition, we efficiently prepared the backbone of a biologically active cyclopentenone via a palladium-mediated enantioselective conjugated addition in good yield and straightforward fashion. We have also shown that these new cyclopentenones are competent substrates for the challenging enantioselective palladium-mediated conjugate addition yielding quaternary centers. Finally, we showed that the Rautenstrauch rearrangement can be combined with the Tsuji–Trost allylation to yield useful chiral cyclopentenone building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02505.

Experimental procedures and full compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(31) Details are included in the Supporting Information.

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