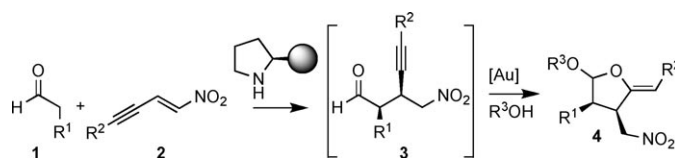


Enantioselective One-Pot Organocatalytic Michael Addition/Gold-Catalyzed Tandem Acetalization/Cyclization**

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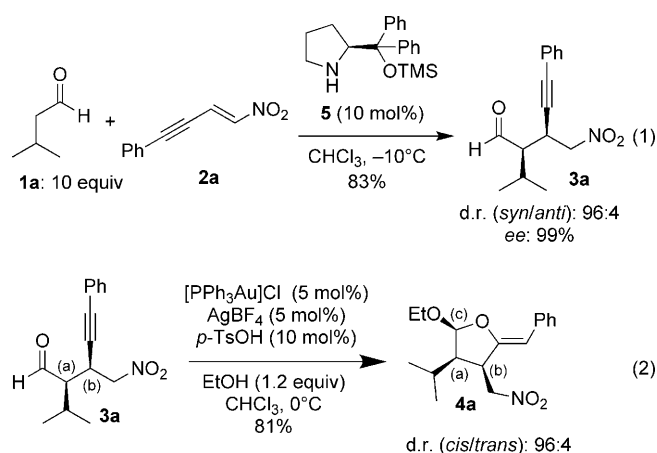
The development of sustainable processes is one of the main priorities for preparative chemistry in the 21st century.^[1] For several decades, a large effort has been devoted to the development of new, efficient catalytic transformations to achieve high molecular complexity from simple starting materials. Consequently, the combination of very efficient catalytic methods (e.g., organocatalysis^[2] and gold catalysis^[3]) in a tandem or one-pot process^[4] should provide a powerful tool for saving both energy and resources. These two powerful methodologies have already been used in total synthesis, although at different steps of the synthesis.^[5]

The asymmetric conjugate addition of aldehydes to nitroolefins catalyzed by a pyrrolidine derivative is an efficient method for the synthesis of γ -nitrocarbonyl building blocks.^[6] Among various nitroolefins, β -nitrostyrenes are the most widely used because of their possible conversion into substituted pyrrolidines,^[7] butyrolactones,^[8] or cyclopentanes.^[9] Other functionalized nitroolefins^[10] have also been used, and some of them applied in target-oriented synthesis.^[11] However, in all cases, the synthesis of the nitrocarbonyl compounds and their subsequent conversions were carried out in a sequential way. Knowing the compatibility of amines and gold catalysts,^[12] and our recent results on 1,4-additions of aldehydes to nitrodienes,^[13] as well as gold-catalyzed transformations of functionalized alkynes,^[14] we envisaged a one-pot process consisting of an enantioselective organocatalytic Michael addition of aldehydes **1** to nitro-alkyne **2**, and a subsequent gold-catalyzed tandem acetalization/cyclization of the corresponding adduct **3** by electrophilic activation^[3] of the triple bond. Herein we disclose our results on this one-pot reaction which leads to nitro-substituted tetrahydrofuran ethers **4** with high diastereo- and enantioselectivities (Scheme 1).



Scheme 1. Proposal: One-pot organocatalysis/gold-catalysis sequence.

First, we optimized the organocatalyzed conjugate addition of isovaleraldehyde (**1a**) to the phenyl-substituted nitro-alkyne **2a** in the presence of diphenylprolinol silyl ether **5**. The best conditions appeared to be 10 equivalents of aldehyde in the presence of 10 mol% of organocatalyst **5** at -10°C [Eq. (1) in Scheme 2 and see the Supporting Information].



Scheme 2. Optimization of the sequential reaction. TMS = trimethylsilyl, *p*-Ts = *para*-toluene sulfonyl.

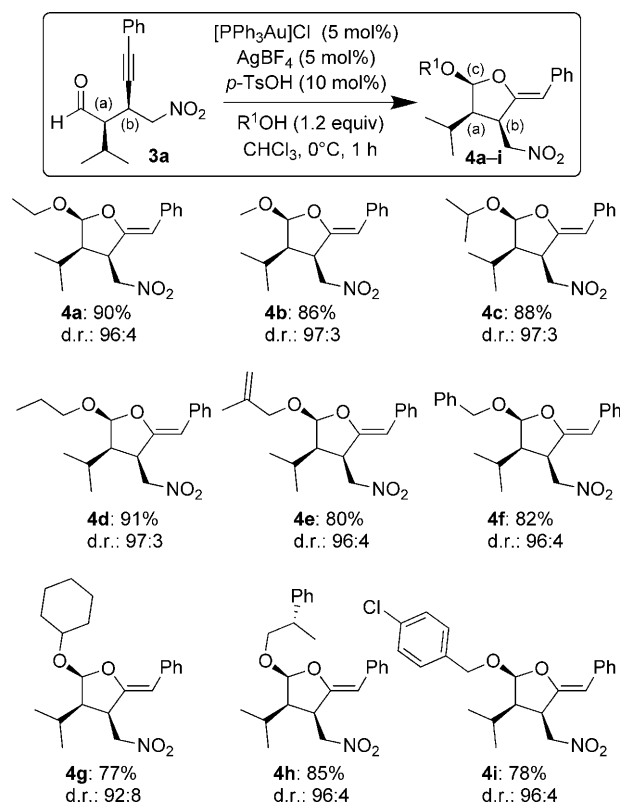
Then we investigated the gold-catalyzed tandem acetalization/cyclization of the aldehyde **3a** into the expected tetrahydrofuran ether **4a** in the presence of various gold sources and additives. After optimization, we carried out the reaction in the presence of $[\text{PPh}_3\text{Au}]\text{Cl}$ and AgBF_4 with 10 mol% of *p*-TsOH and only 1.2 equivalents of ethanol in chloroform at 0°C , and observed the best diastereoselectivity. [Eq. (2) in Scheme 2 and see the Supporting Information].

Having optimized both catalysts and the reaction conditions, we next examined the tandem acetalization/cyclization on the model substrate **3a** in the presence of various alcohols (Scheme 3). Pleasingly, the reaction tolerates a wide range of primary and secondary alcohols and afforded the expected tetrahydrofuran **4a-i** in good yields and diastereoselectivities. Both simple primary alcohols, such as methyl or *n*-propyl alcohol, and more complex primary alcohols, such as

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Scheme 3. Scope of the sequential reaction. The d.r. values are reported for *cis/trans* relationship between the stereogenic centers labeled (a) and (c).

(*R*)-2-phenylpropan-1-ol, and benzylic alcohols work well. Moreover the expected tetrahydrofuran could also be obtained from secondary alcohols (isopropyl alcohol and cyclohexanol). In contrast to this, no reaction took place in the presence of water or *tert*-butyl alcohol. The relative and absolute configuration of **4i** was determined by X-ray crystallography to be *cis* (Figure 1 and see the Supporting Information).^[15] We assume that the other tetrahydrofuranyl

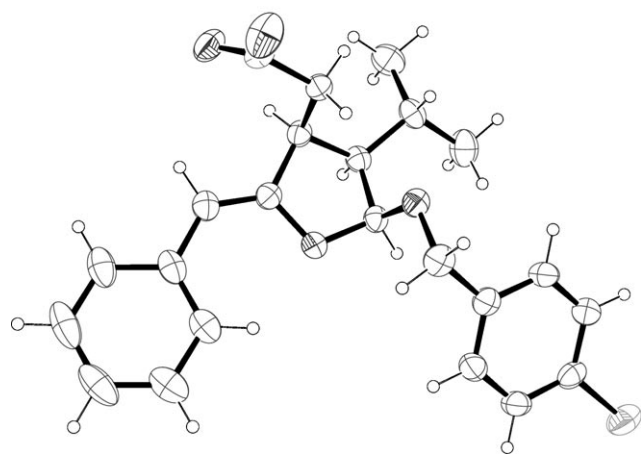


Figure 1. Single-crystal X-ray structure analysis of **4i**. Thermal ellipsoids shown at 70% probability.^[15]

ethers **4a-i** prepared in this work have the same configuration.

To shed light on the reaction mechanism, we performed a deuterium labeling experiment on the tandem acetalization/cyclization of the aldehyde **3a** in the presence of $[PPh_3Au]Cl$, $AgBF_4$, and $p-TsOH$ with 1.2 equivalents of deuterated methanol in chloroform. According to NMR spectra, the deuterium was located on the exocyclic double bond. Therefore, we propose the mechanistic model shown in Scheme 4.

Knowing that the reaction also occurs in the absence of a Brønsted acid, we assume that the reaction is initiated by the formation of the cationic gold catalyst, $[PPh_3Au]BF_4$, which acts as an oxophilic Lewis acid to catalyze the acetalization reaction of the aldehyde **A**. This step enables the generation of the corresponding hemiacetal salt **B**. Then, as gold catalysts are well-known for activating alkynes by forming π -complexes,^[3] the triple bond is activated towards the attack by the oxygen atom, leading to the tetrahydrofuran **C** which then undergoes protodemetalation, because of the presence of HBf_4 , to afford the corresponding tetrahydrofuranyl ether.

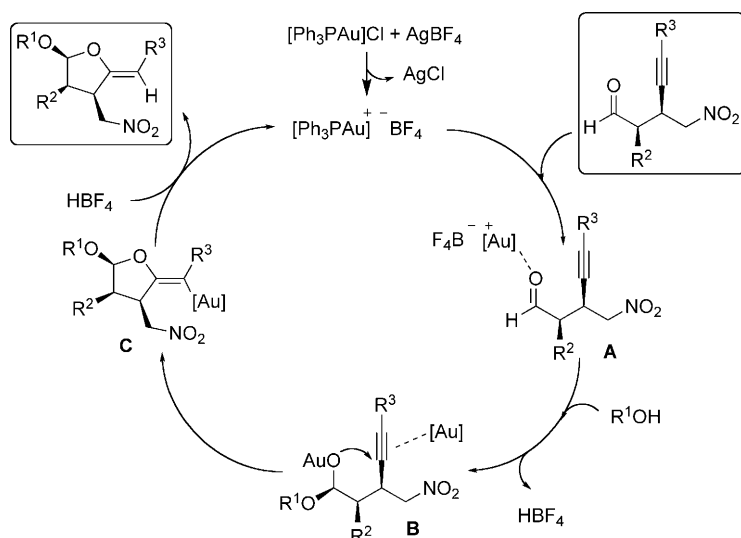
We decided then to turn our attention towards the optimization of the one-pot reaction. To accelerate the study, we optimized the conditions by starting directly from the intermediate **3a** and adding all the components of the organocatalyzed step (i.e., the diphenylprolinol silyl ether **5** and **1a**) and the gold-catalyzed step (e.g., $[PPh_3Au]Cl$, $AgBF_4$, $p-TsOH$, and ethanol). Therefore, the influence of the temperature and the ratio of organocatalyst to $p-TsOH$ upon the reaction could be tested (Table 1).

Table 1: Optimization of the one-pot reaction.

Entry	5 (mol %)	$p-TsOH$ (mol %)	T [$^\circ C$]	t [h]	d.r. ^[a] (<i>cis/trans</i>)	Yield [%] ^[b]
1	20	10	23	24	—	0
2	10	10	23	1	90:10	84
3	10	0	23	24	—	0
4	10	10	0	1	91:9	87
5	10	25	0	1	92:8	79
6	10	50	0	1	93:7	84
7	10	100	0	1	95:5 ^[c]	81
8	10	25	−10	2	93:7	89

[a] The d.r. values are given for the stereogenic centers labeled (a) and (c). Determined by 1H NMR analysis or super critical fluid chromatography (SFC) of the crude product using a chiral stationary phase. [b] Yield of isolated product after a flash column chromatography on SiO_2 . [c] Epimerization of *syn-3a* into the *anti-3a* occurs.

Interestingly, these investigations clearly show a tremendous effect of the $p-TsOH$ upon the reaction. Indeed, no reaction occurred when the amount of organocatalyst **5** exceeded that of $p-TsOH$ (entries 1 and 3, Table 1). However, when equimolar amounts are used, the expected tetrahydrofuran **4a** is formed with nearly the same diastereoselectivity



Scheme 4. Proposed mechanism for the gold-catalyzed tandem acetalization/cyclization.

as obtained in the sequential reaction (entries 2 and 4, Table 1). It seems that the excess of *p*-TsOH prevents deactivation of the gold catalyst by coordination to the nitrogen atom of the diphenylprolinol silyl ether **5**.

When we performed the same reaction with an excess of *p*-TsOH at 0°C, we observed an improvement of the diastereoselectivity (entries 4–7, Table 1). However, in the presence of 100 mol % of acid, we observed an increase of the tetrahydrofuran coming from the *anti* adduct (entry 7, Table 1). This is a result of the conversion of the *syn*-adduct **3a** into the *anti* adduct through epimerization. Indeed experiments clearly showed that the *syn*-**3a** could racemize in the presence of *p*-TsOH to afford the *anti* adduct. Fortunately, the reaction is slow. We also observed a moderate effect of the temperature on the reaction in terms of the diastereoselectivity (entry 8, Table 1). Therefore, after this study, it appears that the best compromise seems to be a slight excess of *p*-TsOH (25 mol %) relative to the diphenylprolinol silyl ether **5** (10 mol %), a temperature of –10°C, and the same concentration of the starting material (0.11 mol L^{–1}) used in the organocatalyzed step.

With the optimized conditions for the one-pot reaction in hand, we investigated the scope of the reaction with the various aldehydes **1** and nitroenynes **2** in the presence of 10 mol % of diphenylprolinol silyl ether **5** in chloroform at –10°C for the first step. After completion of the organocatalyzed conjugate addition, 5 mol % of [PPh₃Au]Cl/AgBF₄, 25 mol % of *p*-TsOH, and 1.2 equivalents of the corresponding alcohol were directly added to the reaction mixture containing the adduct, at –10°C (Table 2). Pleasingly, the gold-catalyzed tandem acetalization/cyclization afforded almost the same diastereoselectivity as observed for the optimization (entry 1, Table 2). As isovaleraldehyde (**1a**) gave the best results for the organocatalyzed step, it was chosen as representative aldehyde for the one-pot reaction. Therefore the scope of the one-pot reaction was studied using isovaleraldehyde with the nitroenynes **2a–f**, and then in

presence of ethanol, methanol, or isopropanol. Pleasingly, in all cases, the tetrahydrofuran ethers **4a–c** and **6–10** were obtained in better yields in the one-pot reaction, when compared to the sequential reaction, and with excellent diastereoselectivities (Table 2).

Independent of the substitution pattern and the electronic character of the functional group attached to the aromatic ring of the nitroenynes, the tetrahydrofuran ethers **4a–c** and **6–9** were obtained in excellent yields and diastereoselectivities either with ethanol, methanol, or isopropanol (entries 1–3, Table 2). Moreover it should be noted that the procedure is applicable to heteroaromatic substituents such as 3-thienyl groups (entry 8, Table 2).

In conclusion, although some asymmetric gold-catalyzed cyclizations are known using either chiral ligands or chiral anions,^[16] we developed a third alternative strategy: a one-pot process consisting of an enantioselective organocatalytic Michael addition

Table 2: Scope of the one-pot reaction.

Entry	R ¹	R ²	Yield [%] ^[a]	d.r. of 3 ^[b] (<i>syn/anti</i>)	d.r. ^[c] (<i>cis/trans</i>)	ee [%] ^[d] (<i>syn</i>)
1	Et	Ph	4a : 80	96:4	92:8	99
2	Me	Ph	4b : 81	96:4	93:7	99
3	<i>i</i> Pr	Ph	4c : 78	96:4	88:12	99
4	Et	<i>p</i> -BrC ₆ H ₄	6 : 86	97:3	92:8	> 99
5	Et	<i>p</i> -MeOC ₆ H ₄	7 : 77	95:5	91:9	> 99
6	Et	<i>p</i> -CF ₃ C ₆ H ₄	8 : 84	96:4	93:7	> 96 ^[e]
7	Et	<i>m</i> -MeC ₆ H ₄	9 : 86	96:4	91:9	> 99
8	Et	3-thienyl	10 : 75	97:3	89:11	99

[a] Overall yield of isolated product. [b] Determined by ¹H NMR analysis or SFC on the crude product using a chiral stationary phase. [c] The d.r. values are given for the stereogenic centers, labeled (a) and (c), of compounds **4a–c** and **6–10**. Determined by ¹H NMR analysis of the crude reaction mixture. [d] Determined by SFC using a chiral stationary phase for the *syn*-adducts **3a–f**. [e] Accuracy problem resulting from the partial separation of the enantiomers.

to a nitroenynone and a subsequent gold-catalyzed acetalization/cyclization. This sequence leads to nitro-substituted tetrahydrofuran ethers with high diastereo- and enantioselectivities. Moreover, we have demonstrated that organocatalysis and gold catalysis are compatible and complementary in a one-pot process, thereby enabling isolation of the products in higher yields relative to those for the sequential

reaction. Work is in progress to enlarge the scope of this methodology.

Experimental Section

Typical procedure: (S)-(-)-(Diphenyltrimethylsiloxymethyl)-pyrrolidine (8 mg, 0.02 mmol) was added to a solution of the nitroenyne (0.23 mmol) and aldehyde (2.30 mmol) in amylene-stabilized chloroform (2 mL) maintained at -10°C . The reaction mixture was stirred at -10°C and the conversion was monitored by TLC analysis. Then the alcohol (0.28 mmol), *p*-TsOH (10 mg, 0.06 mmol), Ph_3PAuCl (6 mg, 0.01 mmol), and AgBF_4 (2 mg, 0.01 mmol) were successively added while maintaining the reaction mixture at -10°C . The resulting heterogeneous reaction mixture was stirred for 3–5 h at -10°C . At this point, water (1 mL) was added, and the mixture was extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

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