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Gold(III) Chloride-Mediated Transformation of Furfural to the *trans-N,N*-4,5-Diaminocyclopent-2-enones in the Presence of Anilines

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Abstract: We investigated the efficient approach of a series of *trans-N,N*-4,5-substituted-diaminocyclopent-2-enones (*trans*-DACPs) from furfural and anilines mediated by Gold(III) chloride ($HAuCl_4$). The present protocol required a low amount of the catalysts, 1.5 mol%, open air conditions, the absence of any additives, and short reaction times. The desired *trans*-DACPs were isolated in good to high yields. The protocol was also applied to secondary amines, leading to the corresponding 4,5-diamino-cyclopent-2-enones in good yields. To the best of our knowledge, this is the first gold-mediated paradigm as an efficient catalyst for the formation of the cyclopentenones core-bearing C-N bonds under mild reaction conditions.

Keywords: gold catalysis; furfural; anilines; diaminocyclopentenones; organic synthesis

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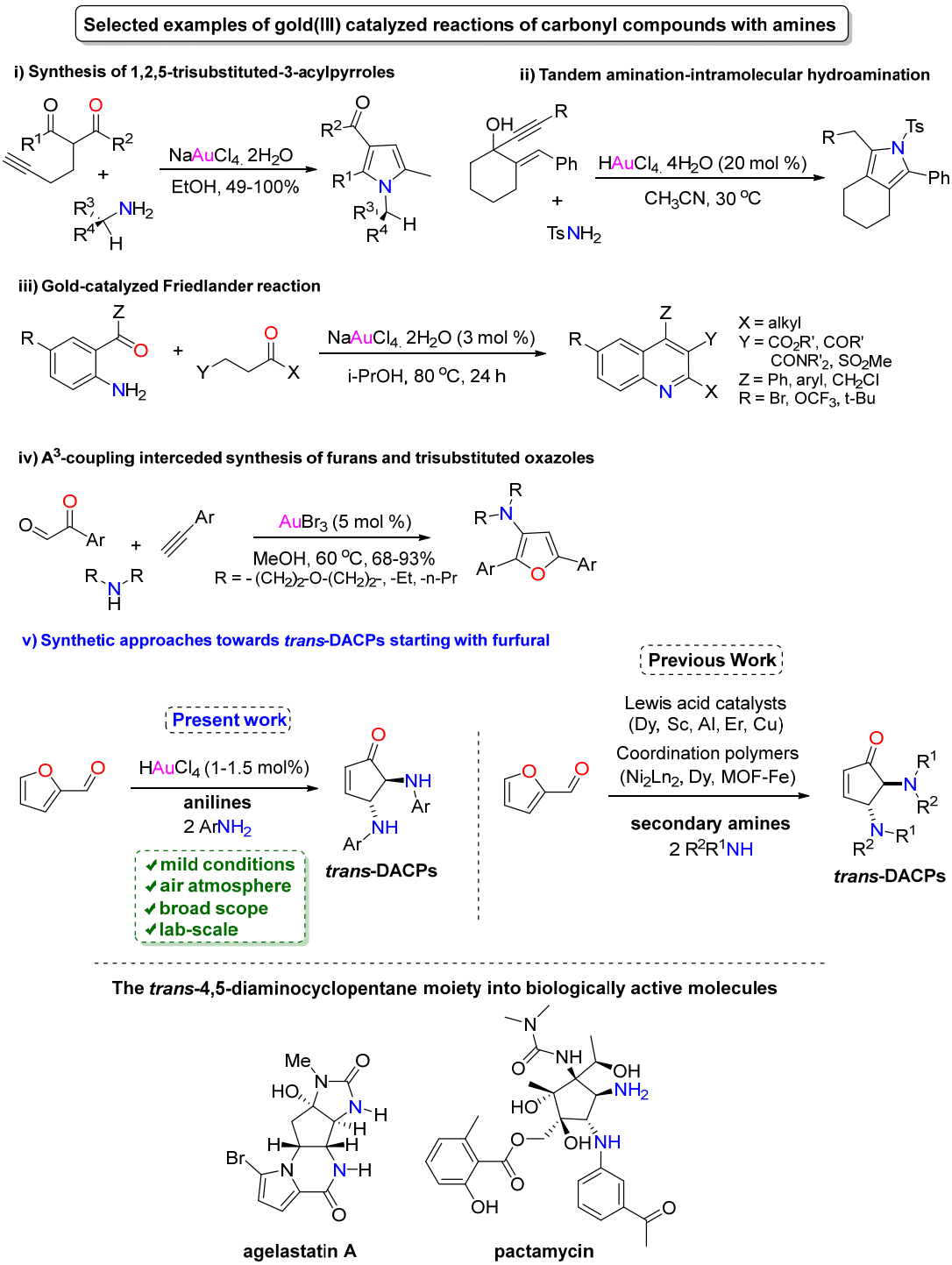
1. Introduction

Gold, either in a homogeneous [1–7] or heterogeneous medium [8–16], can act as a versatile catalyst for a broad range of chemical transformations. The field of homogeneous gold catalysis began to grow in the first decade of the 21st century, enabling the replacement of consolidated organic reactions with more simple, selective, and chemically sustainable alternatives. Gold catalysis is considered a hot topic in organic synthesis, with applications in the general topics of the total synthesis of complex molecular architectures [17,18] asymmetric synthesis [19,20], C-H activation reactions [21,22], and visible photoredox catalysis [23–26]. In the majority of homogeneous Au catalysts, Au exists in the +1 oxidation state and has a soft Lewis acidity. Unlike Au(I), Au(III) is a hard Lewis acid that preferentially binds to the lone pairs of heteroatoms such as O, N, and S [27–30]. The oxophilic Au(III) complexes may be employed to accelerate chemoselective reactions for which piphilic Au(I) complexes are less efficient [31,32]. Therefore, progression in Au(III) catalysis could expand the overall scope of homogeneous Au catalysis. Selected examples of Gold(III)-catalyzed reactions of carbonyl compounds in the presence of amines towards a variety of heterocyclic cores are given in Scheme 1 [33–38]. In most cases, $AuCl_3$ is proposed to efficiently catalyze the formation of the heterocyclic core of the desired products (pyrroles, quinolines, furans, oxazoles, spirochromenes) through tandem amination/annulation and condensation reactions (Scheme 1, i–iii) or A^3-coupling/multi-component-type reactions (Scheme 1, iv) where $AuBr_3$ was used as a catalyst.

The use of renewable and bio-based materials has received considerable attention in the field of green chemistry over recent years. One of the top biomass-derived value-added chemicals, furfural, has been included by the US Department of Energy [39]. The combination of the aldehyde group and the aromatic ring makes furfural an appealing starting material for the synthesis of other *N*, *O*-functionalized compounds [40–45]. Among the most important classes of products derived from furfural, the *trans*-4,5-diaminocyclopent-2-enones (*trans*-DACPs) constitute versatile building blocks in the perfumery industry or in natural products, as shown in Scheme 1 [46–51]. So far, for the convenient yield of

trans-DACPs, several homogeneous [52–61] and heterogeneous [62–64] catalytic conditions were reported; however, heteronuclear $Ni(II)_2Ln(III)_2$ (where Ln = Y, Dy) complexes [65–67] or metal-free systems were also proposed to promote the efficiency formation of the *trans*-DACPs (Scheme 1, v) [68–70]. One study using poly(dopamine)-supported gold nanoparticles on quartz slides as a heterogeneous surface was reported for the construction determination of a donor–acceptor Stenhouse adduct molecular layer, starting with a furfuryl-substituted CF_3-isoxazolone-based acceptor molecule [71].



Scheme 1. (**Upper**) Gold(III)-catalyzed organic transformation in the presence of amines. (**Lower**) Gold(III)-catalyzed transformation of furfural into *trans*-DACPs.

To date, the Lewis acid catalysts that have used in the literature for the efficient *trans*formation of furfural into the corresponding cyclopentenone core, such as $Dy(OTf)_3$, $Sc(OTf)_3$, and $AlCl_3$ with 10% mol loading, have the largest ratios in terms of the price per milligram of the catalyst used in the reaction scale of 0.5 mmol, with $Sc(OTf)_3$ being the most expensive (Table 1). On the contrary, $Cu(OTf)_2$ and $ErCl_3{\cdot}6H_2O$ have the lowest ratios in terms of the price per milligram of the catalyst used in reaction scale of 1 mmol. Although $HAuCl_4$ seems expensive, the low loading of the catalyst accompanied by its non-toxic properties it makes it accessible for the development of the present transformation (Table S1). Thus, herein, we report—to the best of our knowledge—the first protocol that utilizes $HAuCl_4$ for the synthesis of an extended library of *trans*-DACPs under mild conditions and primary or secondary amines (Scheme 1, v). It is worth noting that, in most of the above protocols, the reaction scope was limited to secondary amines. Only very recently our group reported on the polyoxometalate-driven conversion of furfural to the corresponding *trans*-DACPs in the presence of anilines [72].

2. Materials and Methods

2.1. Chemical Reagents

The solvents, amines, anilines, 5-methyl furfural, and furfural were purchased from Sigma-Aldrich, Fluorochem, Acros, and TCI and were used without further purification. For the catalytic reactions, the commercially available AuCl, $HAuCl_4$, $AuClPPh_3$, Au/TiO_2, Au/Al_2O_3, Au/ZnO, $CuCl_2$, CuCl, NH_4Cl, $MgCl_2$, $ZnCl_2$, $CoCl_2$, and $FeCl_3$ were used without further purification.

2.2. Instrumentations

Thin-layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 μm). Nuclear magnetic resonance spectra were recorded on an Agilent 500 (^{1}H NMR (500 MHz), ^{13}C(H) NMR (125 MHz)). Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Infusion experiments were carried out on an Agilent Q-TOF Mass Spectrometer, G6540B model with Dual AJS ESI-MS. All of the compounds (dissolved in LC-MS-grade methanol) were introduced into the ESI source of the MS with a single injection of 15 μL of the sample and with a flow rate of 300 μL/min of 100% methanol as a solvent in the binary pump. The experiments were run using a Dual AJS ESI source, operating in a positive ionization mode. The source operating conditions were 330 °C Gas Temp, 8 L/min Gas Flow, Sheath Gas Temp 250 °C, Sheath Gas Flow 10 L/min, and 150 V Fragmentor. Data-dependent MS/MS analysis was performed in parallel with the MS analysis, in a centroid mode, using different collision energies (10, 20, 30, 40 V). All accurate mass measurement of the $[M+H]^+$, $[M+Na]^+$ $[M-H]^+$ ions were carried out by scanning from 100 to 500 m/z. The Q-TOF was calibrated 1 h prior to the infusion experiments using a calibration mixture. Data were acquired in an external calibration mode.

2.3. Heterogeneous Catalytic Reaction between Furfural and Amines

The appropriate amount of supported gold catalysts 1% *w*/*w* (1 mol% based on furfural amount, ca. 40 mg) was placed in a 4 mL vial, followed by the addition of acetonitrile (0.4 mL), furfural (0.2 mmol), and the appropriate secondary amine (0.44 mmol). The reaction was then stirred at room temperature for 1 h. The reaction was monitored by thin-layer chromatography (TLC, Hexane/EtOAc = 1/1). After completion, the solid catalyst was separated from the reaction mixture with the use of a centrifuge and the solid residue washed twice with acetonitrile (ca 2 × 2 mL). The combined organic solvent was evaporated under vacuum and the crude reaction mixture was determined by ^{1}H NMR spectroscopy.

2.4. Homogeneous Catalytic Reaction between Furfural and Secondary Amines

The $HAuCl_4$ (1.5 mol%, ca. 2.5 mg) was placed in a 4 mL vial, followed by the addition of acetonitrile (0.5 mL), furfural (0.5 mmol), and the appropriate secondary amine (1.2 mmol). The reaction was then stirred at room temperature for the appropriate time. The reaction was monitored by thin-layer chromatography (TLC, Hexane/EtOAc = 1/1) and after completion, the crude mixture was concentrated under vacuum and purified by column chromatography on silica gel using a gradient mixture of EtOAc–Hexane (from 10/1 to 1/1 ratio) to afford the corresponding products in pure forms.

2.5. Homogeneous Catalytic Reaction between Furfural and Substituted Anilines

The $HAuCl_4$ (1.5 mol%, ca. 2.5 mg) was placed in a 5 mL glass reactor (vial), followed by the addition of acetonitrile (0.5 mL), furfural (0.5 mmol), and the appropriate substituted aniline (1.2 mmol). The reaction was then stirred at room temperature for 2 h. The reaction was monitored by thin-layer chromatography (TLC, Hexane/EtOAc = 1/1) and after completion, the crude mixture was either concentrated under vacuum and purified by column chromatography on silica gel using a gradient mixture of EtOAc–Hexane (from 10/1 to 1/2 ratio) or precipitated in the solvent systems chloroform/hexane or THF/Hexane in 1/20 ratio to afford the corresponding products in pure forms.

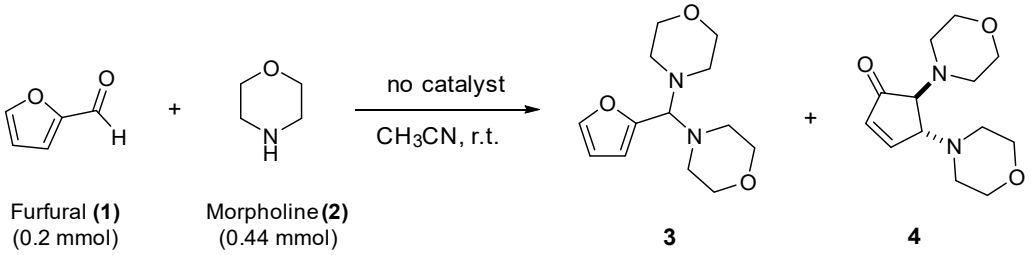
3. Results and Discussion

3.1. Evaluation of Catalytic Conditions for the Reaction of Furfural with Morpholine

To optimize the reaction conditions, furfural (**1**) and morpholine (**2**) were selected as model substrates for the synthesis of the desired *trans*-4,5-dimorpholinocyclopent-2-enone **4** (Table 1). First, control experiments using 3 mol% $HAuCl_3$ in different solvents were tested and the results are summarized in Table 1. Among the used solvents, acetonitrile was found to promote the studied transformation within 1 h and with quantitative formation of the desired product **4** (Table 1, entry 1). In the presence of other polar solvents, such as EtOAc, MeOH, EtOH, or the less-polar DCM, DCE, $CHCl_3$, or even non-polar toluene, a mixture of aminal **3** and the product **4** were observed in different ratios (Table 1). Similar results were also observed in the absence of a catalyst and over a prolonged period of time (18 h) in several solvents (Table S2). Only protic solvents MeOH and EtOH and polar DMF were found to promote the studied transformation over a prolonged period of time, leading to a mixture with the desired **4** as the major product (Table S2 entries 2, 3, and 13). For comparison, the reaction profile was also studied in the absence of $HAuCl_4$ and in CH_3CN as the chosen solvent. The absence of a catalyst, and at a prolonged reaction time of 18 h, revealed the formation of a mixture of aminal **3** and the **4**; however, no reaction completion was observed (Figure 1). The structure of **3** was determined by NMR and compared with the literature data [73].

Then, the development of the catalytic condition in the presence of different gold catalysts was performed in acetonitrile and the results are summarized in Table 2. Commercially available heterogeneous catalysts containing gold nanoparticles (AuNPs) in 1 % *w*/*w*, such as Au/TiO_2, Au/Al_2O_3, and Au/ZnO_2, were tested at 25 °C. In all cases, the corresponding catalyst was used in 1 mol% based on the amount of AuNPs (20 mg), 0.2 mmol of the furfural, and 0.44 mmol of the morpholine, in 0.2 mL of CH_3CN. We observed that aminal **3** was formed as the major product (Table 2, entries 2–4). When TiO_2 and Al_2O_3 were used as heterogeneous catalysts, similar results were observed along with a significant amount of the unreactive furfural **1** (Table 2, entries 4 and 5). These results indicate that AuNPs and the acidic supports TiO_2 and Al_2O_3 are not able to catalyze the formation of the desired *trans*-DACP **4** under the present conditions. For this reason, we further studied the catalytic activity of the commercially available gold salts, i.e., AuCl, $(p\text{Tolyl})_3AuCl$, and $HAuCl_4$, under the above conditions. The Au(I) salts shows media catalytic activity towards the reaction between **1** and **2** (Table 2, entries 6–8); however, $HAuCl_4$ was found to efficiently mediate the studied transformation, quantitatively leading to the desired product **4** (Table 2, entry 9). Based on these results, we continued with the evaluation of the catalytic condi-

tions and found that $HAuCl_4$ can catalyze this transformation even at the lower amount of 1.5 mol% within 2 h (Table 2, 11). However, using 1 mol%, no reaction completion was observed within 2 h and the desired **4** was formed in a 77 % yield (Table 2, entry 12). It is worth noting that when increasing the scale of the reaction to 0.5 mmol and 1 mmol of **1**, a quantitative formation of **4** was observed within 15 min and 30 min, respectively (Table 2, entries 13 and 14). For comparison, HCl was added into the reaction mixture at 3 mol%; however, a lower yield of the desired **4** was measured (40%) with a significant amount of aminal **3** (29%) and an identified product (31%) was observed by ^{1}H NMR of the crude reaction mixture (Table 2, entry 15). These results agree with a Lewis-catalyzed process by the presence of Au(I) and Au(III), with Au(III) as a hard Lewis acid, to preferentially bind to the lone pairs of heteroatoms such as O, N, and S. The oxophilic Au(III) complexes may be employed to accelerate chemoselective reactions for which piphilic Au(I) complexes are less efficient. To support this hypothesis, different commercially available salts ($CuCl_2$, CuCl, NH_4Cl, $MgCl_2$, $ZnCl_2$, $CoCl_2$, $FeCl_3$) were also tested under the same conditions (Table S3). However, in all cases, mixtures of **3** and **4** were observed, with the latter predominating in most cases, accompanied by an unidentified product in significant amounts (Table S3, entries 5, 6, and 13). In most cases, a higher amount of the salt (ca. > 6 mol%) was required for reaction completion (Table S3). Photoirradiation conditions, with a xenon lamp as the light source, were also performed, using either heterogeneous or homogeneous conditions (Table S4). In all cases, no significant changes were measured in the product yields or reaction conversion by ^{1}H NMR spectroscopy.



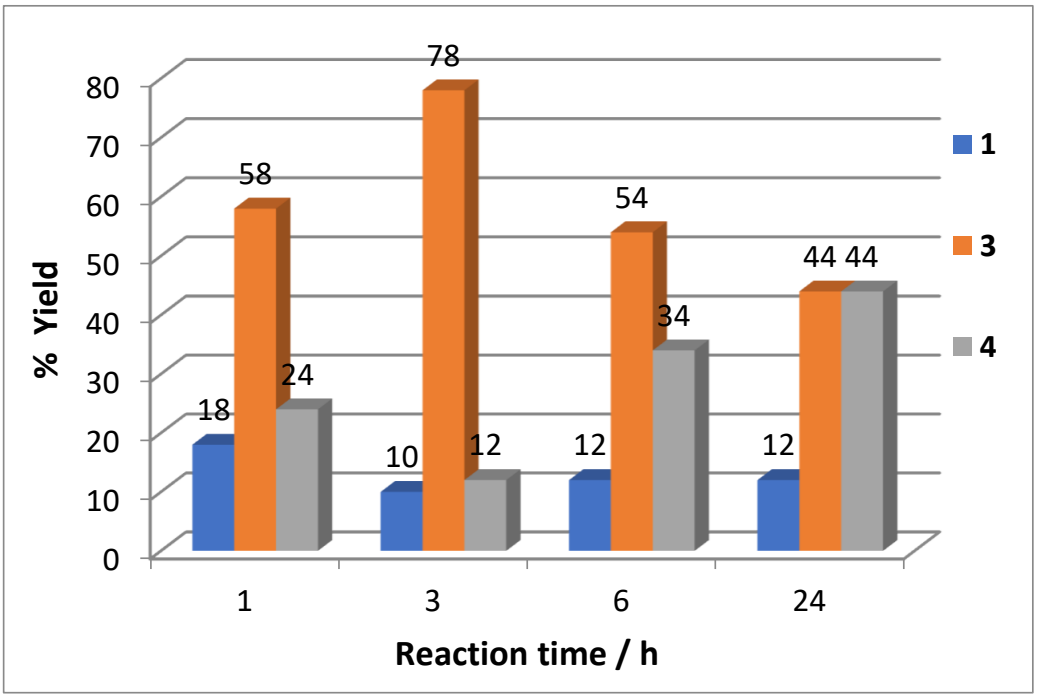
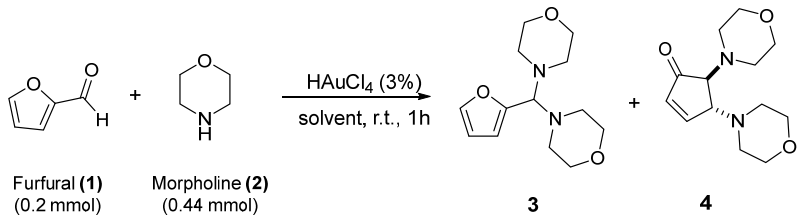


Figure 1. Reaction profile study in the absence of a catalyst and in CH_3CN.

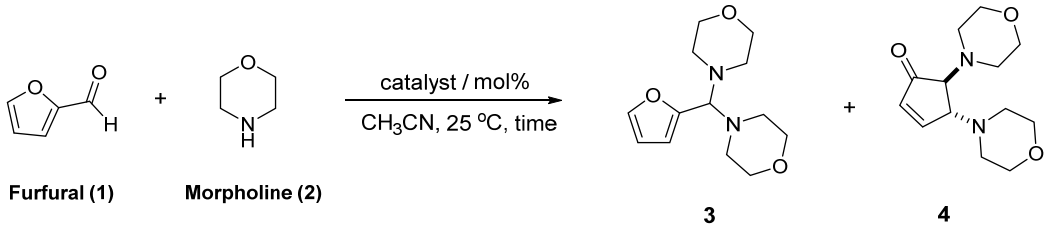
Table 1. Solvent screening in the presence of $HAuCl_4$.



Solvent [a]	1 (%)	3 (%)	4 (%)
CH_3CN	-	-	100
EtOAc	8	75	17
MeOH	-	63	37
EtOH	-	67	33
DCM	13	67	20
DCE	9	75	16
DMC	10	70	20
Toluene	8	80	12
$CHCl_3$	12	79	9

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.44 mmol), solvent (0.2 mL), 25 °C. All yields were determined from the crude ^{1}H NMR mixture of the reaction, and calculated by the addition of 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard.

Table 2. Gold catalyst screening for the synthesis of *trans*-DACPs **4** from **1** and **2**.

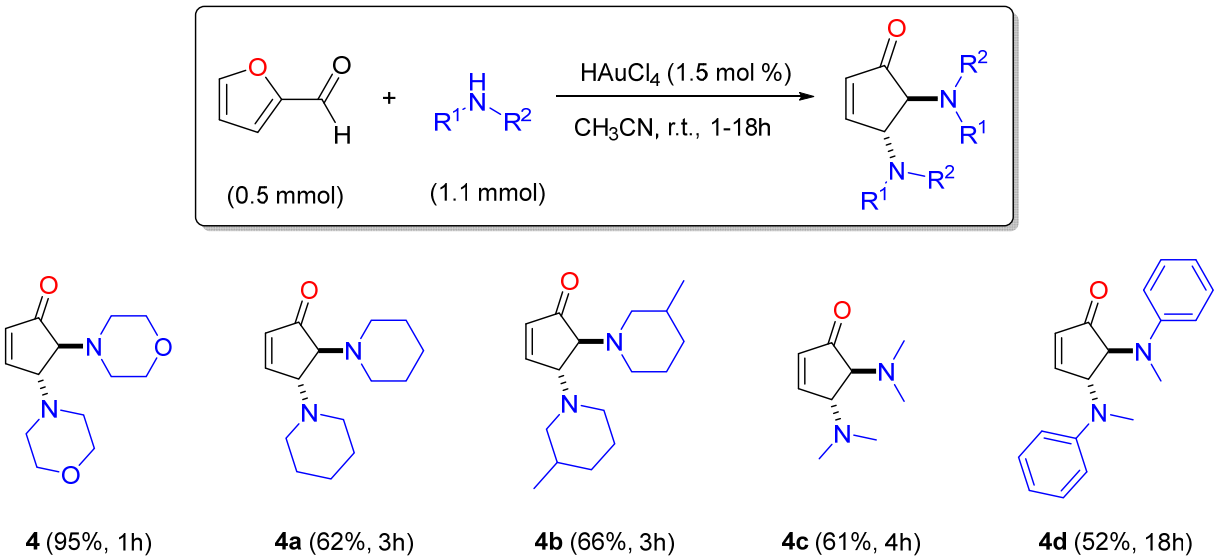


Entry	Catalyst/mol% [a]	Time	1 (%)	3 (%)	4 (%)
1	No catalyst	1 h	18	58	24
1	Au/TiO_2 / 1 mol%	1 h	-	100	-
2	Au/Al_2O_3 / 1 mol%	1 h	8	92	-
3	Au/ZnO / 1 mol%	1 h	13	74	13
4	TiO_2	1 h	32	68	-
5	Al_2O_3	1 h	25	75	-
6	AuCl / 3 mol%	1 h	12	51	37
7 [b]	AuCl / 3 mol%	1 h	16	37	47
8 [c]	(pTolyl)$_3$PAuCl / 3 mol%	1 h	14	33	33
9	$HAuCl_4$ / 3 mol%	1 h	-	-	100
10	$HAuCl_4$/ 3 mol%	15 min	14	18	68
11	$HAuCl_4$/ 1.5 mol%	2 h	-	-	100
12	$HAuCl_4$/ 1 mol%	2 h	9	14	77
13 [b]	$HAuCl_4$/ 3 mol%	15 min	-	-	100
14 [d]	$HAuCl_4$/ 3 mol%	30 min	-	-	100
15 [b,e]	HCl / 3 mol%	1 h	-	29	40

[a] Reaction conditions: 1 (0.2 mmol), 2 (0.44 mmol), CH_3CN (0.2 mL), 25 °C. All yields were determined from the crude ^{1}H NMR mixture of the reaction, and calculated by the addition of 1,3,5-trimethoxybenzene (0.1 mmol) as an internal standard. [b] 1 (0.5 mmol), 2 (1.1 mmol), CH_3CN (0.5 mL), 25 °C. [c] 20% of an unidentified product was observed by ^{1}H NMR. [d] 1 (1 mmol), 2 (2.2 mmol), solvent-free conditions, 25 °C. [e] 31% of an unidentified product was observed by ^{1}H NMR.

3.2. Application of Catalytic Conditions to the Synthesis of trans-DACPs **4**, **4a**–**4d**, *and* **5a**–**5o**

Based on the above optimum conditions, we further examined the possible application into the direct synthesis of a series of substituted *trans*-DACPs (Scheme 2). Several substituted secondary amines (1.1 mmol) and furfural (0.5 mmol) were added into 0.5 mL of CH_3CN in the presence of 1.5 mol% of $HAuCl_4$ at 25 °C. Indeed, under these conditions, the substituted *trans*-DACPs (**4**, **4a**–**4d**) were synthesized and isolated in moderate to high yields of 52–95% (Scheme 2) using the commonly available starting secondary amines, such as morpholine, pyrrolidine, 3-methylpyrolidine, dimethylamine, and *N*-methylaniline, respectively.

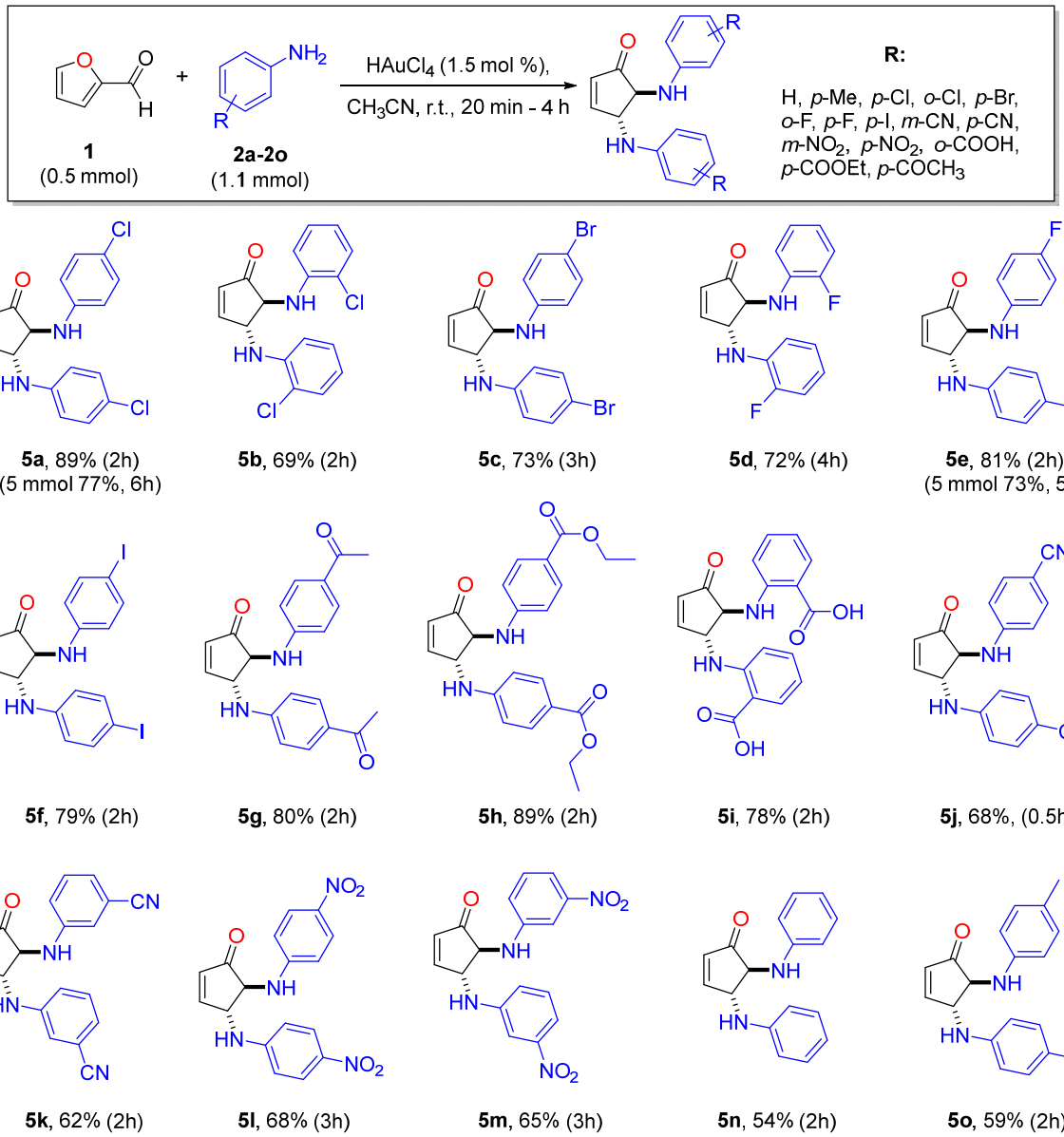


Scheme 2. Synthetic application for the substituted *trans*-DACPs (**4**, **4a**–**4d**) formation from the reaction of **1** and secondary amines mediated by the presence of $HAuCl_4$.

With these encouraging results, we further examined the possible application of the present optimum conditions using substituted anilines (1.1 mmol) instead of secondary amines. As far as we know, only aniline was used in sporadic examples for the synthesis of the corresponding *trans*-DACPs; however, low yields were reported. Only polyoxometalates were reported to successfully drive the conversion of furfural to the corresponding *trans*-DACPs in the presence of anilines [72]. Thus, a series of substituted anilines (1.1 mmol) were studied in the presence of 0.5 mmol of furfural in 0.5 mL of CH_3CN at room temperature. Indeed, under the proposed conditions, a series of substituted *trans*-DACPs (**5a**–**5o**) were synthesized and isolated in moderate to high isolated yields of 54–89% (Scheme 3). More specifically, substituted anilines with electron withdrawing groups (**5a**–**5m**) were found to lead the reaction in higher yields; however, the corresponding aniline and *p*-toluidine derivatives were formed in lower yields (**5n**, 54% and **5o**, 59%). In addition to this observation, the *m*-NO_2-substituted aniline reacted in lower yields than the corresponding *p*-NO_2 aniline, leading to the desired *trans*-DACPs **5l** and **5m** of 68% and 65%, respectively. It is interesting to note that **5a** and **5e** were also synthesized at the 5 mmol lab-scale and were isolated in 77% and 73% yields, respectively, in the presence of 3 mol% of $HAuCl_4$ and in 3 mL of CH_3CN (Scheme 3, values in parentheses).

It is worth noting that *p*-MeO-aniline (pK_b~8.6) does not lead to the desired cyclopentanone derivate; however, the corresponding imine **6** was formed quantitatively (Scheme 4). Accordingly, using the primary aliphatic amine *n*-butylamine (pK_b~3.2) and benzylamine (pK_b~4.6), the corresponding imines **7** and **8** were observed as the only product, even at the prolonged reaction time (18 h) (Scheme 4). It is noting that, in the presence of pyrrolidine, an equimolar mixture of the desired *trans*-4,5-*N*,*N*-disubstituted cyclopent-2-en-1-one **9a** and the thermodynamic 2,4-disusbtituted cyclopentenone **9b** was observed; however, no

reaction process was observed in the presence of diisopropylamine, 1*H*-indole, or *L*-proline (Scheme 4). Based on these results, it seems that the protocol was applied to anilines and secondary amines with pK_b higher than ca. 9.

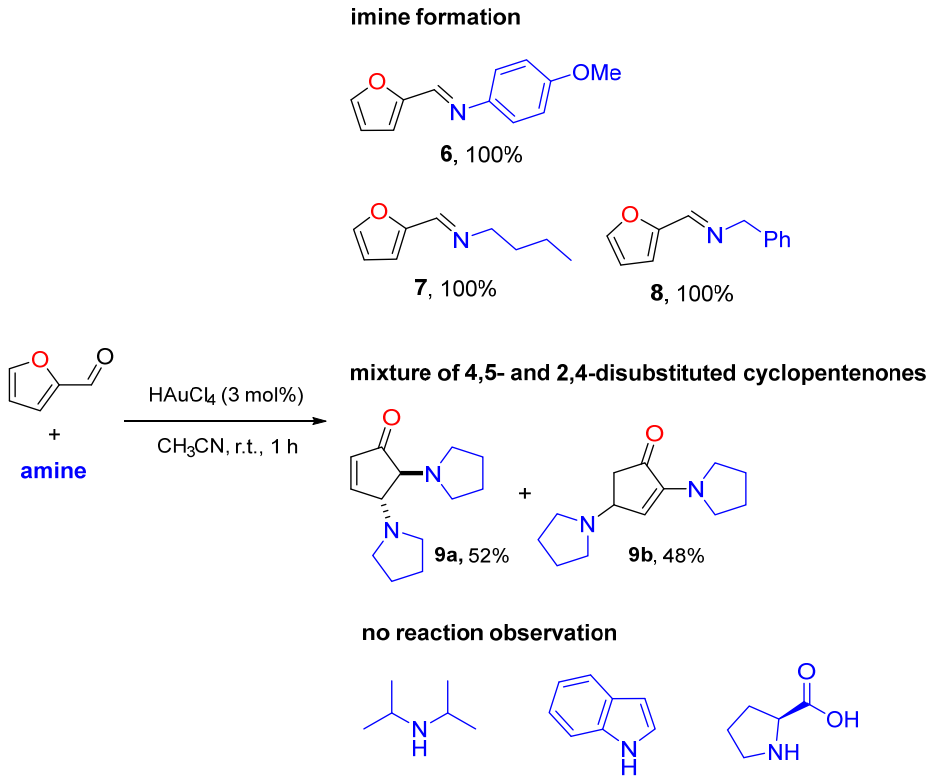


Scheme 3. Synthesis of substituted *trans*-DACPs (**5a-5o**) from the reaction of **1** and anilines mediated by the presence of $HAuCl_4$.

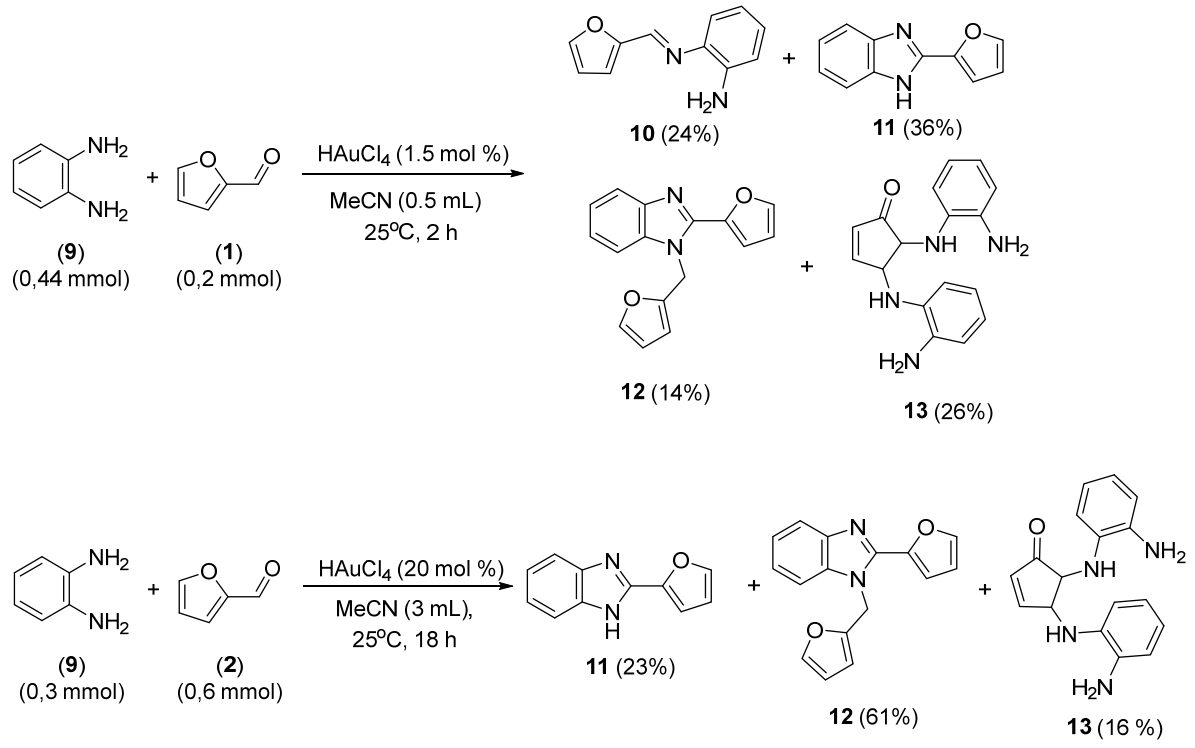
3.3. Reaction Profile Evaluation of the Reaction between Furfural and o-Phenylenediamine

To synthetically explore the present catalytic conditions using aryl diamines, we initially studied the reaction between *o*-phenylenediamine (**9**) and furfural (**1**). The reaction process was monitored by ^{1}H NMR, and after completion (the consumption of furfural based on TLC), four products were observed: the corresponding *trans*-DACPs (**13**) in a 26% yield, 2-furyl-benzimidizole (**11**) as the major one in a 36% yield, 1,2-disubstituted benzimidazole (**12**) in a 14% yield, and the corresponding imine (**10**) in a 24% yield (Scheme 5). By increasing the amount of furfural and catalyst and at a prolonged reaction time, the desired product **13** was formed in a lower yield (16%); however, the corresponding benzimidazole derivatives **11** and **12** were formed in 23% and 61% yields,

respectively (Scheme 5). This result agrees with our previous work on benzimidazole synthesis from aldehydes and *o*-phenylenediamine catalyzed by Au/TiO_2 [74].



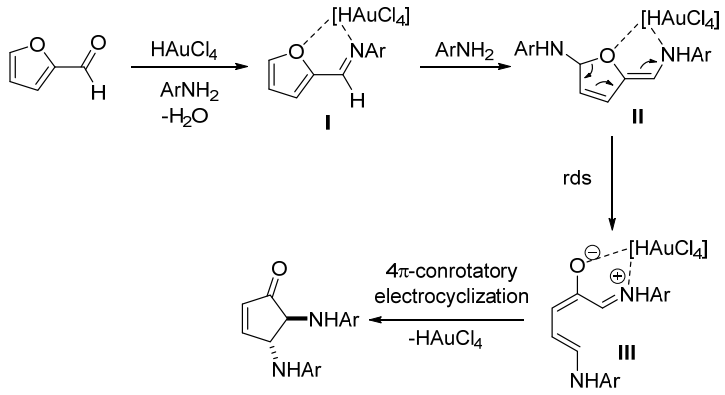
Scheme 4. Amine structure limitations under the present protocol conditions.



Scheme 5. Reaction between *o*-phenylenediamine and furfural mediated by $HAuCl_4$.

3.4. Proposed Mechanistic Pathway for the Reaction of Furfural with Anilines

From a mechanistic point of view, during the present catalytic conditions, the oxophilic Au(III) complexes mediated the initial formation of **I** and the further transformation to intermediate **II** (Scheme 6). The nucleophilic attack of the amine to the 3-position of the cyclopentenone core of **II** led to the formation of Stenhouse salt intermediate **III**, which subsequently transformed to the final product through a 4π-conrotatory electrocyclization pathway with the exclusive *trans*-diastereoisomer (*trans*-DACPs) (Scheme 6). This plausible pathway is in agreement with the literature reports in which the corresponding Stenhouse salt, derived by the reaction of furfural with aniline, was isolated and characterized by XRD [67]. It is worth noting that no reaction process was observed by ^{1}H NMR when 5-methylfurfural was mixed with 4-chloroanilne, a result that further supports the proposed mechanism.



Scheme 6. Plausible reaction paths for the transformation of furfural into *trans*-DACPs mediated by $HAuCl_3$.

4. Conclusions

Herein is presented, for the first time, the efficient approach of a series of *trans*-*N*,*N*-4, 5-substituted-diaminocyclopent-2-enones from furfural and anilines mediated by Gold(III) chloride. With the proposed protocol, a library of *trans*-DACPs were synthesized and isolated with good to high yields, using a low amount of the catalyst (1.5 mol%), under ambient conditions, in the absence of additives and using short reaction times. Under the same conditions, secondary amines were also reacted with furfural to produce the corresponding *trans*-DACPs in high yields. The present catalytic synthetic protocol has an extended substrate scope with high yields and represents, to the best of our knowledge, the first gold-driven paradigm as an efficient method for the formation of the cyclopentenones core under mild reaction conditions.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry5010029/s1, Tables S1–S4, NMR and HRMS data, NMR spectra.

Author Contributions: M.A.T. and I.N.L. conceived the study. M.A.T. performed the experimental methodology, catalytic study, and product analysis. I.N.L. supervised the study and wrote and corrected the manuscript. All authors have read and agreed to the published version of the manuscript.

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