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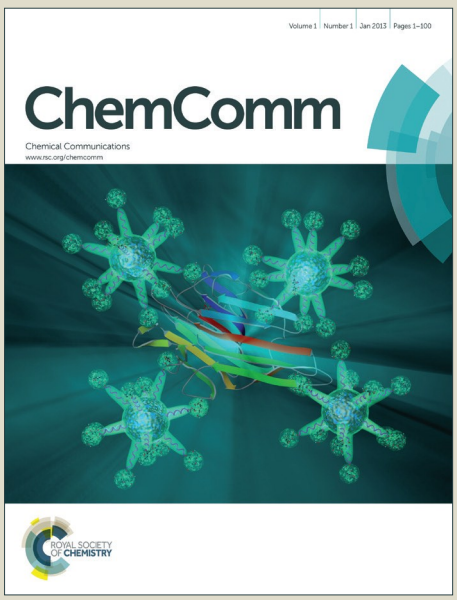

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Synergistic Gold and Enamine Catalysis: Intermolecular α-Alkylation of Aldehydes with Allenamides

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Aldehydes can be α-alkylated with allenamides by the combined action of an organocatalyst and a gold complex. The reaction requires the simultaneous generation of an enamine and a gold-activated allenamide. Importantly, by using a chiral amine as organocatalyst it is possible to obtain aldehyde products featuring all-carbon quaternary stereocenter at their α-position, with moderate to good levels of enantioselectivity.

Enamine-mediated organocatalysis has proven to be a invaluable tool for the asymmetric α-functionalization of carbonyl derivatives.[1] Despite its enormous power and versatility, the application of enamine-mediated carbon–carbon bond forming processes usually requires the use of carbonyls, imines, or α,β-unsaturated derivatives as electrophilic partners.[1,2] Catalytic enamine-mediated α-alkylations of aldehydes with carbon-based electrophiles that lack such type of electron-activating groups are much more scarce.[3,4] Considering the well-known ability of gold (I or III) complexes to activate C–C unsaturated bonds,[5] we envisioned that being able to combine such activation with enamine organocatalysis might offer the opportunity to discover new and valuable chemical transformations.

The synergistic action of an amine organocatalyst and a transition metal catalyst has already been elegantly demonstrated in processes such as the α-allylation, vinylation or trifluoromethylation of aldehydes, using either Pd, Ru, Ir or Cu complexes.[6,7] However, similar synergistic processes that combine enamine and gold-promoted catalytic cycles remain essentially underdeveloped. [8] Indeed, to the best of our knowledge, they are restricted to the intramolecular alkylation of transient enamines with allylic alcohols,[9] or with alkynes,[10] as well as to an intermolecular α-vinylidation of aldehydes with ethynyl-1,2-benziodoxol-3(1H)-one, EBX.[11]

Herein we describe a new intermolecular reaction involving the synergistic action of an amine and a gold (I) catalyst. The reaction consists of the α-alkylation of aldehydes with *N*-allenamides, and can be even achieved in an asymmetric fashion by using chiral amines.

N-Allenamides have been recently used as reaction partners in a variety of gold-catalysed processes.[12,13] These reactions usually involve the formation of a gold-zwitterionic electrophilic species of type **I** (Figure 1).[14] We envisioned that this gold-intermediate (**I**) could be trapped by an in situ generated enamine, thus leading to α-alkyl substituted aldehydes like **3** (Figure 1). However, such an intermolecular synergistic process faced important challenges associated to the potential incompatibility between the Au catalyst and the amine or enamine,[15] or to the requirement of an exquisite synchronization between both catalytic cycles in order to minimize self-aldol condensations or alternative reactions of allenamides, such as their Au-catalysed [2 + 2] homodimerizations (**4**)[12a] and self-polymerizations.[16]

To initially assess the viability of the process, we tested the reaction of the allenamide **1a** and 2-phenylpropanal (**2a**) in the presence of pyrrolidine (100 mol%) and the phosphite-gold catalyst **Au1** (5%), which had been previously shown to be very effective in several gold-catalysed allenamide annulations.[12]

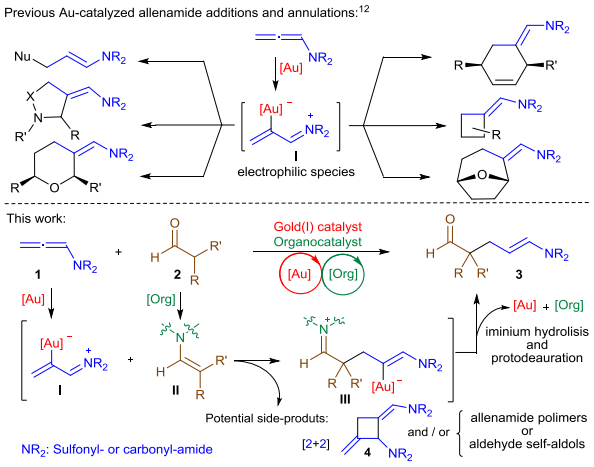

Figure 1. Previous Au-catalysed reactions of *N*-allenamides, and current proposal

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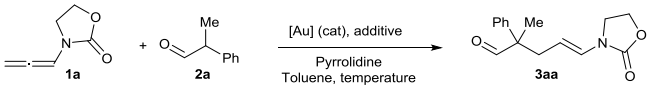
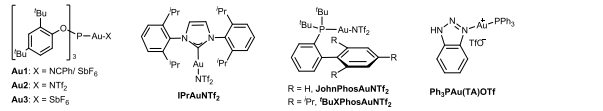
Although traces of the desired aldehyde (**3aa**) were detected, the conversion was very low even after several hours at rt (Table 1, entry 1). Running the reaction with 30% of pyrrolidine, in the presence of BzOH (20 mol%) as co-catalyst, led to a marginal benefit (entry 2).[17] However, an increase of the reaction temperature up to 60 ºC led to a better 30% yield (entry 3). More excitingly, carrying the reaction in refluxing toluene for 15 min led to a 90% yield (entry 4). Although this was a satisfactory yield, the requirement of heating might represent a drawback in terms of synthetic utility as well as to implement an enantioselective variant. Thus, we analysed several other gold(I) catalysts and additives that could eventually allow the reaction at lower temperatures. Gratifyingly, we identified that the use of $Ph_3PAuNTf_2$ as catalyst, in combination with 2,2'-bipyridine (Bpy) and BzOH (20 mol% each), provided an equally rapid reaction at just 60 ºC, and **3aa** could be isolated in a good 83% yield (entry 5).[18] A control experiment with Et_3N (30%) instead of pyrrolidine led to recovery of **1a**, thus confirming the participation of the enamide. As can be deduced from the entry 6, the use of Bpy was relevant to obtain a good yield at this moderate temperature, albeit other parameters like the type of ancillary ligand are also influential (entry 5 vs 7-11). Thus, while $(p\text{CF}_3\text{Ph})_3PAuNTf_2$, **Au2**, and $IPrAuNTf_2$ afforded comparable yields, although with variable reaction times (entries 7-9), diarylphoshine gold catalysts were completely ineffective (entries 10, 11). On the other hand, the use of a coordinating counterion like triflimide is also crucial to achieve useful yields at 60 ºC (entry 5 vs 12-13 and entry 9 vs 14-15).[19]

Table 1. Preliminary screening of catalysts and reaction conditions[a]



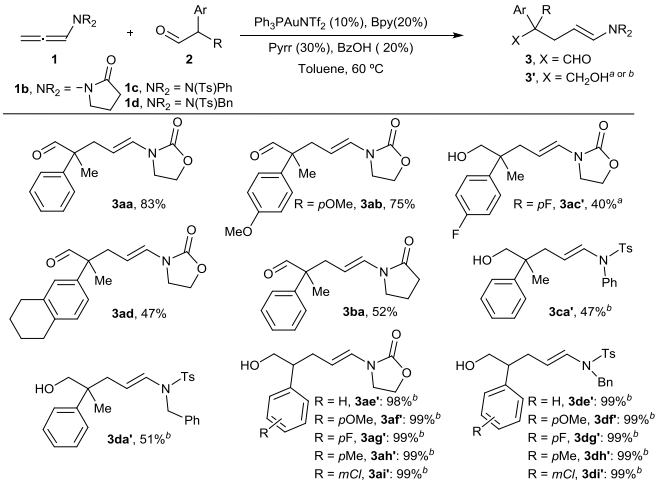
	[Au] (X mol%)	Pyrr (%)	T (ºC)	Additives (mol %)	t (h)[b]	**3aa**[c]
1	**Au1** (5)	100	rt	-	4	3%[d]
2	**Au1** (5)	30	rt	BzOH (20)	4	7%[e]
3	**Au1** (5)	30	60	BzOH (20)	1.2	30%
4	**Au1** (5)	30	110	BzOH (20)	0.2	90%
5	$Ph_3PAuNTf_2$ (10)	30	60	BzOH (20) / Bpy (20)	0.3	83%[f]
6	$Ph_3PAuNTf_2$ (10)	30	60	BzOH (20) / Bpy (0)	0.5	30%
7	$p\text{CF}_3\text{Ph}_3PAuNTf_2$ (10)	30	60	BzOH (20) / Bpy (20)	0.7	73%
8	$IPrAuNTf_2$ (10)	30	60	BzOH (20) / Bpy (20)	3	68%
9	**Au2** (10)	30	60	BzOH (20) / Bpy (20)	3	88%
10	JohnPhosAuNTf$_2$ (10)	30	60	BzOH (20) / Bpy (20)	0.5	6%
11	^{t}BuXPhosAuNTf$_2$ (10)	30	60	BzOH (20) / Bpy (20)	0.5	5%
12	$Ph_3PAu(TA)OTf$ (10)	30	60	BzOH (20) / Bpy (20)	6	63%
13	$Ph_3PAuCl/AgSbF_6$ (10)	30	60	BzOH (20) / Bpy (20)	18	23%
14	**Au1** (10)	30	60	BzOH (20) / Bpy (20)	1	30%
15	**Au3** (10)	30	60	BzOH (20) / Bpy (20)	3	25%[d]

[a] **1a** (1 equiv) was added dropwise to a solution of [Au], pyrrolidine (Pyrr), aldehyde (1.5 equiv), and additives, and heated at the indicated temperature. [b] Full conversion (**1a**) was observed at the specified time, unless otherwise noted. [c]. Yields calculated by ^{1}H-NMR with internal standard unless otherwise noted. [d] 50% conversion. [e] 65% conversion. [f] Isolated yield.



With these results in hand, we next explored the generality of the method using the conditions of Table 1, entry 5. As can be seen in Table 2, other 2-aryl propanals were also suitable substrates for the reaction, providing the corresponding aldehydes of type **3** (in some cases isolated after reduction to the alcohols **3'**) in moderate to good yields and complete *E*-selectivity at the enamide moiety. On the other hand, other allenamides such as the pyrrolidinone analog **1b** or the *N*-tosyl allenamides **1c** and **1d** also reacted with these aldehydes providing the desired products with good yields and full *E*-selectivity. Remarkably, 2-phenylacetaldehyde (**2e**, R = H, Ar = Ph) provided the desired product (**3ae**) in almost quantitative yield and in just 15 min, but as non-reproducible *E*/*Z* mixtures. However, quenching the reaction with $NaBH_4$ allowed to obtain the corresponding alcohol (**3ae'**) as a single *E* isomer, thus confirming that the *E*/*Z* mixture results from a isomerization of the initially formed *E*-enamide.[20] Other 2-arylacetaldehydes, with different electron-withdrawing or electron-donating groups on the aryl ring, also provided the desired alcohols in yields above 98% (**3af'**-**3ai'** / **3de'**-**3di'**), regardless of the allene (**1a** or **1d**). It is relevant to note that in the case of 2-arylacetaldehydes, the reaction can also be achieved without Bpy (yields are reduced from 10 to 15%)

Table 2. Substrate scope of the synergistic gold(I) / enamine catalysis

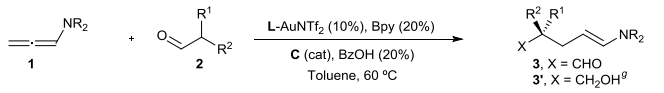


[a] Quenched with $NaBH_4$ to facilitate the isolation. [b] Quenched with $NaBH_4$ to avoid the formation of enamide *E* / *Z* isomers. Pyrr: pyrrolidine.

We next explored the viability of an enantioselective variant using privileged chiral amine organocatalysts that might discriminate between the enantiotopic faces of the putative intermediate **I** (Figure 1). Amongst several MacMillan's imidazolidinones, only the catalyst **C1** provided the desired aldehyde **3aa**, although with a poor yield and a modest 38% ee (Table 3, entry 1). The cinchona alkaloid **C2** led to a better enantioselectivity (60% ee), but the yield was of only 15% (entry 2). Curiously, whereas the TMS-prolinol[21] **C3** provided

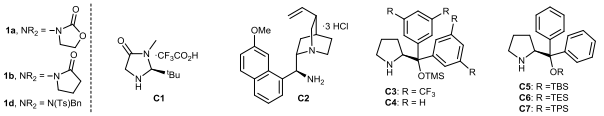
only traces of the desired adduct (entry 3), the analog with unsubstituted phenyl rings (**C4**) provided a good 68% yield and a promising 59% ee (entry 4). The enantioselectivity could be further improved up to 72% ee by using IPrAuNTf$_2$ as catalyst, which also allowed to reduce the loading of the organocatalyst down to 20 mol% (entry 5). Curiously, the additive Bpy not only seem to influence the reaction yield, like in the racemic series, but also the ee, albeit in a minor extent. Thus, the reaction without Bpy provided a lower 37% yield (75% ee, entry 6), whereas using 1,10-phenanthroline increased the ee up to 81% but affected the yield (entry 7).[18] We next analysed the performance of several prolinol silyl ethers with diverse steric requirements (**C5**–**C7**).[18] As can be deduced from entries 8-10, by increasing the size of the ether, the ee of **3aa** becomes higher, up to 83% (entry 10); however, the efficiency of the process becomes damaged, providing modest yields of **3aa**. This is probably due to a ralentization of the synergistic process, so the polymerization of the allenamide becomes more competitive.

Table 3. Enantioseletive transformations. Optimization and preliminary scope[a]



Entry	1	2	R^1	R^2	C (mol %)	L	t (h)[b]	3/3', yield[c]	3/3', ee
1	**1a**	**2a**	Me	Ph	**C1** (30)	Ph_3P	0.2	**3aa**, 13%	38%
2	**1a**	**2a**	Me	Ph	**C2** (30)	Ph_3P	5.5	**3aa**,15%	60%
3	**1a**	**2a**	Me	Ph	**C3** (30)	Ph_3P	3	**3aa**, 5%	-
4	**1a**	**2a**	Me	Ph	**C4** (30)	Ph_3P	0.5	**3aa**, 68%	59%
5	**1a**	**2a**	Me	Ph	**C4** (20)	IPr	0.5	**3aa**, 66%	72%
6[d]	**1a**	**2a**	Me	Ph	**C4** (20)	IPr	0.5	**3aa**, 37%	75%
7[e]	**1a**	**2a**	Me	Ph	**C4** (20)	IPr	1	**3aa**, 33%	81%
8	**1a**	**2a**	Me	Ph	**C5** (20)	IPr	0.5	**3aa**, 30%	81%
9	**1a**	**2a**	Me	Ph	**C6** (20)	IPr	0.7	**3aa**, 25%	81%
10	**1a**	**2a**	Me	Ph	**C7** (20)	IPr	0.7	**3aa**, 23%	83%
11	**1a**	**2b**	Me	*p*MeOPh	**C4** (20)	IPr	0.2	**3ab**, 40%	68%
12[f]	**1b**	**2a**	Me	Ph	**C4** (20)	IPr	0.5	**3ba**, 52%	82%
13[g]	**1d**	**2a**	Me	Ph	**C4** (20)	IPr	3	**3da'**, 50%	80%
14[g]	**1a**	**2e**	H	Ph	**C4** (20)	IPr	0.2	**3ae'**, 99%	30%
15[g]	**1a**	**2h**	H	*p*MePh	**C4** (20)	IPr	0.2	**3ah'**, 96%	40%
16[g]	**1a**	**2i**	H	*m*ClPh	**C4** (20)	IPr	0.2	**3ai'**, 99%	44%
17[g]	**1d**	**2e**	H	Ph	**C4** (20)	IPr	0.2	**3de'**, 99%	70%
18[g]	**1d**	**2g**	H	*p*FPh	**C4** (20)	IPr	0.5	**3dg'**, 99%	48%
19[g]	**1d**	**2h**	H	*p*MePh	**C4** (20)	IPr	0.5	**3dh'**, 99%	72%
20[g]	**1d**	**2i**	H	*m*ClPh	**C4** (20)	IPr	0.5	**3di'**, 99%	67%

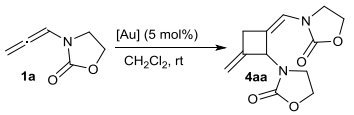
[a]: **1** (1 equiv) was added dropwise to a solution of **L**-AuNTf$_2$, organocatalyst, aldehyde (1.5 equiv), BzOH (20%) and Bpy (20%), and heated at 60 ºC unless otherwise noted. [b] Full conversion (**1**) was observed at the specified time. [c] Isolated yields. [d] Carried out without Bpy. [e] Carried out with 1,10-phenanthroline instead of Bpy. [f] Carried out at 40 ºC. [g] Obtained after treatment with $NaBH_4$.



We next explored the conditions of Table 3, entry 5 with different aldehydes and allenamides. Thus, aldehyde **2b** provided the corresponding product **3ab** with a similar 68% ee (entry 11).[22] Moreover, as shown in entries 12-13, allenamides **1b** and **1d** also reacted with **2a** providing the desired products with moderate yields and ee's from 80 to 82%. On the other hand, the reaction of allenamide **1a** with several aryl-acetaldehydes lacking the α-methyl group (**2e**,**2h**,**2i**), provided the corresponding products of type **3'** (after work-up with $NaBH_4$) in almost quantitative yields, and ee's ranging from 30 to 44% (entries 14-16). Gratifyingly, these enantioselectivities were significantly improved by using the NTs-allenamide **1d**, so the corresponding alcohols (**3de'**, **3dg'** - **3di'**) were isolated in 99% yield and ee's varying from 48 to 72% (entries 17-20).[23]

A major issue in this type of synergistic enamine/gold catalysis is related to compatibility between the amine reactants and an active gold catalyst. Therefore, we performed NMR and ESI-MS experiments to detect gold complexes that could be operating in the reactions. Mixing $Ph_3PAuNTf_2$ with Bpy (1:1 ratio) in d8-toluene at 60 ºC immediately led to the quantitative formation of the complex $Ph_3PAu(Bpy)NTf_2$ {^{31}P-NMR: 31.52 ppm; m/z (M^+) = 615.17; (M^-) = 279.84}.[24] Similarly, mixing $Ph_3PAuNTf_2$ with **C4** led to the immediate formation of the gold-amine complex Ph_3PAu(**C4**)NTf_2 {^{31}P-NMR: 30.56 ppm; m/z (M^+) = 784.43; (M^-) = 279.84}. Moreover, by adding **C4** to $Ph_3PAu(Bpy)NTf_2$ (1:1 ratio), the formation of Ph_3PAu(**C4**)NTf_2 was cleanly observed by ^{31}P-NMR and by ESI-MS, although a small peak of $Ph_3PAu(Bpy)NTf_2$ could still be detected by ESI-MS.[25] The reverse process, the addition of Bpy (2 equiv) to Ph_3PAu(**C4**)NTf_2, again allowed to detect by ESI traces of $Ph_3PAu(Bpy)NTf_2$, while the ^{31}P-NMR just showed a slight 0.1 ppm downfield shift of the Ph_3PAu(**C4**)NTf_2 signal.[26]

Overall, these data suggest that the organocatalyst **C4** establishes a stronger interaction than Bpy with $[Ph_3PAu]^+$, but when Bpy is present, the complex $Ph_3PAu(Bpy)NTf_2$ becomes available, at least to some extent. Most probably, Bpy facilitates the decomplexation of the secondary amine (**C4**) from Ph_3PAu(**C4**)NTf_2, and thereby the activation of the allenamide by the gold cation. In consonance with this hypothesis, the [2 + 2] homodimerization of allenamide **1a** provided very different outcomes with these three gold complexes (Scheme 1). Whereas the reaction catalysed by $Ph_3PAuNTf_2$ was completed in 0.5 h, providing **4aa** in 60% yield, Ph_3PAu(**C4**)NTf_2 did not afford this adduct even after 24h.[17a] Meanwhile, $Ph_3PAu(Bpy)NTf_2$ showed a moderate activity, leading to full conversion after 20h at rt (21% yield).[17a]



[Au]	time (h)[a]	yield
$Ph_3PAuNTf_2$	0.5	61%
$Ph_3PAu(Bpy)NTf_2$	20	21%
Ph_3PAu(**C4**)NTf_2	>24	0%

[a] Time requiered for full conversion

Scheme 2. Homodimerization experiments of **1a** with relevant gold-complexes.

To sum up, we have developed an intermolecular reaction involving a synergistic combination of enamine-mediated organocatalysis and gold (I) catalysis. The process, which involves the alkylation of an aldehyde with an allenamide, affords aldehydes incorporating tertiary and even quaternary α-stereocenters. While the reaction outcome is influenced by several parameters, we have found conditions that provide the products with moderate to good levels of enantioselectivity.

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17 (*a*) The allenamide **1a** polymerizes under the reaction conditions; (*b*) **3aa** was the only low molecular weight product detected in the crude mixture.

18 For further details, see the Electronic Supp. Info. (ESI).

19 It is known that he use of $^{-}NTf_2$ or the benzotriazole-based catalysts improves the stability of the Au(I) species in the presence of water and acids, see: (*a*) M. Jia and M. Bandini, *ACS Catal.,* 2015, **5**, 1638; (*b*) D. Wang, Y. Zhang, R. Cai and X. Shi, *Beilstein J. Org. Chem.,* 2011, **7**, 1014; (c) Control experiments using $HNTf_2$ or HOTf instead of the gold catalyst did not lead to the formation of the product **3aa**.[18]

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23 Aldehydes **3ae**-**3ai** and **3de**-**3di** are also obtained as E/Z mixtures. Thus, reactions were quenched with $NaBH_4$ to yield pure alcohols *E*-**3'**. The ee's of the parent aldehydes **3** were equal to those of their respective alcohols **3'**.

24 For a related complex, $Ph_3PAu(Bpy)PF_6$, see: (*a*) W. Clegg, *Acta Crys. Sect. B,* 1976, **32**, 2712; See also: (*b*) R. Cai, M. Lu, E. Y. Aguilera, Y. M. Xi, N. G. Akhmedov, J. L. Petersen, H. Chen and X. Shi, *Angew. Chem. Int. Ed.,* 2015, **54**, 8772.

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26 When adding 4 equiv. of Bpy to Ph_3PAu(**C4**)NTf_2, this shift became larger (0.15 ppm) and the peak of $Ph_3PAu(Bpy)NTf_2$ became more evident by ESI, further confirming the equilibrium.[18]

