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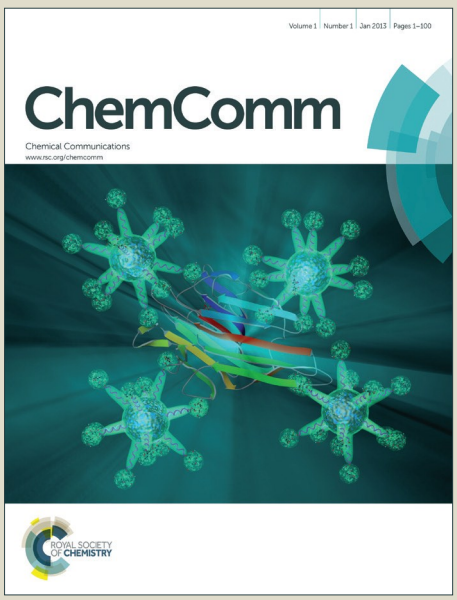

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Gold(I) Operational in Synergistic Catalysis for the Intermolecular α-Addition Reaction of Aldehydes across Allenamides

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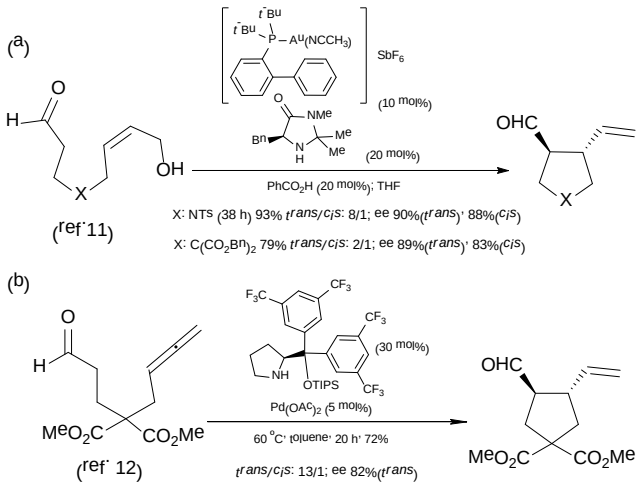
The intermolecular reaction of allenamides with aldehydes is reported. The designed approach relies on gold(I) and organocatalysis for activating the allenamide and the aldehyde respectively. Conditions to achieve an enantioselective version of this intermolecular reaction are defined.

Synergistic catalysis creates opportunities for designing carbon-carbon bond-making processes through polar reactions in which, simultaneously, synthetic catalytic access to the nucleophile and electrophile is granted. Thus, the reactivity of the precursors would be triggered by two different catalysts in synchronized but independent selective cycles. On this conceptual basis, unique catalytic approaches have been established.[1] The development of methodology for the enantioselective intermolecular α-allylic alkylation reactions of aldehydes is among those processes.[2] Often, the proposed reaction comprises trapping a catalytically generated allylic intermediate by an *in situ* formed enamine; typically, the former species roots from a productive metal-catalyzed activation of an allylic precursor, while the reactivity of the aldehyde is triggered by an organocatalyst.[3,4] Conceptually differentiate catalytic systems[5] have been recognized from combining asymmetric organocatalysis with metal catalysis, which resulted in processes of practical utility.[6] Moreover, gold catalysis has been a major player in advancing contemporary synthetic organic methodology.[7] In this respect, the merger of gold catalysis with organocatalysis is well established[8] and relevant examples of cascade catalysis have been disclosed.[9] However, its potential to devise synergistic approaches to the intermolecular aldehyde α-allylic alkylation reactions remains elusive.[10] Worth noting, the intramolecular process has been elegantly approached combining organocatalysis and cationic gold catalysis, using an alcohol as the required allyl donor (see Scheme 1).[11] Likewise, allene functionality has been used as the precursor for the allyl appendage in a synergistic approach to the same intramolecular process, which combines palladium and organocatalysis.[12] Furthermore, gold and enamine catalysis were early found useful for the direct intramolecular α-vinylation reactions of aldehydes with alkynes.[13] Allenamides are subject of current attention for the development of new gold-catalyzed reactions.[14] Now, we report the ability of gold-catalysis to merge with organocatalysis to accomplish an intermolecular α-addition reaction of aldehydes across allenamides, resulting in a new allylation event based on the principles of synergistic catalysis.

Far from kinetic constrains associated with the coordination of the two different catalytic cycles, competitive aldol condensation and allenamide [2+2] reactions must be carefully controlled. Initial trials focused on the reactivity of *N,4*-dimethyl-*N*-(1,2-propadienyl)benzenesulfonamide **1a** and 4-methyl-*N*-phenyl-*N*-(1,2-propadienyl) **1b** towards butanal **2a**, in search for catalysts that would afford the desired cross-adducts. Previous studies proved that $(2,4\text{-}t\text{Bu}_2\text{C}_6\text{H}_3\text{O})_3\text{PAuNTf}_2$ (***I***) is an efficient gold catalyst for the allenamide [2+2] reaction,[15] and also that the rate of dimerization of



Scheme 1. Synergistic catalysis: Intramolecular aldehyde α-allylation reaction.

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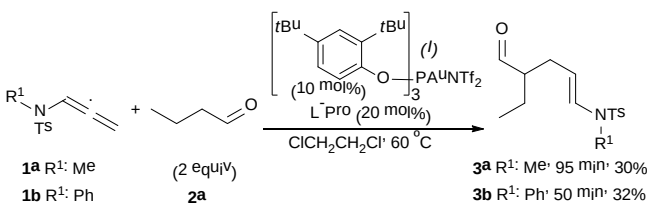
allenylsulfonamides is dependent on the additional substituent bonded to nitrogen, with aliphatic chains reacting under milder conditions. Furthermore, the electrophilic nature of ***I*** suggests that a certain degree of acidity would be beneficial to avoid catalysts passivation as the consequence of a likely unproductive complexation of ***I*** with the organocatalyst. Satisfyingly, it was discovered that ***I*** and *L*-proline synergistically work to furnish the target intermolecular α-aldehyde functionalization reaction with allenamides, yet in modest yield (Scheme 2). The reaction was conducted by slow addition of the allenamide **1** for a period of 15 minutes over a solution containing the catalysts and the excess of aldehyde, to minimize allenamide dimerization. The use of stoichiometric aldehyde (1 equiv) and organocatalyst did not result in improved formation of **3**, but in lowering the yield by a third.

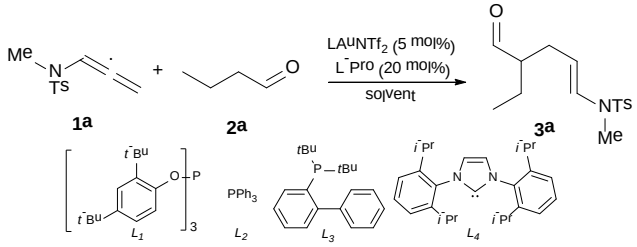
The absence of any of the two catalysts translates in lack of formation of **3**. Next, different experimental conditions and several catalyst modifications were tested, in an attempt to improve the efficiency of this new C-C bond-forming event. Representative data are summarized in Table 1.

The reaction takes place diminishing the catalyst loading by half but requires longer time. $IPrAuNTf_2$ (***IV***) is the more active catalyst (entries 1-6), and acetonitrile is a convenient media to conduct the target transformation (entries 7-13). Increasing the amount of **2a** up to 5 equiv and modifying the protocol for mixing reactants and catalysts (**2a** being stirred with proline before adding ***IV*** and **1a**) resulted in improved yield for forming **3a** (entry 14). A control experiment replacing the gold catalyst by $HNTf_2$ was performed for 3-phenylpropanal. The desired product was formed in only 11% (see ESI), highlighting the merit of merging gold and organocatalysis for triggering the process. Although enantiopure L-Pro was used, **3a** was obtained racemic. It might reflect an insufficient bulkiness of the carboxylic functionality to allow the required productive facial discrimination along the attack of the enamine to the gold-activated allenamide, at the time of **1a** lacking properly located hydrogen-bond acceptors for the key step. Alternative organocatalysts were tested under this experimental protocol. In all cases, the aldehyde-allenamide cross-reaction either failed or was less efficient than for proline. Representative examples are collected in Scheme 3 (yield from 1,3,5-trimethoxybenzene as internal standard). On this basis, the potential of the simultaneous catalytic activation of **1** and **2** by $IPrAuNTf_2$ and L-Pro was explored. The conditions in entry 14, Table 1 were chosen to check the scope of this addition to allenamides that, by prior standard reduction before isolation, resulted in the different alcohols depicted in Scheme 4.[16] Linear and β-branched aldehydes react towards allenamides to



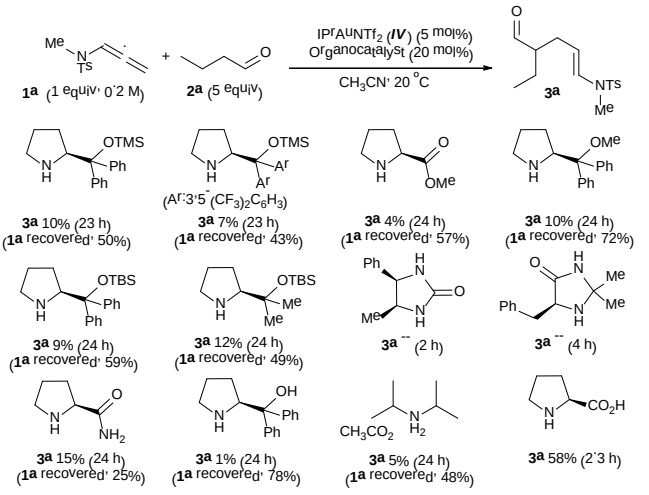
Scheme 2. Intermolecular allenamide reaction with aldehyde: initial results.

Table 1. Optimization of intermolecular allenamide-aldehyde cross-reaction



Entry	Gold cat.	Solvent	T (ºC)	t (h)[a]	Yield (%)[b]
1	***I*** (*L*: *L1*)	$ClCH_2CH_2Cl$	60	24	25[c]
2	***II*** (*L*: *L2*)	$ClCH_2CH_2Cl$	60	24	17[d]
3	***III*** (*L*: *L3*)	$ClCH_2CH_2Cl$	60	5.5	15
4	***IV*** (*L*: *L4*)	$ClCH_2CH_2Cl$	60	5.5	24
5	$AuCl_3$	$ClCH_2CH_2Cl$	60	2	7
6	$PtCl_4$	$ClCH_2CH_2Cl$	60	1	6
7	***IV***	THF	60	6.5	40
8	***IV***	Toluene	60	6	37
9	***IV***	CH_3CN	60	1.7	42
10	***IV***	CH_2Cl_2	40	21	37
11	***IV***	*t*BuOCH$_3$	60	7.8	35
12	***IV***	1,4-dioxane	60	22	40
13	***IV***	CH_3CO_2Et	60	21.5	38
14	***IV***	CH_3CN	20[e]	2.3	58

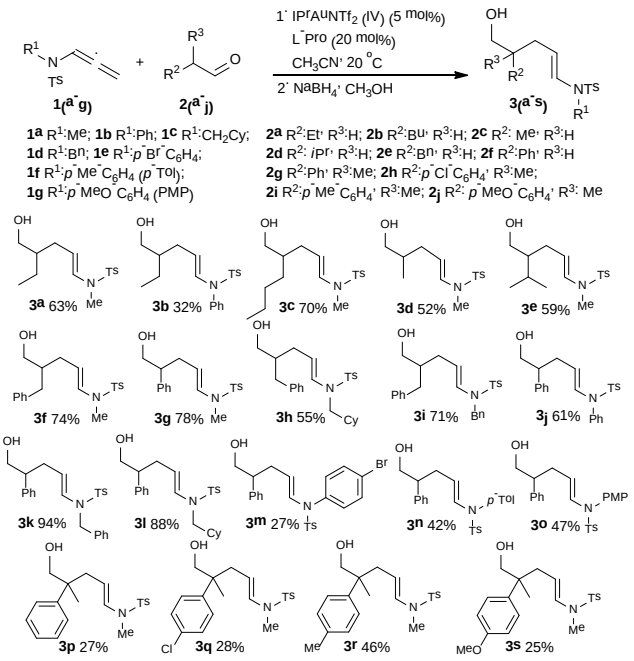
[a] Monitoring the disappearance of **1a** by TLC, unless otherwise specified. [b] Based on ^{1}H NMR analysis of crude reaction, adding 1,3,5-trimethoxybenzene as internal standard. [c] **1a** remains partly unreacted (25%). [d] 12% of **1a** unreacted. [e] 5 equiv of **2a** stirred with the organocatalyst for 10 min, and then ***IV*** and **1a** were added. The reaction was quenched adding Ph_3P.



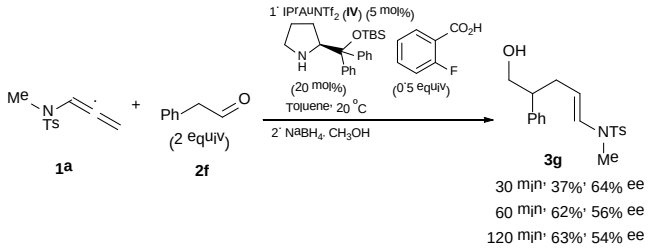
Scheme 3. Organocatalysts activity for **2a** addition to $IPrAuNTf_2$-activated **1a.**

furnish the target adducts (**3a**-**3l**) as the result of this intermolecular C-C bond-forming carbonyl α-functionalization process. For a given aldehyde, an *N*-alkyl allenamide gives higher yield than an *N*-aryl-substituted one; for instance, see the formation of **3g** vs. **3j**. At the same time, aldehydes giving conjugated enamines offer better performance than simple linear ones (**3g** against **3a**). Although quaternary centres can be assembled the yields range only from modest to moderate. Alternatively, excellent results are obtained from suitable partners, such as for getting **3k** from aldehyde **2f** and **1d.**

Next, the search for alternative experimental conditions was further pursued with the aim of overcoming the limitations evidenced by the first generation. Attention was paid to prepare quaternary centres in respectable chemical yield and to accomplish an enantioselective version. On the basis of the above quoted findings, an acid additive could help to broach the potential of other common but better space-shielding organocatalyst.[17] Under this assumption, some molecules early tested (Scheme 3) could be proper catalysts for this purpose. In this preliminary screening, attention was paid to render diaryl prolinol silyl ethers active catalyst for this synergistic transformation.[18] The reaction in presence of different acids was tested, and *ortho*-fluorobenzoic acid is a beneficial additive, as illustrated in Scheme 5 for the synthesis of **3g** from **1a** and aldehyde **2f**. Extended reaction time gives **3g** in higher yield but concomitant loss of steroselectivity is noticed, likely due to its partial epimerization under the reaction conditions. Exploring the utility of this protocol for preparing quaternary stereocenters is an attractive option. The reaction is sluggish but, as epimerization is not operating, the amount of acid can be increased up to 1 equiv to speed the reaction. Also, the more polar acetonitrile was chosen as the solvent, and the results are collected in Table 2. A control experiment replacing



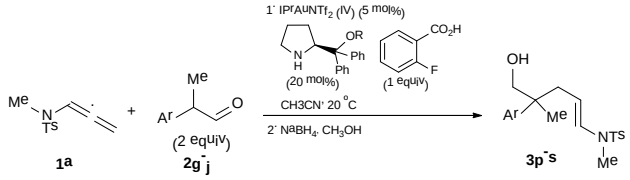
Scheme 4. Intermolecular aldehyde **1** α-addition reaction to allenamides **2.**



Scheme 5. Activation of TBS-masked diaryl prolinol for adding **2f** to **1a.**

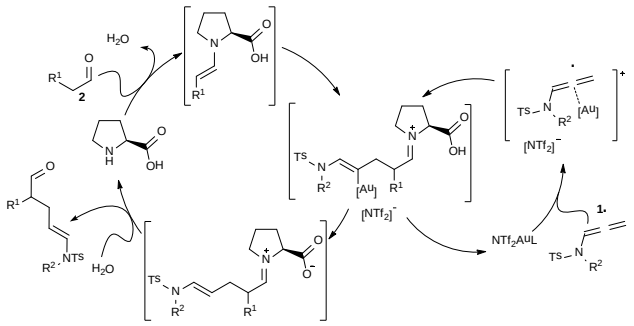
gold by $HNTf_2$ was tested for preparing **3p**. The desired adduct was formed in 18% yield (vs. 72%, Table 2). Interestingly, it works nicely for accessing the racemic product using a highly enolizable aldehyde, modifying the first generation conditions in Scheme 4 (**3p** now isolated in convenient 51% yield, see ESI). As depicted in Table 2, the efficiency of the diarylprolinol frame was further tested using two different *O*-protected silyl derivatives. As early noticed,[19] the more sterically demanding TIPS-masked prolinol affords improved stereocontrol although only modest chemical yield. Conversely, using the related TBS-protected organocatalyst, the quaternary center is formed in excellent yield although in lower, but still respectable, enantiomeric excess for the different α-aryl propanals assayed. A tentative proposal that accounts for the formation of the observed products matching the characteristic of this new C-C bond-forming event and lining up with previous mechanistic insights in the field[20] is graphically outlined in Scheme 6. Activation of allenamide **2** by gold(I) gives rise to the required electrophile, which is trapped by the in situ formed enamine from reacting aldehyde **1** with the organocatalyst. The Brønsted acid facilitates both, the enamine formation and the regeneration of both types of active catalysts.

Table 2. Quaternary stereocenters from enantioselective addition of **2** to **1.**



Entry	Ar / **2**	R	t (h)[a]	**3** (%)[b]	ee (%)
1	C_6H_5 / **2g**	TBS	4	**3p** 72	76
2	C_6H_5 / **2g**	TIPS	3	**3p** 25	86
3	*p*-$MeOC_6H_4$ / **2j**	TBS	4	**3s** 73	68
4	*p*-$MeOC_6H_4$ / **2j**	TIPS	7	**3s** 32	80
5	*p*-ClC_6H_4 / **2h**	TBS	8	**3q** 27	24
6	*p*-ClC_6H_4 / **2h**	TIPS	8	**3q** 23	60
7	*p*-MeC_6H_4 / **2i**	TBS	2.25	**3r** 80	60
8	*p*-MeC_6H_4 / **2i**	TIPS	7	**3r** 35	82

[a] Monitoring reaction progress until disappearance of **1a**. [b] Isolated yield.



Scheme 6. Proposed gold-organocatalyzed synergistic C-C bond-formation

In short, a C-C bond-forming reaction by adding the Cα-H bond of an aldehyde to the distal bond of an allenamide is presented. The reaction relies on the power of synergistic catalysis merging gold with organocatalysis. Its usefulness to approach the preparation of quaternary carbon-stereocenters is covered and an asymmetric version presented.

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