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Head-to-tail homo- and heterodimerization of vinylamides by hidden proton catalysis

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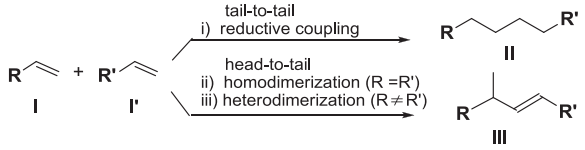
ABSTRACT

Chemoselective dimerization of vinylamides is reported. A number of vinylacylamides were shown to undergo stereoselective cationic intermolecular head-to-tail homodimerization. Correspondingly, chemoselective heterodimerization reactions readily afforded hydroalkenylation of vinylacylamide with vinylsulfonamide. Different mild methods for hidden proton catalysis were studied. The in situ generation of, e.g., $HSbF_6$ from the [Au]SbF_6–PhC≡CH] catalytic systems was applied. Successful vinylacylamide head-to-tail dimerizations seem to be dependant on the ability of N–C–O acylamide electron delocalization, affording stabilized intermediates. In general, the reactions demonstrate the ability of vinylacylamides to effectively undergo hydroalkenylation to afford 1,3-*N*,*N*-functionalized (*E*)-but-1-ene products.

1. Introduction

Alkenes may undergo different chemoselective dimerization processes (Scheme 1; (i)–(iii)). Aliphatic coupling products **II** may be obtained through metallacycle intermediates by some transition-metal catalyzed (i) reductive tail-to-tail dimerization of alkenes **I** and **I′**.[1] Homodimerization of alkenes **I** may take place by tail-to-tail or head-to-head couplings. In contrast, the (ii) head-to-tail homodimerization would afford the respective branched vinylic dimers **III** (R≡R′). Correspondingly, (iii) heterodimers **III** (R=R′) may chemoselectively be provided by mixed dimerization of two different vinyl moieties **I** and **I′** in a hydroalkenylation manner.



Scheme 1. Dimerization processes.

Studies of styrene (ii) homodimerization catalyzed by acid zeolites[2] or with liquid acids (H_2SO_4)[3] have shown that such reactions suffer from low selectivity since the (cyclo)dimers are formed together with variable amounts of trimers and oligomers with nearly lack of *Z*/*E* stereoselectivity. A variety of catalytic conditions, based on e.g., Pd,[4a–c] Co[4d] and Ni[4e] complexes are known to promote selective (ii) head-to-tail homodimerization. Lewis acids, such as Fe(III) complexes[4f] or $In(OTf)_3$,[4g] catalyze regio- and stereoselective head-to-tail homo- and heterodimerization of vinylarenes. Such reactions are suggested to take place through a cationic mechanism.

We have recently studied the chemoselective cyclopropanation and [2+3] cycloaddition reaction pathways taking place by gold(I) catalyzed reactions of propargyl derivatives with vinylic compounds directly connected to a heteroatom, such as vinylic acetates, ethers and amides (Scheme 2).[5] In some cases, the expected cyclopropanation or [2+3] cycloaddition pathways to give products **3** or **3′** were not favoured. However, in a reaction of vinylpyrrolidone (**2a**) and phenylpropargyl pivaloate (**1**) in the presence of the gold catalyst Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN]SbF_6, an intermolecular vinyl homodimerization mainly took place by hydroalkenylation of the vinylamide and, thus, the head-to-tail *E*-homodimer **4a** was isolated in 85% yield. The unpredicted outcome of the reaction was limited to the vinylacylamides, such as the vinylpyrrolidinone **2a**. A possible reaction pathway includes the vinylamide, acting both as a nucleophile and an electrophile, which is surprising due to their relatively poor nucleophilicity compared

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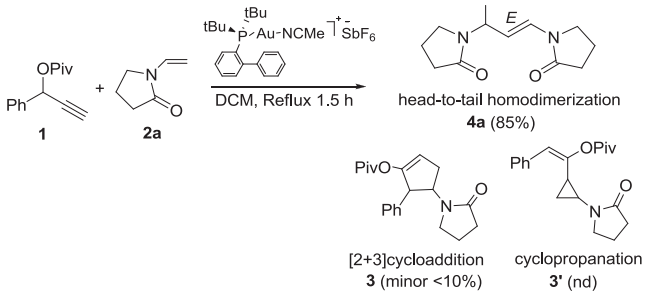


Scheme 2. Gold(I) catalyzed cycloaddition and dimerization processes.

with, e.g., electron-rich enamines used for nucleophile activation in organocatalysis.

Despite the variety of protocols developed for vinylarene dimerization, to the best of our knowledge, only a few homo- or heterodimerization reactions of vinylamides have been reported. Ruthenium catalyzed codimerization of *N*-vinylacylamides with alkenes afforded moderate yields of heterodimers (**III**, Scheme 1) with >88% *E*-selectivity.[4h] Only *N*-vinylacylamides did undergo successful heterodimerization, whereas no codimerization took place with *N*-methyl-*N*-vinyltoluenesulfonamide (see our NMeTs-vinylamide **2g** below), explained by the lack of Ru-chelation ability of the tosylamide (S=O in contrast to acylamide C=O). A mechanistic study of cationic polymerization of *N*-vinylacylamides[4i] has been carried out, due the fact that *N*-vinylacylamides, being important monomers for industrial free-radical polymerization, are less frequently applied in cationic induced polymerizations.[4j–m] Different outcomes of the reactions of two secondary and two tertiary vinylacylamides were observed as, respectively, cationic polymerization and head-to-tail homodimerization took place. No optimization studies were carried out.

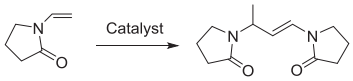
We wanted to explore the potential and limitations of head-to-tail intramolecular homo-coupling of tertiary *N*-vinylacylamides and -sulfonamides, as well as the ability of such substrates to undergo more challenging heterodimerization. In order to identify the active catalyst and investigate the effect of different catalytic systems, a further study and optimization of the catalytic system was essential. We herein report our investigations on catalyzed vinylamide dimerization reactions.

2. Results and discussion

2.1. Studies on the catalytic system

With the aim of revealing the true nature of the active catalyst, promoting the vinylamide dimerization, we investigated the effect of modified catalytic systems based on the originally applied reaction conditions (Scheme 2) with vinylpyrrolidone (**2a**) and phenylpropargyl pivaloate (**1**) in the presence of the gold catalyst Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$ (Table 1), affording the head-to-tail homodimer **4a** as the major product. However, we observed that the propargylic ester **1** was not involved in the reaction, as the propargyl compound was fully recovered (entry 1). On the other hand, the gold-catalyzed dimerization of the vinylic substrate **2a** was unsuccessful in the absence of propargyl compound **1** (entries 2 and 3), demonstrating its essential effect on the reaction. Further studies showed that effective dimerization was also obtained by replacing the propargylic compound **1** by other terminal alkynes, such as phenylacetylene (84% yield **4a**, entry 4). The outcome of the reaction was unaffected by applying the normal Au(I)Cl/SbF$_6$ counter-ion exchange

Table 1
Studies on catalysts to promote vinylamide dimerization



2a **4a**

Entry	Conditions[a]	Dimer **4a**; isolated yield (**2a** conversion)
1	Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$ Propargyl ester **1**	85% (99%)
2	Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$	nd[b]
3	Au[P(*t*-Bu)$_2$(*o*-biphenyl)Cl+AgSbF$_6$	nd[b]
4	*Au[P(t-Bu)$_2$(o-biphenyl)CH$_3$CN]SbF$_6$ Phenylacetylene*	84% (99%)
5	Au[P(*t*-Bu)$_2$(*o*-biphenyl)Cl+AgSbF$_6$ Phenylacetylene	73% (99%)
6	AgSbF$_6$, Phenylacetylene	nd[b]
7	Phenylacetylene	nd[b]
8	Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$ 1-Phenyl-1-propyne	nd[b]
9	AgSbF$_6$	nd[b]
10	Au[P(*t*-Bu)$_2$(*o*-biphenyl)Cl	nd[b]
11	HSbF$_6$[c]	60% (99%)
12	TFA[c]	35% (40%)
13	HOTf[c]	43% (80%)
14	H$_2$SO$_4$[c]	51% (99%)
15	AgSbF$_6$, DCE[d]	72%
16	AgOTf, DCE[d]	74%
17	AgOTf, DCE+*t*-BuCl[d]	77%

[a] Catalyst (5 mol %), DCM (10 mL/mmol substrate), reflux, 1.5 h.
[b] No dimer formation.
[c] Bronsted acid (2.5–5 mol %).
[d] Silver salt (5 mol %)+DCE (10 mL/mmol substrate) (+*t*-BuCl; 0.1 equiv).

procedure, even if some lower yields of dimer **4a** were obtained (73%, entry 5). No dimerization took place in the absence of the gold(I)SbF$_6$ catalyst (entries 6 and 7) and non-terminal alkynes did not afford dimerization (entry 8). Simpler Ag(I) or Au(I) catalytic systems also failed to catalyze the reaction (entries 9 and 10).

The fact that the presence of a terminal alkyne was crucial for the vinyl dimerization to take place, would indicate that a gold(I)-acetylide complex was formed by PhCCH deprotonation and a subsequent MeCN–acetylide ligand exchange. The rapid acetonitrile ligand exchange was demonstrated by NMR studies of a 1:1 mixture of propargyl ester **1** and the applied [Au(I)NCMe]SbF$_6$ complex, shown by the instant disappearance of the liganded acetonitrile ^{1}H NMR singlet (1.50 ppm) and the new recorded 'free' acetonitrile new singlet (2.32 ppm).[5b]

Dual gold catalysis including geminal digold complexes as well as dinuclear gold(I) σ,π-acetylide complexes, is currently given considerable attention.[6] Actually, gold-catalyzed reactions involving terminal alkynes have been reported to involve formation of gold(I) σ,π-acetylide digold species.[6e,f] Due to the generation of a strong Brønsted acid during the reaction, it has been remarked that the potential involvement of proton catalysis should be considered in gold-catalyzed transformations involving terminal alkynes. Studies of [2+2] phenylacetylene–alkene cycloaddition in the presence of $[Au(L)NCMe]^+SbF_6^-$ catalysts showed the generation of the HSbF$_6$ bronsted super-acid by the formation of digold $[(AuL)_2CCPh]^+SbF_6^-$ complexes:[6g]

$$PhC{\equiv}CH + 2\left[[Au(L)NCMe]^+SbF_6^-\right] \rightarrow \left[[(AuL)_2C{\equiv}CPh]^+SbF_6^-\right] + 2MeCN + \mathit{HSbF_6} \quad (1)$$

Control experiments indicated that $HSbF_6$ directly promoted the formation of mixtures of α-methylstyrene (cyclo)dimer products.

There is a recent focus on reactions catalyzed by in situ generated Bronsted acids from Lewis acid or metal triflate pre-catalysts. The use of the so-called 'Hidden Brønsted acid catalysis' was lately studied and successfully applied in hydroalkoxylation reactions by generation of HOTf from AgOTf and 1,2-dichloroethane (DCE) or *t*-BuCl by chloride abstraction.[7] The AgCl precipitate was either initially filtered off or left in the resulting suspension to allow in situ proton generation and a one-pot reaction protocol.

We wanted to study whether the present vinylamide dimerization would take place by the alternative hidden proton-catalyzed pathway from the [$AuSbF_6$–PhC≡CH] catalytic system. Thus, by replacing the gold(I)SbF_6/terminal alkyne system with the direct addition of $HSbF_6$ super-acid or other acids (entries 11–14), it would become clear whether the vinylamide **2a** dimerization actually was catalyzed by $HSbF_6$, generated in situ. In fact, the dimerization took place in the presence of approximately 2.5–5 mol % $HSbF_6$ (entry 11), affording full conversion of vinylamide **2a**, but only moderate yield of dimer **4a** (60%). Other acids, such as TFA, HOTf and sulfuric acid also afforded dimerization, but lower conversion of **2a** and poorer yields of dimer **4a** (35–51%, entries 12–14) were obtained.

Such control experiments were shown to be less reliable, due to problems arising from the handling of small amounts of strong acids.[7] The hidden proton catalysis methods allow milder conditions by controlled generation of the acid catalyst. Therefore, an alternative experiment with in situ generation of $HSbF_6$ super-acid from $AgSbF_6$ in DCE, based on an established protocol,[7] was tested. The dimer **4a** was isolated in high yields (72%, entry 15) from vinylamide **2a** (entry 15). Correspondingly, the previously established method,[7] generating HOTf from AgOTf and DCE or *t*-BuCl, afforded similar yields of product **4a** (74–77%, entries 16 and 17).

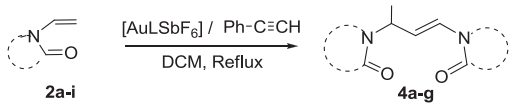
Thus, the protocols for hidden Bronsted acid catalysis, generating $HSbF_6$ or HOTf from the [$AuSbF_6$–PhC≡H] (entries 4 and 5) catalytic system or from the respective silver salts ($AgSbF_6$/AgOTf and DCE/*t*-BuCl; entries 15–17), afforded higher yield (more than 72%) of dimer **4a** from vinylamide **2a** than corresponding control experiments with direct acid catalysis with $HSbF_6$ or HOTf (60 and 43%, entries 11 and 13).

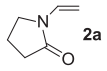
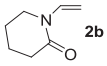
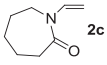
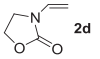
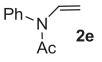
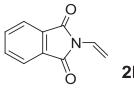
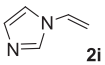
Most of these one-pot methods (entries 5 and 15–17) cause precipitation of AgCl. The resulting suspensions seem to reduce the dimer yields (72–77%) relative to the catalysis with proton generation from the [$AuSbF_6$–alkyne] systems (84–85%, entries 1 and 4), not including chloride counter-ion exchange and AgCl precipitation. A similar observation was made for the homodimerization of *N*-methyl *N*-acetamide **2f** ($AgSbF_6$/DCE; 49% vs $AuSbF_6$/alkyne; 69% yield of dimer **4f**; Table 2, entry 6 below). Hence, the most effective and convenient one-pot reaction was obtained by the hidden Bronsted acid catalysis protocol by in situ generation of $HSbF_6$ from the catalytic [Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH_3CN]SbF_6–PhC≡CH] system in refluxing dichloromethane (Table 1, entry 4), which was used in the subsequent study.

2.2. Homodimerization

A number of vinylacylamide compounds were shown to undergo homodimerization to afford 1,3-*N*,*N*-functionalized (*E*)-but-1-ene products (Table 2). Heterocyclic vinylacylamides (vinyl-pyrrolidinone, -piperidinone, -azepanone, -oxazolidinone, **2a**–**d**) afforded the respective dimers **4a**–**d** in high yields (72–89%; entries 1–4). Likewise, the open-chained vinyl *N*-phenyl- and *N*-methyl *N*-acetamides **2e** and **2f** readily gave homodimers **4e** (64%, entry 5) and **4f** (69% (49% obtained with $AgSbF_6$/DCE), entry 6). Some degree of isomerization of the main *N*-acetamide product **4f** took place, as shown by the presence of minor amounts of amide rotamers of **4f** (approx. 25% in total by ^1H NMR), as also reported by others.[4i] A corresponding isomerization of the *N*-phenyl product **4e** was not observed. In contrast to the rapid reactions of **2a** and **2f** (1.5 h and 30 min, entries 1 and 6), the corresponding dimerization of the heterocyclic vinylacylamides **2b**–**d** was slower (more than 20 h, entries 2–4).

Table 2
Vinylamide homodimerization catalyzed by Au(I)SbF_6–alkyne



Entry	Monomer	Reaction time[a]	Dimer (yield)
1	 **2a**	1.5 h	**4a** (84%)
2	 **2b**	24 h	**4b** (79%)
3	 **2c**	24 h	**4c** (89%)
4	 **2d**	20 h	**4d** (72%)
5	 **2e**	2 h	**4e** (64%)
6	 **2f**	30 min	**4f** (69%)[d]
7	 **2g**	30 min[b]	nd[c]
8	 **2h**	24 h	nd[e]
9	 **2i**	24 h	nd[e]

[a] Reaction time needed to give full conversion (GLC).
[b] Reaction at 0 °C.
[c] No dimer, complex product mixture.
[d] 49% obtained by in situ $HSbF_6$ generation from $AgSbF_6$/DCE.
[e] No dimer, no conversion.

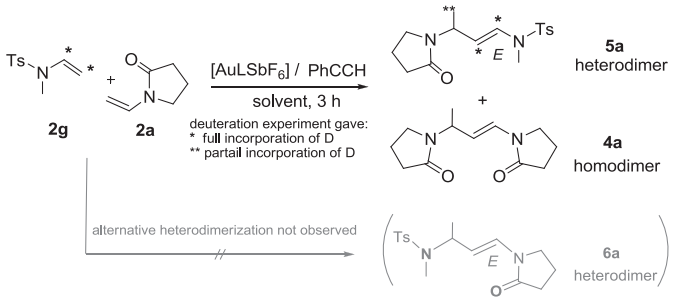
The NMeTs-vinylsulfonamide **2g** was, however, far too reactive and gave instantly complex product mixtures, also at 0 °C (entry 7). Our previous studies[5a] on gold(I) catalyzed cyclizations of propargyl esters have shown that NMeTs-vinylamide **2g** follows a different reaction pathway than other vinylic reactants tested, showing the deviating reactivity of this vinylic compound. The *N*-vinylphthalimide **2h** and vinylimidazole **2i** compounds were not reactive and no conversion could be observed, even after 24 h (entries 8 and 9).

2.3. Heterodimerization

By tuning the reactivity of two different vinylamide reactants, heterodimerization reactions could take place by vinylamide hydroalkenylation in a mixed dimerization manner. In order to study possible chemoselective formation of heterodimers, the

electronic or steric nature of different vinylamide substrates was varied. The results from reactions based on this strategy in the presence of the [$AuSbF_6$–alkyne] system, are shown in Tables 3 and 4. Since the NMeTs-vinylsulfonamide **2g** was too reactive to allow controlled homodimerization, this compound was chosen for heterodimerization with less reactive vinylacylamide reactants.

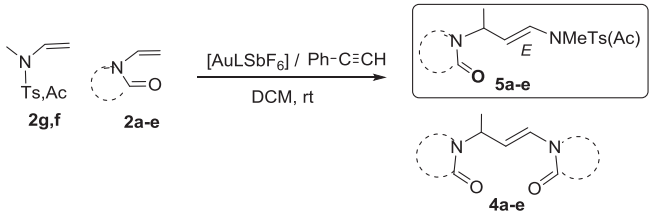
Table 3
Optimization of mixed dimerization in the presence of $Au(I)SbF_6$–phenylalkyne



Entry	2g (equiv)	2a (equiv)	PhCCH (equiv)	Temp, solvent	Conv. (%)	**5a** Yield,[a] % (ratio, %)	**4a** Yield[a] (ratio, %)
1	1	1	1	rt, DCM	99	43 (58)	32 (42)
2	1	1	1	0 °C, DCM	50	(74)	(26)
3	1	2	1	rt, DCM	99	(39)	(61)
4	2	1	1	rt, DCM	99	53 (75)	21 (25)
5	2	1	1	rt, THF	78	50[b]	28[b]
6	2	1	1	rt, CH_3NO_2	85	23[b]	62[b]
7	2	1	1	rt, CH_3CN	36	10[b]	26[b]
8	2	1	1	rt, toluene	39	12[b]	27[b]
9	2	1	1	rt, MeOH	nd[c]	—	—
10[d]	2	1	1	AgOTf in DCE[7]	99	50	19
				$AgSbF_6$ in DCE	99	52	20

[a] Isolated yield.
[b] Yield by GLC.
[c] No dimer, complex product mixture.
[d] (i) HOTf[7]/$HSbF_6$ generated from AgOTf[7]/$AgSbF_6$ (5 mol %) in DCE (10 mL/mmol substrate), reflux, 2 h; (ii) dimerization of **2g** (2 equiv)+**2a** (1 equiv), rt, 3 h.

Table 4
$Au(I)SbF_6$–PhC≡CH catalyzed heterodimerization reactions[a]



Entry	Monomer	Monomer	Reaction time	Heterodimer (yield, %)	Homodimer (yield, %)
1[b]	**2g**	**2a**	2 h	**5a** (53)	**4a** (21)
2[b]	**2g**	**2b**	24 h	**5b** (46)	**4b** (19)
3[b]	**2g**	**2c**	24 h	**5c** (48)	**4c** (25)
4[b]	**2g**	**2f**	1 h	**5f** (43)	**4f** (15)
				6 (5%)	

Table 4 (*continued*)

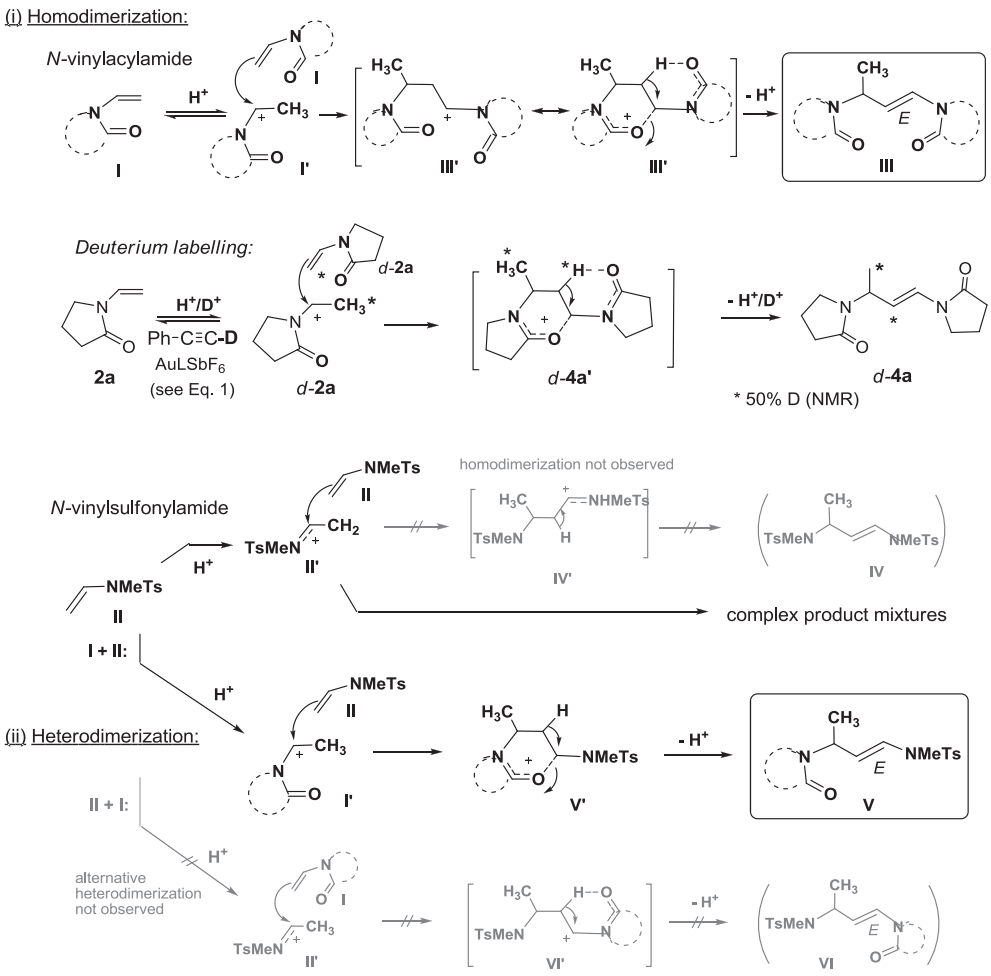
Entry	Monomer	Monomer	Reaction time	Heterodimer (yield, %)	Homodimer (yield, %)
5[c]	**2f**	**2a**	1 h	nd[d]	**4a** (49) **4f** (Traces)
				7 (<5%)	

[a] The reactions were performed with phenylacetylene (1.0 equiv), vinylamide **I** (**2g**, **2f**) (2.0 equiv) and vinylacylamide **II** (**2a**, **2b**, **2c**, **2f**) (1.0 equiv) in DCM (10 mL/mmol) and gold catalyst (0.05 equiv) dissolved in DCM (10 mL/mmol).
[b] Product **6** was formed in minor amounts.
[c] Product **7** was formed in minor amounts.
[d] Not detected.

Full conversion of NMeTs-vinylamide **2g** with vinylpyrrolidinone **2a** (1:1) was obtained in 3 h at room temperature in DCM (Table 3, entry 1). The *E*-heterodimer **5a** was formed by hydroalkenylation of vinylacylamide **2a** with vinylsulfonamide **2g**. The alternative heterodimer **6a**, formed by the opposite hydroalkenylation of vinylsulfonamide **2g** with vinylacylamide **2a** was not observed. A distinction between the possible structures **5a** and **6a** of the isolated dimer could not be concluded based on NOESY NMR experiments, due to the highly flexible nature of the product. The identity of the isolated heterodimer was, however, particularly based on 2D HMBC NMR data, as shown by the explicit C/H correlations between the pyrrolidinone CH_2–N–*C*O structure moiety and the neighbouring *CH*–CH_3 group. Also, a general comparison of NMR data of all heterodimer products discussed below (**5a**, **b**, **c**, **f**, Table 4) with the corresponding homodimers **4a**, **b**, **c**, **f** supported the identity of the formed heterodimer. The formation of heterodimer **5a** is in accordance with the proposed favoured reaction pathway discussed below (Scheme 3). The structure of the dimeric product was finally verified by a deuteration experiment with 1,1,2-d_3-vinylsulfonamide d_3-**2g** and vinylacylamide **2a**. Product *d*-**5a** was formed with selective and complete deuterium incorporation in positions 1 and 2 as well as partial deuteration of the methyl group (approx. 50% D), as indicated by asterisk labelling in Table 3 (see discussion on mechanism and formation of deuterated *d*-**4a** in Part 2.4 and Scheme 3 below).

Product **5a** was isolated in 43% yield from a 58:42 mixture of hetero- and homodimers **5a** and **4a**. Higher hetero-/homo-chemoselectivity (74:26), but only 50% conversion, was obtained at 0 °C (Table 3, entry 2). As expected, a 2:1 ratio of vinylacylamide **2a** and vinylsulfonamide **2g** favoured the formation of homodimer **4a** (entry 3).

However, a 1:2 ratio of substrates **2a** and **2g** would compensate for the high reactivity of NMeTs-vinylamide **2g** and afforded full conversion of monomer **2a** and 53% yield of heterodimer **5a**, isolated from a 75:25 mixture of hetero- and homodimers (Table 3, entry 4). By varying the solvent, lower conversion and lower yields were obtained, as the reactions in both THF and nitromethane did not afford complete conversion (Table 3, entries 5 and 6; 78–85%) and, hence, lower yield of heterodimer **5a** was obtained (23–50% by GLC). The effectivity of the reaction was dramatically reduced in acetonitrile and toluene (Table 3, entries 7 and 8), in contrast to high yields in toluene being used by others.[4i] No dimerization took place in methanol, since conversion into other products was seen (Table 3, entry 9).



Scheme 3. Proposed mechanism for acid catalyzed vinylamide head-to-tail homo- and heterodimerization.

Similar results as for the [$AuSbF_6$—alkyne] system (Table 3, entry 4) were obtained by hidden proton catalysis performed with the $AgSbF_6$/DCE or AgOTf/DCE[7] methods (Table 3, entry 10) However, the silver salt protocols require an additional reflux period (2 h) for the in situ generation of the Bronsted acids before the dimerization reaction at room temperature (3 h).

These optimization studies indicated that the most convenient and effective reactions were obtained a 2:1 ratio of vinylamides **2a** and **2g** at room temperature in dichloromethane by in situ generation of $HSbF_6$ from [$AuSbF_6$—PhCCH] (Table 3, entry 4), which was used in the subsequent study (Table 4, entry 1).

NMeTs-vinylamide **2g** did also undergo heterodimerization with other heterocyclic vinylacylamides, such as vinylpiperidin-2-one **2b** and vinylazepan-2-one **2c** (46 and 48%, Table 4, entries 2 and 3). In contrast to the rapid reactions of **2g** with substrate **2a** (2 h, Table 4, entry 1), the corresponding heterodimerization with the heterocyclic vinylacylamides **2b**,**c** were slower (24 h, entries 2 and 3). This is in accordance with observations for homodimerizations (Table 3). Rapid heterodimerization of **2g** did also take place with the noncyclic *N*-methyl *N*-acetamide **2f** and afforded 43% of heterodimer **5f** in 1 h (Table 4, entry 4). Heterodimerization of vinyl *N*-methyl-*N*-acetamide **2f** with vinylpyrrolidinone **2a** was unsuccessful, as only homodimer **4a** was formed as a major product (49%, Table 4, entry 5).

Minor amounts (<5%) of acetylide coupling product **6** were isolated from the reaction with NMeTs-vinylamide **2g** (entry 4). The analogous formation of a corresponding alkyne product **7** (5%) from *N*-methyl-*N*-acetamide **2f** was indicated by ^{1}H NMR (entry 5). These observations demonstrate that the present phenylalkyne compound reacted to give hydroalkynylation of vinylacetamide **2f** and vinylsulfonamide **2g**. This hydroalkynylation of vinylamides supports the assumption that an acetylide nucleophile would be generated by PhCCH deprotonation to give a gold(I)-acetylide complex, as discussed above. The present observation may also be relevant for the mechanistic understanding of similar previously reported gold(I)[8] and silver(I)[9] catalyzed hydroalkynylation reactions.

2.4. Rationalization of the dimerization process

Our results discussed above demonstrate the ability of vinylamides to act both as nucleophiles and electrophiles to undergo dimerization. In fact, vinylamides and vinylsulfonamides, similar to the vinyl pyrrolidine-2-one **2a** (as well as **2b**,**d**) and the vinyl N(Me)Ts **2g** structure moieties, have been used as π-nucleophiles.[10] These deactivated vinylamides had the capacity to undergo intramolecular alkyne addition as a part of tandem cyclizations, due to Pt(II), Ag(I) or gold(I) catalysis. Nevertheless, in some instances both the latent nucleophilic and electrophilic nature of vinylsulfonamides (NTs) were observed.[10b]

In our acid catalyzed vinyl dimerization reactions, the acylamide functionality attached to at least one of the vinylic substrate appears to be a crucial prerequisite for vinyl dimerization reactions.

(i) *Homodimerization* (Scheme 3i). Although the electron density and the nucleophilic character of the vinylic moiety in heterocyclic vinylacylamides **I** are moderate, the protonation of vinylamide monomer **I** may afford a carbocationic intermediate **I′**, activated for subsequent nucleophilic attack by a second monomer of vinylamide **I**. The driving force in successful vinylamide

homodimerization reactions seems to be caused by essential amide N–C–O electron delocalization. Hence, the C–C bond formation is favoured, since the second carbocationic intermediate allows stabilization through a six-membered cyclic species **III′**, formed by an internal C=O/carbocation coordination. This reaction mechanism is in accordance with previous studies.[4i] It was shown that the secondary *N*-vinylformamide and *N*-vinylacetamide monomers readily afford oligomers by polymerization with various cationic initiators, while the tertiary substituted *N*-vinylacylamides, *N*-methyl-*N*-vinylformamide and *N*-vinylpyrrolidinone (compound **2a** above), unexpectedly gave the homodimeric head-to-tail *E*-products, corresponding to products **III**. Neither dimeric nor oligomeric products could be obtained from *N*-methyl-*N*-vinylacetamide (compound **2f** above). The reactions were carried out in toluene at room temperature and different cationic initiators were applied (HOTf, TMST, iodine, bromine), but no optimization studies were carried out. The different outcome of the reactions of secondary and tertiary vinylacylamides was explained by the important role of the acidic NH in secondary amides, allowing imine–enamide tautomerization and proton transfer of the amide-bonded hydrogen to a second monomer to provide polymerization. In tertiary vinylacylamides, the amide hydrogen has been substituted by an alkyl group, preventing analogous polymerizations. Thus, the reaction was suggested to follow the alternative homodimerization pathway, favoured and rationalized by the stabilized intermediate **III′**.[4i] Furthermore, we think that the final β-H elimination from the carbocationic precursor **III′** to afford the homodimeric product **III** would be assisted by internal H-bonding, due to N–C–O electron delocalization of the second amide moiety.

Thus, the mechanism would explain why head-to-tail homodimerization of the heterocyclic vinylacylamide **I** is preferred and why further polymerization does not take place. The locked configuration of the stabilized bicyclic intermediate **III′** would also rationalize the preferred and exclusive stereoselective formation of *E*-products **III**.

The faster conversion of vinylpyrrolidinone **2a** (1.5 h, entry 1, Table 2) than the other vinyl heterocyclic amides **2b**,**c** (20–24 h, entries 2 and 3), may be caused by more efficient stabilization of intermediate **I′** since the five-membered pyrrolidinone-ring allows a nearly planar sp^2-nitrogen. The delocalization capacity of the vinylic cyclic carbamate **2d** (20 h, entry 4) would also be lower than the corresponding vinylacylamide **2a**.

A catalytic system based on *deuterium*-phenylalkyne [Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$–PhC≡D] would afford in situ generation of D^+ (see Eq. 1) and, hence, enable a deuterium labelling experiment. The results obtained from vinylpyrrolidinone (**2a**) and 1 equiv *d*-phenylalkyne confirmed the proposed mechanism (Scheme 3i). Substrate **2a** would undergo a partly proton–deuterium exchange to give approximately 50% incorporation of deuterium in the terminal vinylic positions (*d*-**2a**), since the reaction would take place in an approximately 50:50% D^+/H^+ mixture, due to the release of a proton in the final product forming step (**III′** to **III**; *d*-**4a′** to *d*-**4a**). This is in accordance with the observed 50% deuterium incorporation (NMR) in the 2- and 4-positions of the isolated 1,3-*N*,*N*-functionalized (*E*)-but-1-ene dimer product *d*-**4a**.

The corresponding open-chained *N*-methyl- and *N*-phenyl-*N*-acetamide substrates **2f** and **2e** were highly reactive. However, controlled homodimerization was obtained in 30 min to 2 h (entries 5 and 6), in contrast to the unsuccessful dimerization previously reported[4i] for vinyl-NMePh **2f**. The high reactivity of this flexible substrate may be a result of the excellent delocalization and stabilization of cation intermediates **I′** and **III′**, since a planar sp^2-nitrogen centre readily may be formed. The vinylsulfonylamide **II** (Table 2, **2g**, entry 7) may not enable intermediate stabilization by sulfonamide electron delocalization (**IV′**), similar to the acylamides **I** above. Thus, NMeTs-vinylamide **II** instantly gave complex product mixtures and no homodimers **IV** (Scheme 3i) were formed.

The *N*-vinylphthalimide **2h** and vinylimidazole **2i** compounds did not afford the respective dimerization products, probably due to their lower or missing ability to stabilize intermediates by amide N–C–O electron delocalization.

(ii) *Heterodimerization* (Scheme 3ii). In contrast to the uncontrolled reactions of NMeTs-vinylamide **II** and the homodimerization of vinylacylamides **I**, a competing reaction pathway was taking place in the presence of both vinylamides **I** and **II**. The carbocationic intermediate **I′**, formed by protonation of vinylacylamide **I**, may readily be trapped in a heterodimerization manner (Table 4) by NMeTs-vinylamide **II** to give heterodimers **V**. The total outcome of the reaction is a hydroalkenylation of vinylacylamide **I**. In analogy to the homodimerization reactions above (Scheme 3i), the driving force would be the favoured formation of a similar stabilized six-ring oxygen bridged intermediate **V′**, allowing the selective formation of head-to-tail heterodimerization *E*-products **V** by a final proton elimination.

The fact that the opposite heterodimer **VI** was not formed by hydroalkenylation of vinylsulfonamide **II**, is in line with the reaction mechanism, emphasizing the importance of N–C–O electron delocalization for controlled chemoselective dimerizations to take place, and explains why the acylamide group is a crucial prerequisite for vinylamide dimerization reactions.

The high reactivity of vinyl-NMeTs **2g**, observed by the unsuccessful controlled homodimerization, may explain why heterodimerization and vinylacylamide homodimerization reactions were taking place at room temperature and at reflux, respectively. As discussed above for homodimerization, the conversion of *N*-methyl-*N*-acetamide **2f** and vinylpyrrolidinone **2a** (1–2 h, Table 4, entries 4 and 1) took place faster than the vinyl heterocyclic amides **2b** and **c** (24 h, entries 2 and 4).

3. Conclusions

We have presented an acid catalyzed chemoselective head-to-tail dimerization method to readily afford intermolecular homodimerization of a series of vinylacylamides as well as heterodimerization of different vinylacylamides with a vinylsulfonamide reactant. The results demonstrate the ability of vinylacylamides to effectively undergo hydroalkenylation to afford 1,3-*N*,*N*-functionalized (*E*)-but-1-ene products. The success of the dimerization of the vinylacylamides seems to be determined by the ability of N–C–O acylamide electron delocalization, affording intermediate stabilization.

The hidden acid catalysis by in situ generation of HSbF$_6$ from the catalytic [Au[P(*t*-Bu)$_2$(*o*-biphenyl)CH$_3$CN]SbF$_6$–PhCCH] system allowed milder and more convenient reaction conditions and afforded higher yield than the direct HSbF$_6$ super-acid catalyzed reactions, and also compared to other hidden acid catalysis methods based on silver salts. The [AuSbF$_6$–alkyne] protocol provides a straightforward and efficient method for the stereoselective synthesis of 1,3-*N*,*N*-functionalized (*E*)-but-1-enes by homo- and heterodimerization of vinylamides.

4. Experimental

4.1. General

All reactions were performed under an argon atmosphere. Commercial grade reagents were used as received. Dry solvents were collected from an MB SPS-800 solvent purification system. All reactions were monitored by GC and thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} (0.25 mm thickness). Flash chromatography was carried out using Merck silica gel 60

(0.040–0.063 mm). High Througput Flash Purification (HPFP) (SUPELCO®) was performed on prepacked cartridges (VersaPak™). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance DPX 300 or 400 MHz spectrometer, respectively. Chemical shifts are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (J) are reported in hertz (Hz). The attributions of the chemical shifts were determined by means of COSY, HMQC, HMBC and NOESY experiments. Melting points (mp) were determined using a Stuart apparatus. High resolution mass spectra (HRMS) were determined with an Agilent 6520 QTOF MS instrument equipped with a MAT 95XL (TermoQuest Finnigan) MS instrument. IR spectra were obtained with a Nicolet 20SXC FT-IR spectrometer by using a Smart Endurance reflexion cell. (Acetonitrile)[(2-biphenyl)di-*tert*-butyl-phosphine]gold(I) hexafluoroantimonate and vinyl amides **2a**, **2c**, **2f**, **2h**, **2i** were purchased from Aldrich and were used as received. Vinyl amides **2b**, **2d**, **2e** and **2g** were prepared as described elsewhere.[10]

4.2. General [$AuSbF_6$–PhCCH] procedure for (i) homo- and (ii) heterodimerization

(i) *Homodimerization:* To a Schlenk flask, the gold catalyst (0.05 equiv) was added and dissolved in DCM. Phenylacetylene (1.0 equiv) and vinylacylamide (1.0 equiv) in DCM (10 mL/mmol) were added simultaneously to the gold catalyst. The reaction mixture was stirred at reflux for 0.5–24 h.

(ii) *Heterodimerization:* To a Schlenk flask, the gold catalyst (0.05 equiv) was added and dissolved in DCM (10 mL/mmol). A solution of phenylacetylene (1.0 equiv), vinylamide I (**2g**, **2f**) (2.0 equiv) and vinylacylamide II (**2a**, **2b**, **2c**, **2f**) (1.0 equiv) in DCM (10 mL/mmol) was added simultaneously to the gold catalyst. The reaction mixture was stirred at rt for 1–24 h.

Upon completion, in both cases the reaction mixture was quenched with NEt_3, filtered through Celite™ and rinsed with DCM. The solvent was removed in vacuo to obtain the crude product, which was purified with silica gel Versa Flash, using an appropriate MeOH/DCM eluent system to afford the dimer product, pure by NMR.

4.3. General [[$AgSbF_6$/AgOTf]–alkylchloride] procedure for (i) homo- and (ii) heterodimerization

(i) *Homodimerization:* To a Schlenk flask, the $AgSbF_6$/AgOTf (0.05 equiv) was added and dissolved in DCE (10 mL/mmol). An alternative procedure included the addition of *t*-BuCl (0.1 equiv), as well. The vinylacylamide (1.0 equiv) in DCE (10 mL/mmol) was added. The reaction mixture was stirred at reflux for 1.5 h.

(ii) *Heterodimerization:* To a Schlenk flask, $AgSbF_6$/AgOTf (0.05 equiv) was added and dissolved in DCE (10 mL/mmol). The solution was stirred at reflux for 2 h and vinylsulfonamide (**2g**) (2.0 equiv) and vinylacylamide (**2a**) (1.0 equiv) in DCE (10 mL/mmol) were added simultaneously. The reaction mixture was stirred at rt for 3 h.

Upon completion, in both cases the reaction mixture was filtered through Celite™ and rinsed with DCE. The solvent was removed in vacuo to obtain the crude product, which was purified with silica gel Versa Flash, using an appropriate MeOH/DCM eluent system to afford the dimer product, pure by NMR.

*4.3.1. (E)-1,1′-(But-1-ene-1,3-diyl)bis(pyrrolidin-2-one) (**4a**).* The title compound was synthesized according to *General procedure (i)* from vinyl pyrrolidin-2-one **2a** (60.0 mg, 0.54 mmol), phenylacetylene (55.0 mg, 0.54 mmol) and gold(I) catalyst (20.8 mg, 0.027 mmol) in DCM. The reaction mixture was stirred at reflux for 1.5 h. Flash chromatography (DCM/MeOH 50:1) yielded dimer **4a** (50.4 mg, 84%) as a light yellow oil; R_f 0.35 (DCM/MeOH 50:1); ν_{max} (neat, cm^{-1}) 3194, 3111, 2979, 2359, 1676, 1270, 957 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.00 (d, J 14.0 Hz, 1H, NCH=), 4.85–4.96 (m, 2H, CH=, CH), 3.49 (t, J 7.2 Hz, 2H, CH_2), 3.24–3.34 (m, 2H, CH_2), 2.49 (t, J 7.6 Hz, 2H, CH_2), 2.39 (t, J 8.0 Hz, 2H, CH_2), 2.07–2.15 (m, 2H, CH_2), 1.96–2.03 (m, 2H, CH_2), 1.29 (d, J 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 174.2 (C=O), 173.2 (C=O), 125.1 (NCH=CH), 110.7 (NCH=*C*H), 46.0 (=CHCH), 45.2 (NCH_2), 42.3 (NCH_2), 31.4 ($COCH_2$), 31.1 ($COCH_2$), 17.9 (CH_2), 17.4 (CH_2), 17.0 (CH_3), HRMS (EI) calcd for $C_{12}H_{18}N_2O_2$ $[M]^+$ 222.1363, obsd 222.1361.

*4.3.2. (E)-1,1′-(But-1-ene-1,3-diyl)bis(piperidin-2-one) (**4b**).* The title compound was synthesized according to *General procedure (i)* from 1-vinylpiperidin-2-one **2b** (54.6 mg, 0.436 mmol), phenylacetylene (44.4 mg, 0.436 mmol) and gold(I) catalyst (16.8 mg, 21.8 μmol) in DCM. The reaction mixture was stirred at reflux for 24 h. Flash chromatography (DCM/MeOH 40:1) yielded dimer **4b** (86.3 mg, 79%) as a white solid; mp 119–121 °C; R_f 0.24 (DCM/MeOH 20:1); ν_{max} (thin film) 3293, 3064, 2973, 2359, 1656, 1260, 957 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48, 7.52 (dd, J 14.9, 1.4 Hz, 1H, NCH=), 5.39–5.42 (m, 1H, CH), 4.99–5.05 (dd, J 5.6, 14.9 Hz, 1H, CH=), 3.36–3.39 (t, 2H, NCH_2), 3.12–3.14 (m, 2H, OCH_2), 2.46–2.50 (t, J 8.0 Hz, 2H, NCH_2), 2.38–2.41 (m, 2H, $COCH_2$), 1.78–1.92 (m, 2H, CH_2), 1.69–1.74 (m, 6H, CH_2), 1.27–1.29 (d, J 7.2 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 169.3 (C=O), 168.5 (C=O), 128.3 (NCH=CH), 110.1 (NCH=*C*H), 48.1 (=CHCH), 45.2 (NCH_2), 41.7 ($COCH_2$), 32.9 (NCH_2), 32.5 ($COCH_2$), 23.2 (CH_2), 22.6 (CH_2), 21.0 (CH_2), 20.5 (CH_2), 16.3 (CH_3); HRMS (EI) calcd for $C_{14}H_{22}N_2O_2$ $[M]^+$ 250.1676, obsd 250.1676.

*4.3.3. (E)-1,1′-(But-1-ene-1,3-diyl)bis(azepan-2-one) (**4c**).* The title compound was synthesized according to *General procedure (i)* from 1-vinylazepan-2-one **2c** (40.0 mg, 0.28 mmol), phenylacetylene (28.8 mg, 0.28 mmol) and gold(I) catalyst (10.8 mg, 0.014 mmol) in DCM. The reaction mixture was stirred at reflux for 24 h. Flash chromatography (DCM/MeOH 50:1) yielded dimer **4c** (36 mg, 89.0%) as a light yellow solid; R_f 0.41 (DCM/MeOH 50:1); mp 135–141 °C; ν_{max} (thin film) 3198, 3053, 2989, 2299, 1673, 1245, 958 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (dd, J 14.8, 1.2 Hz, 1H, NCH=), 5.38–5.44 (m, 1H, CH), 5.00 (dd, J 14.8, 4.8 Hz, 1H, CH=), 3.53 (t, J 4.8 Hz, 2H, CH_2), 3.17 (t, J 4.0 Hz, 2H, CH_2), 2.62 (t, J 6.0 Hz, 2H, CH_2), 2.53 (t, J 5.2 Hz, 2H, CH_2), 1.54–1.74 (m, 12H, CH_2), 1.24 (d, J 7.2 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 175.2 (C=O), 174.1 (C=O), 128.0 (NCH=CH), 110.3 (NCH=*C*H), 48.3 (=CHCH), 45.2 (NCH_2), 43.1 (NCH_2), 37.6 ($COCH_2$), 37.1 ($COCH_2$), 29.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.2 (CH_2), 23.4 (CH_2), 23.3 (CH_2), 16.7 (CH_3); HRMS (EI) calcd for $C_{16}H_{26}N_2O_2$ $[M]^+$ 278.1989, obsd 278.1983.

*4.3.4. (E)-3,3′-(But-1-ene-1,3-diyl)bis(oxazolidin-2-one) (**4d**).* The title compound was synthesized according to *General procedure (i)* from 3-vinyloxazolidin-2-one **2d** (113.4 mg, 1.00 mmol), phenylacetylene (102.0 mg, 1.0 mmol) and gold(I) catalyst (38.6 mg, 0.05 mmol) in DCM. The reaction mixture was stirred at reflux for 20 h. Flash chromatography (DCM/MeOH 30:1) yielded dimer **4d** (81.6 mg, 72.0%) as a light yellow solid; R_f 0.65 (DCM/MeOH 20:1); ν_{max} (neat, cm^{-1}): 3293, 2923, 1731, 1480, 1230, 697; δ_H (400 MHz, $CDCl_3$) 6.82 (d, J 14.8 Hz, 1H, NCH=), 4.87 (dd, J 5.9, 8.6 Hz, 1H, CH), 4.54–4.61 (q, J 6.6 Hz, 1H, CH=), 4.46 (t, J 7.8 Hz, 2H, OCH_2), 4.31 (t, J 7.9 Hz, 2H, OCH_2), 3.70 (t, J 8.2 Hz, 2H, NCH_2), 3.41–3.52 (m, 2H, NCH_2), 1.35 (d, J 7.0 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 157.7 (C=O), 157.3 (C=O), 126.2 (NCH=CH), 108.9 (NCH=*C*H), 62.3 (OCH_2), 62.0 (OCH_2), 48.2 (=CHCH), 43.2 (NCH_2), 40.3

(NCH_2), 17.0 (CH_3); HRMS (EI) calcd for $C_{10}H_{14}N_2O_4$ $[M]^+$ 226.0948, obsd 226.0949.

*4.3.5. (E)-N,N′-(But-1-ene-1,3-diyl)bis(N-phenylacetamide) (**4e**).* The title compound was synthesized according to *General procedure (i)* from *N*-phenyl-*N*-vinylacetamide **2e** (77.1 mg, 0.48 mmol), phenylacetylene (48.9 mg, 0.48 mmol) and gold(I) catalyst (18.5 mg, 24.0 μmol) in DCM. The reaction mixture was stirred at reflux for 2 h. Flash chromatography (DCM/MeOH 30:1) yielded compound **4e** (49.3 mg, 64%) as a yellow oil; R_f 0.13 (DCM/MeOH 20:1); ν_{max} (thin film, cm^{-1}) 3293, 3064, 2973, 2359, 1656, 1260, 957; δ_H (400 MHz, $CDCl_3$) 7.45–7.54 (m, $4H_{arom}$), 7.28–7.35 (m, $4H_{arom}$), 7.04 (d, *J* 5.8 Hz, $2H_{arom}$), 6.90 (br, 1H, NCH=), 5.47–5.52 (q, *J* 6.8 Hz, 1H, NCH), 4.25–4.30 (dd, *J* 6.8, 14.5 Hz, 1H, CH=), 1.82 (s, 3H, $COCH_3$), 1.69 (s, 3H, $COCH_3$), 1.16–1.18 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 169.65 (C=O), 168.68 (C=O), 139.34 (C_{arom}), 130.15 (C_{arom}), 129.99 (CH_{arom}), 129.01 (2C, CH_{arom}), 128.91 (2C, CH_{arom}), 128.73 (2C, CH_{arom}), 128.13 (2C, CH_{arom}), 124.06 (CH_{arom}), 119.81 (NCH=CH), 114.31 (1C, NCH=*C*H), 49.80 (=CHCH), 24.54 ($COCH_3$), 23.30 ($COCH_3$), 18.25 (CH_3); HRMS (EI) calcd for $C_{20}H_{22}N_2O_2$ $[M]^+$ 322.1763, obsd 322.1762.

*4.3.6. (E)-N,N′-(But-1-ene-1,3-diyl)bis(N-methylacetamide) (**4f**).* The title compound was synthesized according to *General procedure (i)* from *N*-methyl-*N*-vinylacetamide **2f** (53.4 mg, 0.54 mmol), phenylacetylene (55.0 mg, 0.54 mmol) and gold(I) catalyst (20.8 mg, 0.027 mmol) in DCM. The reaction mixture was stirred at reflux for 0.5 h. Flash chromatography (DCM/MeOH 50:2) yielded compound **4f** (37.0 mg, 69%) as a colourless oil; R_f 0.33 (DCM/MeOH 50:1); ν_{max} (thin film, cm^{-1}) 3323, 3123, 2975, 2410, 1655, 1198, 963; δ_H (400 MHz, $CDCl_3$) 6.80 (d, *J* 14.0 Hz, 1H, NCH=), 5.30–5.43 (m, 1H, CH), 4.90–4.97 (m, 1H, CH=), 3.05 (s, 3H, NCH_3), 2.84 (s, 3H, NCH_3), 2.21 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 1.24 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 170.1 (1C, C=O), 169.2 (1C, C=O), 131.0 (1C, NCH=CH), 109.9 (1C, NCH=*C*H), 47.8 (1C, =CHCH), 29.8 (1C, NCH_3), 29.2 (1C, NCH_3), 22.3 (1C, $COCH_3$), 21.8 (1C, $COCH_3$) 17.6 (1C, CH_3); HRMS (EI) calcd for $C_{10}H_{18}N_2O_2$ $[M]^+$ 198.1363, obsd 198.1361.

*4.3.7. (E)-N,4-Dimethyl-N-(4-(2-oxopyrrolidin-1-yl)but-3-en-2-yl) benzenesulfonamide (**5a**).* The title compound was synthesized according to *General procedure (ii)* from 1-vinyl pyrrolidin-2-one **2a** (15.5 mg, 0.14 mmol), *N*-methyl-*N*-tosylacetamide **2g** (59.0 mg, 0.28 mmol), phenylacetylene (14.2 mg, 0.14 mmol) and gold(I) catalyst (5.4 mg, 0.007 mmol) in DCM. The reaction mixture was stirred for 2 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded heterodimer **5a** (20.4 mg, 53%) as yellow oil; R_f 0.40 (DCM/MeOH 50:1) and homodimer **4a** (6.3 mg, 21%) as a light yellow oil; R_f 0.35 (DCM/MeOH 50:1). Compound **5a**: ν_{max} (thin film) 3200, 3113, 2929, 2289, 1663, 1195, 957 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (d, *J* 8.0 Hz, 2H, H_{arom}), 7.31 (d, *J* 8.0 Hz, 2H, H_{arom}), 6.88 (dd, *J* 14.4, 1.2 Hz, 1H, NCH=), 4.80–4.86 (m, 1H, CH), 4.67 (dd, *J* 14.4, *J* 6.0 Hz, 1H, CH=), 3.16–3.31 (m, 2H, CH_2), 2.83 (s, 3H, NCH_3), 2.42 (s, 3H, $ArCH_3$), 2.35–2.39 (m, 2H, CH_2), 1.94–2.01 (m, 2H, CH_2), 1.25 (d, *J* 7.2 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 174.0 (C=O), 143.8 (C_{arom}), 134.3 (C_{arom}), 129.7 (2C, CH_{arom}), 129.6 (NCH=CH), 126.9 (2C, CH_{arom}), 109.5 (NCH=*C*H), 45.9 (=CHCH), 42.1 (NCH_2), 32.0 (NCH_3), 31.4 ($COCH_2$), 21.4 ($ArCH_3$), 17.8 (CH_2), 17.4 (CH_3); HRMS (EI) calcd for $C_{15}H_{19}N_2O_3S$ $[M-CH_3]^+$ 307.1111, obsd 307.1114.

*4.3.8. (E)-N,4-Dimethyl-N-(4-(2-oxopiperidin-1-yl)but-3-en-2-yl)benzenesulfonamide (**5b**).* The title compound was synthesized according to *General procedure (ii)* from 1-vinylpiperidin-2-one **2b** (28.5 mg, 0.28 mmol), *N*-methyl-*N*-tosylacetamide **2g** (10.8 mg, 0.014 mmol), phenylacetylene (58.8 mg, 0.54 mmol) and gold(I) catalyst (20.8 mg, 0.027 mmol) in DCM. The reaction mixture was stirred for 24 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded heterodimer **5b** (43.0 mg, 46%) as a yellow oil; R_f 0.41 (DCM/MeOH 50:1) and homodimer **4b** (13.3 mg, 19%) as a light yellow oil; R_f 0.29 (DCM/MeOH 50:1). **5b**: ν_{max} (thin film) 3205, 3095, 2919, 2310, 1646, 1229, 939 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (d, *J* 8.4 Hz, 2H, H_{arom}), 7.30 (d, *J* 8.4 Hz, 2H, H_{arom}), 6.85 (dd, *J* 14.4, 1.6 Hz, 1H, NCH=), 5.35–5.42 (m, 1H, CH), 4.68 (dd, *J* 14.4, 5.6 Hz, 1H, CH=), 3.04–3.08 (m, 2H, CH_2), 2.83 (s, 3H, NCH_3), 2.42 (s, 3H, $ArCH_3$), 2.38–2.41 (m, 2H, CH_2), 1.66–1.78 (m, 4H, CH_2), 1.23 (d, *J* 7.2 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 169.1 (C=O), 143.8 (C_{arom}), 134.3 (C_{arom}), 129.7 (2C, CH_{arom}), 129.7 (NCH=CH), 126.9 (2C, CH_{arom}), 110.0 (NCH=*C*H), 47.2 (=CHCH), 41.3 (NCH_2), 32.4 (NCH_3), 32.1 ($COCH_2$), 23.1 (CH_2), 21.4 ($ArCH_3$), 21.0 (CH_2), 16.4 ($1CH_3$); HRMS (EI) calcd for $C_{16}H_{21}N_2O_3S$ $[M-CH_3]^+$ 321.1267, obsd 321.1267.

*4.3.9. (E)-N,4-Dimethyl-N-(4-(2-oxoazepan-1-yl)but-3-en-2-yl)benzenesulfonamide (**5c**).* The title compound was synthesized according to *General procedure (ii)* from 1-vinylazepan-2-one **2c** (40.0 mg, 0.28 mmol), *N*-methyl-*N*-tosylacetamide **2g** (118.0 mg, 0.54 mmol), phenylacetylene (28.5 mg, 0.28 mmol) and gold(I) catalyst (10.8 mg, 0.014 mmol) in DCM. The reaction mixture was stirred for 24 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded heterodimer **5c** (48.0 mg, 48%) as yellow oil; R_f 0.43 (DCM/MeOH 50:1) and homodimer **4c** (20.0 mg, 25%) as a light yellow solid; R_f 0.32 (DCM/MeOH 50:1). Compound **5c**: ν_{max} (thin film) 3196, 3105, 2939, 2289, 1673, 1224, 945 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (d, *J* 8.4 Hz, 2H, H_{arom}), 7.30 (d, *J* 8.0 Hz, 2H, H_{arom}), 6.84 (dd, *J* 14.4, 1.6 Hz, 1H, NCH=), 5.32–5.39 (m, 1H, CH), 4.67 (dd, *J* 14.4, 5.2 Hz, 1H, CH=), 3.09–3.13 (m, 2H, CH_2), 2.82 (s, 3H, NCH_3), 2.50–2.52 (m, 2H, CH_2), 2.42 (s, 3H, $ArCH_3$), 1.64–1.67 (m, 6H, CH_2), 1.20 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 175.2 (1C, C=O), 143.8 (1C, C_{arom}), 134.3 (1C, C_{arom}), 129.7 (2C, CH_{arom}), 129.6 (1C, NCH=CH), 126.9 (2C, CH_{arom}), 110.9 (1C, NCH=*C*H), 47.8 (1C, =CHCH), 42.9 (1C, NCH_2), 37.5 (1C, NCH_3), 32.1 (1C, $COCH_2$), 29.9 (1C, CH_2), 29.5 (1C, CH_2), 23.3 (1C, CH_2), 21.4 (1C, $ArCH_3$), 17.0 (1C, CH_3); HRMS (EI) calcd for $C_{17}H_{24}N_2O_3S$ $[M-CH_3]^+$ 336.1457, obsd 336.1460.

*4.3.10. (Z)-N-(3-(N,4-Dimethylphenylsulfonamido)but-1-en-1-yl)-N-methylacetamide (**5f**) and N,4-dimethyl-N-(4-phenylbut-3-yn-2-yl) benzenesulfonamide (**6**).* The title compounds were synthesized according to *General procedure (ii)* from *N*-methyl-*N*-vinylacetamide **2f** (53.4 mg, 0.54 mmol), *N*-methyl-*N*-tosylacetamide **2g** (236.0 mg, 1.08 mmol), phenylacetylene (55.0 mg, 0.54 mmol) and gold(I) catalyst (20.8 mg, 0.027 mmol) in DCM. The reaction mixture was stirred for 1 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded heterodimer **5f** (71.9 mg, 43%) as a yellow oil; R_f 0.56 (DCM/MeOH 50:1), homodimer **4f** (16.2 mg, 15%) as a light yellow solid; R_f 0.43 (DCM/MeOH 50:1) and compound **6** (17.5 mg, 5%) as a yellow oil R_f 0.76 (DCM/MeOH 50:1). Compound **5f**: ν_{max} (thin film) 3199, 3095, 2925, 2309, 1686, 1254, 924 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (d, *J* 8.0 Hz, 2H, H_{arom}), 7.30 (d, *J* 8.0 Hz, 2H, H_{arom}), 6.84 (dd, *J* 14.4, 1.6 Hz, 1H, NCH=), 5.33–5.40 (m, 1H, CH), 4.65 (dd, *J* 14.0, 5.2 Hz, 1H, CH=), 2.83 (s, 3H, NCH_3), 2.73 (s, 3H, NCH_3), 2.42 (s, 3H, $ArCH_3$), 2.07 (s, 3H, $COCH_3$), 1.20 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 170.1 (C=O), 143.8 (C_{arom}), 134.3 (C_{arom}), 129.7 (2C, CH_{arom}), 129.6 (NCH=CH), 126.8 (2C, CH_{arom}), 110.2 (NCH=*C*H), 47.2 (=CHCH), 32.0 (NCH_3), 29.8 (NCH_3), 22.2 ($COCH_3$), 21.4 ($ArCH_3$), 16.6 (CH_3); HRMS (EI) calcd for $C_{14}H_{20}N_2O_3S$ $[M-CH_3]^+$ 296.1247, obsd 296.1250. Compound **6**: δ_H (400 MHz, $CDCl_3$) 7.77 (d, *J* 8.4 Hz, 2H, H_{arom}), 7.21–7.29 (m, 5H, H_{arom}), 7.30 (d, *J* 6.4 Hz, 2H, H_{arom}), 5.11 (q, *J* 6.4 Hz, 1H, CH), 2.84 (s, 3H, NCH_3), 2.35 (s, 3H, $ArCH_3$), 1.50 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 143.3 (C_{arom}), 134.6 (C_{arom}), 131.3 (2C, CHAr), 129.3 (2C, CH_{arom}), 128.2 (CH_{arom}), 128.0 (2C, CH_{arom}), 127.8 (2C, CH_{arom}), 122.1 (C_{arom}), 85.4 (C_{alkyne}),

85.1 (C_{alkyne}), 46.0 (CH_3CH), 29.3 (NCH_3), 21.3 ($ArCH_3$), 20.8 (CH_3); HRMS (EI) calcd for $C_{18}H_{19}NO_2S$ $[M+H]^+$ 314.1215, obsd 314.1216.

*4.3.11. N-Methyl-N-(4-phenylbut-3-yn-2-yl)acetamide (**7**).* The title compound was synthesized according to *General procedure (ii)* from *N*-methyl-*N*-vinylacetamide **2f** (53.4 mg, 0.54 mmol), vinyl pyrrolidin-2-one **2a** (31.0 mg, 0.28 mmol), phenylacetylene (28.5 mg, 0.28 mmol) and gold(I) catalyst (10.8 mg, 0.014 mmol) in DCM. The reaction mixture was stirred for 1 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded homodimer **4a** (15 mg, 49%, see above) and compound **7** (5.4 mg, 5%) as a yellow oil R_f 0.68 (DCM/MeOH 50:1). Compound **7**: δ_H (400 MHz, $CDCl_3$) 7.42 (d, *J* 7.2 Hz, 2H, H_{arom}), 7.32 (m, 3H, H_{arom}), 5.85 (q, 6.9 Hz, 3H, CH_3), 3.08 (s, 3H, NCH_3), 2.13 (s, 3H, $COCH_3$), 1.42 (d, *J* 6.9 Hz, 3H, CH_3).

*4.3.12. 2,4-d_2-(E)-1,1′-(But-1-ene-1,3-diyl)bis(pyrrolidin-2-one) (d-**4a**).* The title compound was synthesized according to *General procedure (i)* from vinyl pyrrolidin-2-one **2a** (60.0 mg, 0.54 mmol), d_1-phenylacetylene (55.6 mg, 0.54 mmol) and gold(I) catalyst (20.8 mg, 0.027 mmol) in DCM. The reaction mixture was stirred at reflux for 1.5 h. Flash chromatography (DCM/MeOH 50:1) yielded dimer *d*-**4a** (50.9 mg, 84%) as a light yellow oil; R_f 0.36 (DCM/MeOH 50:1); ν_{max} (neat, cm^{-1}) 3199, 3109, 2963, 2367, 1655, 1211, 947 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.00 (d and s, *J* 14.0 Hz, 1H, NCH=CH/D), 4.85–4.96 (m, 1.5H, =CH/D, CH), 3.49 (t, *J* 7.2 Hz, 2H, CH_2), 3.24–3.34 (m, 2H, CH_2), 2.49 (t, *J* 7.6 Hz, 2H, CH_2), 2.39 (t, *J* 8.0 Hz, 2H, CH_2), 2.07–2.15 (m, 2H, CH_2), 1.96–2.03 (m, 2H, CH_2), 1.29 (d, *J* 6.8 Hz, 2.5H, CH_3/CH_2D); δ_C (100 MHz, $CDCl_3$) 174.2 (C=O), 173.2 (C=O), 125.1/125.0 (NCH=CH/NCH=CD), 110.7 (s)/110.4 (t, *J* 23.5 Hz) (CH=CHCH/CH=CDCH), 45.9–46.0 (m, =CHCH/=CDCH), 45.1 (NCH_2), 42.3 (NCH_2), 31.4 ($COCH_2$), 31.1 ($COCH_2$), 17.9 (CH_2), 17.4 (CH_2), 16.5–17.0 (m, CH_3/CH_2D); HRMS (EI) calcd for $C_{12}H_{17}DN_2O_2$ $[M]^+$ 223.1426, obsd 223.1425.

*4.3.13. 1,3,4-d_3-(E)-N,4-Dimethyl-N-(4-(2-oxopyrrolidin-1-yl)but-3-en-2-yl)benzenesulfonamide (d-**5a**).* The title compound was synthesized according to *General procedure (ii)* from 1-vinyl pyrrolidin-2-one **2a** (15.5 mg, 0.14 mmol), 1,2,2-d_3-*N*-methyl-*N*-tosylvinylamide, d_3-**2g** (60.0 mg, 0.28 mmol), phenylacetylene (14.2 mg, 0.14 mmol) and gold(I) catalyst (5.4 mg, 0.007 mmol) in DCM. The reaction mixture was stirred for 2 h at room temperature. Flash chromatography (DCM/MeOH 50:1) yielded heterodimer *d*-**5a** (18.7 mg, 48%) as yellow oil; R_f 0.38 (DCM/MeOH 50:1) and homodimer **4a** (7.2 mg, 25%) as a light yellow oil; R_f 0.32 (DCM/MeOH 50:1). Compound *d*-**5a**: ν_{max} (thin film) 3216, 3109, 2903, 2271, 1712, 1189, 955 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71 (d, *J* 8.2 Hz, 2H, H_{arom}), 7.33 (d, *J* 8.2 Hz, 2H, H_{arom}), 4.84–4.86 (m, 1H, CH), 3.24–3.36 (m, 2H, CH_2), 2.76 (s, 3H, NCH_3), 2.44 (s, 3H, $ArCH_3$), 2.33–2.42 (m, 2H, CH_2), 1.95–2.10 (m, 2H, CH_2), 1.23 (d, *J* 7.0 Hz, 2.5H, CH_3/CH_2D); δ_C (100 MHz, $CDCl_3$) 174.9 (C=O), 143.5 (C_{arom}), 133.9 (C_{arom}), 129.7 (2C, CH_{arom}), 128.7 (t, *J* 23.5 Hz NCD=CD), 127.0 (2C, CH_{arom}), 108.2 (t, *J* 21.8 Hz NCD=CD), 43.8 (=CDCH), 42.1 (NCH_2), 31.7 (NCH_3), 31.2 ($COCH_2$), 21.5 ($ArCH_3$), 18.3 (CH_2), 17.2–17.4 (m, CH_3/CH_2D); HRMS (ESI) calcd for $C_{16}H_{20}D_3N_2O_3S$ $[M+H]^+$ 326.1618, obsd 326.1613.

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