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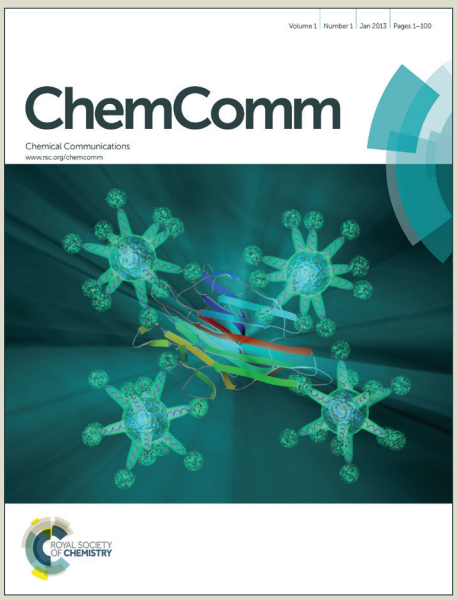

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Catalyst-controlled divergence in cycloisomerisation reactions of *N*-propargyl-*N*-vinyl sulfonamides: Gold-catalysed synthesis of 2-sulfonylmethyl pyrroles and dihydropyridines

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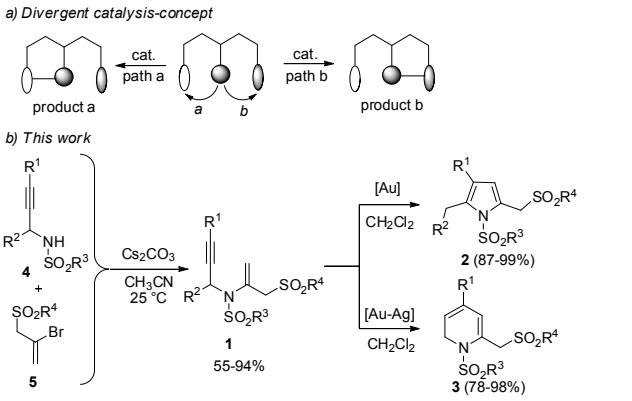
Gold-catalysed, divergent synthesis of 2-sulfonylmethyl pyrroles and dihydropyridines from *N*-propargyl-*N*-vinyl sulfonamides has been achieved. Echavarren's gold(I) catalyst promoted the formation of pyrrole derivatives whereas the combination of $PPh_3AuCl/AgSbF_6$ afforded dihydropyridines. The aza-enyne precursors for the cycloisomerisation reaction were prepared by a base-mediated formal vinylic substitution reaction of 2-bromoallyl sulfones.

The development of suitable catalysts and conditions for promoting a desired reaction pathway of multifunctional substrates is one of the fundamental challenges of catalysis.[1] An additional level of selectivity may be contemplated wherein a common substrate can be transformed into more than one products by careful choice of catalysts/conditions. Such endeavors, commonly known as *divergent catalysis,* are highly attractive for the discovery of drugs and functional materials (Scheme 1a).[2] Although the benefits of divergent catalytic processes are obvious, their development is extremely challenging.[3]

Catalytic cylcoisomerisation of enynes constitute a powerful, modern method for the construction of a variety of carbocycles and heterocycles.[4] Among the various catalysts that are employed for enyne cycloisomerisation, gold complexes stand out owing to their ability to selectively activate alkynes in complex molecular settings.[5] As a result, tremendous progress has been made in the recent years in this area.[4,5a-b,6] Often, two or more cyclisation pathways are avilable for substituted enynes and a complex interplay of inherent substrate bias and catalysts dictate the outcome of the cycloisomerisation.[7] While it is highly desirable, control over the available divergent pathways is realised rather rarely.[8] Here we report gold-catalysed divergent cycloisomerisation reactions of *N*-propargyl-*N*-vinyl sulfonamides **1** to afford 2-sulfonylmethyl pyrroles **2** or 2-sulfonylmethyl-1,2-dihydropyridines **3** (Scheme 1b). Remarkably, complete selectivity can be achieved by the choice of catalysts under otherwise identical conditions. Additionally, the cyclisation precursors were assembled via a novel, base-mediated formal vinylic substitution reaction of propargyl sulfonamides **4** and 2-bromoallylsulfones **5** (Scheme 1b).



Scheme 1. a) Conceptual framework of divergent catalysis. b) Synthesis of aza-enynes and their divergent cycloisomerisation. [Au] = [JohnPhosAu(CH_3CN)]SbF_6. [Au-Ag] = Ph_3PAuCl/ $AgSbF_6$.

Discovery of the above-described vinylic substitution has its origins in our recent investigations on the cyclocondensation reactions of unsaturated sulfones.[9] We were interested in allenyl sulfones as potential building blocks for sulfone-containing cyclic systems. In view of the rich and versatile chemistry of allenoates,[10] allenyl sulfones appear to hold significant but largely untapped synthetic potential. The relative scarcity of studies involving allenyl sulfones may be attributed to their base-sensitivity and propensity to undergo nucleophile-triggered oligomerisation reactions.[11] Our efforts to circumvent this problem culminated in the development of a base-mediated formal vinylic substitution reaction of the 2-bromoallyl sulfones **5a-b**[12] and various sulfonamide nucleophiles **4a-h** to afford the *N*-propargyl-*N*-vinyl sulfonamide **1aa-hb** (Table 1). The intermediacy of 1-(phenylsulfonyl)allene was confirmed by further experiments (See supporting information for details).

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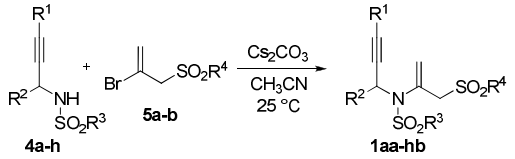
The *N*-propargyl-*N*-vinyl sulfonamides **1aa-hb** constitute an assortment of 3-aza-1,5-enynes with structural features that make them attractive substrates for catalytic processes for the synthesis of nitrogen heterocycles.[13] The activation of the alkyne subunit by π-acids such as gold and silver catalysts was investigated with a view to promote cyclisation reactions. Screening of a handful of gold and silver catalysts revealed that two cyclisation pathways are operative leading to the formation of the pyrrole derivative **2aa** and the dihydropyridine product **3aa** (Table 2).

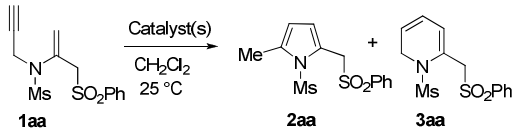
Table 1. CS_2CO_3-mediated formal vinylic substitution of 2-bromoallyl sulfones **5a-b** for the synthesis of *N*-propargyl-*N*-vinyl sulfonamides **1aa-hb**.[a]



Entry	Sulfonamides **4a-h**	Bromoallyl sulfones **5a-b**	Product	Yield[a]
1	**4a**, $R^1 = R^2 = H$, $R^3 = Me$	**5a**, $R^4 = Ph$	**1aa**	94%
2	**4a**	**5b**, $R^4 = p$-tolyl	**1ab**	89%
3	**4b**, $R^1 = R^2 = H$, $R^3 = Ph$	**5a**	**1ba**	96%
4	**4b**	**5b**	**1bb**	92%
5	**4c**, $R^1 = R^2 = H$, $R^3 = p$-tolyl	**5a**	**1ca**	93%
6	**4c**	**5b**	**1cb**	90%
7	**4d**, $R^1 = Ph$, $R^2 = H$, $R^3 = Me$	**5a**	**1da**	95%
8	**4d**	**5b**	**1db**	90%
9	**4e**, R^1 = thiophene-2-yl, $R^2 = H$, $R^3 = Me$	**5a**	**1ea**	82%
10	**4e**	**5b**	**1eb**	94%
11	**4f**, R^1 = 2-bromophenyl, $R^2 = H$, $R^3 = Me$	**5a**	**1fa**	93%
12	**4f**	**5b**	**1fb**	89%
13	**4g**, R^1 = 4-methoxyphenyl, $R^2 = H$, $R^3 = Me$	**5a**	**1ga**	88%
14	**4g**	**5b**	**1gb**	84%
15	**4h**, $R^1 = H$, $R^2 = Ph$, $R^3 = Me$	**5b**	**1hb**	55%

[a]Reaction conditions: **4a-g** (1mmol), **5a-b** (1.2 mmol), Cs_2CO_3 (2.2 mmol), acetonitrile (5mL), 25 °C, 4 h. [b]Yields of products isolated after column chromatography. [c]Reaction conditions **4h** (1mmol), **5b** (1.2 mmol), NaH (2.2 mmol), THF (5mL), 0 °C, 0.5 h and **1hb** obtained as a mixture of isomers (see supporting information for details).

Table 2. Optimisation of reaction conditions for cycloisomerisation of *N*-propargyl-*N*-vinyl sulfonamide **1aa**.[a]



Entry	Catalysts (mol%)	Time (h)	Yield of **2aa**[b]	Yield of **3aa**[b]
1	$AuCl_3$ (5)	3	78%	-
2	**(JohnPhos)Au(CH_3CN)SbF_6 (2)**	**1**	**89%**	**-**
3	Ph_3PAuCl (5)	2	-	58%
4	$AuCl_3$ (5) & $AgSbF_6$ (5)	2	Traces	46%
5	(JohnPhos)Au(CH_3CN)SbF_6 (2) & $AgSbF_6$ (5)	1	-	48%
6	**Ph_3PAuCl (2) & $AgSbF_6$ (5)**	1	-	**92%**
7	$AgSbF_6$ (10)	4	-	66%
8[c]	AgOTf (10)	2	-	-
9[d]	No catalyst	24	-	-

[a]Reaction conditions: **1aa** (0.5 mmol), catalysts, CH_2Cl_2 (2 mL). [b]Isolated yield after chromatography. [c]Hydrolysis of **1aa** was observed. [d] **1aa** was unchanged [Ms = methanesulfonyl, JohnPhos = (2-biphenyl)di-*tert*-butylphosphine].

Gold(III) chloride (entry 1) and Echavarren's gold(I) catalyst [JohnPhosAu(CH_3CN)]SbF_6 (entry 2) promoted the formation of the pyrrole derivative **2aa** in 78% and 89% yields respectively, whereas Ph_3PAuCl catalysed the formation of the dihydropyridine **3aa** in 58% yield (entry 3). Interestingly, dihydropyridine **3aa** was selectively formed when a silver co-catalyst $AgSbF_6$ was used with any of these gold catalysts (entries 4-6). Selective formation of the dihydropyridine **3aa** in a reasonably good yield (66%) was also observed when $AgSbF_6$ alone was employed as a catalyst (entry 7). Silver triflate, however, failed to promote the cyclisation reaction altogether (entry 8). The combination of 2 mol% Ph_3PAuCl and 5 mol% $AgSbF_6$ afforded the best yield of dihydropyridine **3aa**, while Echavarren's catalyst (2 mol%) furnished the highest yield of the pyrrole **2aa**. It may be noted that, in almost all cases, the cyclisation afforded either the dihydropyridine or the pyrrole exclusively.

The position of substituents on the pyrrole ring of **2aa** indicated that **1aa** has undergone a gold-catalysed propargyl-Claisen rearrangement[14] prior to the final cyclisation, whereas the skeletal reorganisation was not apparent in the structure of dihydropyridine **3aa**. The intriguing catalyst-controlled divergence in the cyclisation pathways called for further investigations. Thus, the *N*-propargyl-*N*-vinyl sulfonamides **1aa-bh** (table 1), prepared via the formal vinylic substitution method, were separately subjected to the optimised conditions for both the cycloisomerisation reactions. A variety of pyrrole derivatives **2aa-hb** and dihydropyridines **3aa-hb** were formed in these reactions and they are listed in Table 3. It was evident that the cycloisomerisation reactions and the catalyst-

controlled divergence were general. The sulfonyl groups on the nitrogen (from alkyne component) as well as carbon (allene component) can be varied. Cycloisomerisations of aza-enynes with arenes or a heteroarene (2-thienyl) as the alkyne substituent (R^1) afforded 3-(hetero)arylpyrroles (**2da-fb**) and 4-(hetero)aryldihydropyridines (**3da-fb**) in excellent yields. Single crystal X-ray analysis of the representative pyrrole **2da** confirmed the assigned structure.[15]

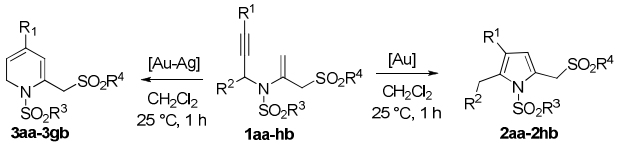
Interestingly, dihydropyridine formation was not observed when the aza-enyne **1hb** carrying a propargylic phenyl substituent (R^2 = Ph) was subjected to either of the conditions for cyclisation. In both instances, 2-benzyl-5-sulfonylmethyl pyrrole **2hb** was formed as the sole product. Presumably, presence of the propargylic phenyl substituent imparts a substrate bias for pyrrole formation that overrides the catalyst-control of cycloisomerisation pathways.

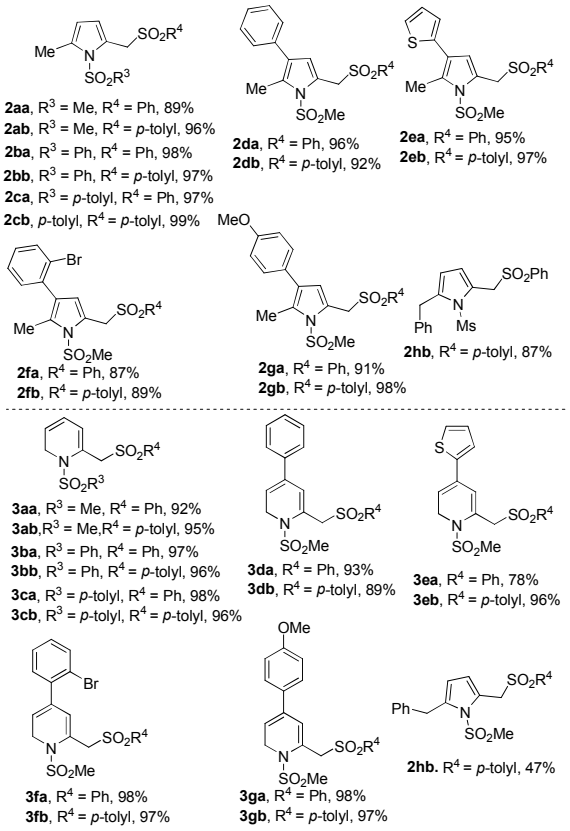
It is important to note that 3-arylpyrroles are much-preferred intermediates for the synthesis of a number of natural products such as rhazinilam, lamellarins and pyrrolnnitrin.[16] Similarly, 1,2-dihydropyridines are useful precursors for the preparation of polysubstituted 6-membered nitrogen heterocycles and isoquinuclidines.[17] Therefore, the quick and efficient assembly reported here, of pyrroles and 1,2-dihydropyridines armed with readily malleable substituents at 2- and 4-positions, has the potential to find applications in targeted synthesis.

A tentative mechanistic rationalisation for the formation and cycloisomerisation of the representative aza-enyne **1da** is depicted in Scheme 2. The control experiments indicated that the allenyl sulfone **6** is a plausible intermediate in the formation of the aza-enyne **1**. The latter undergoes a metal-mediated propargyl-Claisen rearrangement[14] to generate the β-allenyl imine **7A**. It may be noted that the aza-enyne **1aa** did not undergo any rearrangement in the absence of catalysts (table 2, entry 9). Gold-mediated 5-exo-dig cyclisation of **7A** and subsequent aromatisation via hydrogen shift affords the pyrrole derivative **2da**. The dihydropyridine **3da** is presumably formed *via* the tautomerisation[18] of **7A** to the aza-triene **7B** and subsequent 6π-aza-electrocyclisation.

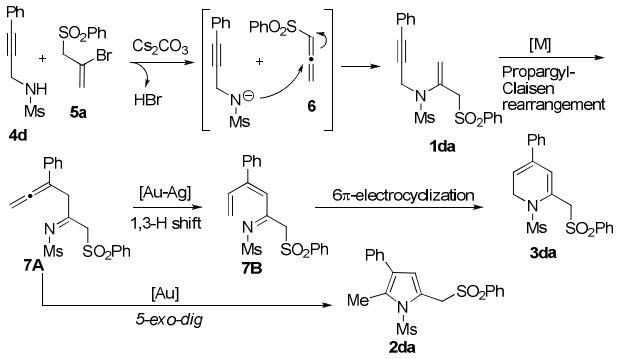
The transformations listed in Scheme 3 provide a glimpse of the synthetic potential embedded in the heterocycles generated in this study. A regioselective bromination of the pyrrole **2aa** to afford 3-bromopyrrole **8** was achieved by treatment with *N*-bromosuccinimide in THF. Similarly, site-selective catalytic hydrogenation of the dihydropyridine **3ab** furnished the tetrahydropyridine **9**. The dihydropyridine **3ab** was also converted smoothly into the corresponding pyridine derivative **10**[19] via base-promoted elimination of methanesulfinate group. The phenylsulfonyl group has been termed 'arguably the most versatile functional group' by Fuchs[20] and it is conceivable that its potential may be exploited in further synthetic elaboration at the methylenesulfonyl unit of the products.

Table 3. Gold and silver-catalysed divergent cycloisomerisation of aza-enynes **1aa-hb**.[a]

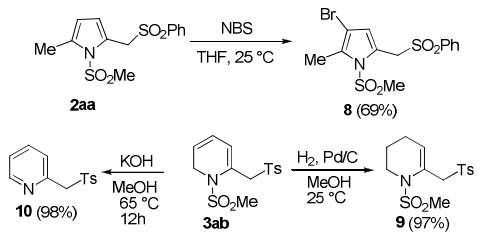




[a]Reaction conditions: **1aa-hb** (0.5mmol), catalysts, CH_2Cl_2 (2 mL), 25 °C, 1 h. Isolated yields. [Au] = 2 mol% (JohnPhos)Au(CH_3CN)SbF_6; [Au-Ag] = 2 mol% Ph_3PAuCl & 5 mol% $AgSbF_6$.



Scheme 2. Mechanistic rationalisation for the formation and cycloisomerisation of aza-enyne **1da**.



Scheme 3. Synthetic applications of the pyrrole **2aa** and dihydropyridine **3ab**.

In summary, a catalyst-controlled divergent cycloisomerisation reaction of *N*-propargyl-*N*-vinyl sulfonamides to selectively afford either 2-sulfonylmethyl pyrroles or dihydropyridines was developed. The *N*-propargyl-*N*-vinyl sulfonamides were in turn prepared via a novel, base-mediated formal vinylic substitution reaction of 2-bromoallyl sulfones. A variety of 2,3,4-substituted pyrroles and 2,4-substituted dihydropyridines were assembled in two steps from propargyl sulfonamides and 2-bromoallyl sulfones. It is presumable that the rich chemistry of the methylenesulfonyl moiety may be exploited for further elaboration of the heterocycles into important natural products and analogues. Efforts along this direction and a detailed investigation of the cesium carbonate mediated vinylic substitution reaction are currently underway.

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