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Gold-Catalyzed Tandem Cyclizations of 1,6-Diynes Triggered by Internal N- and O-Nucleophiles

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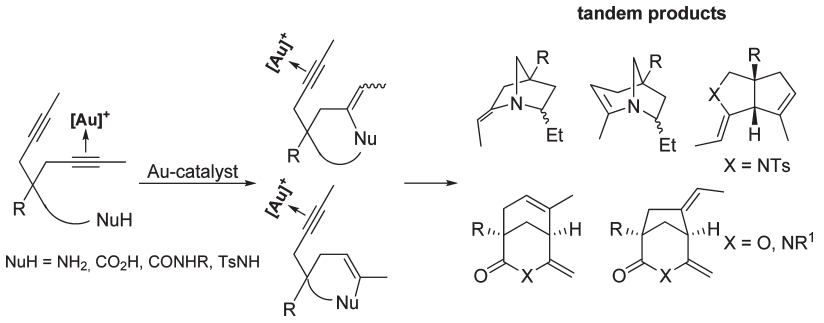
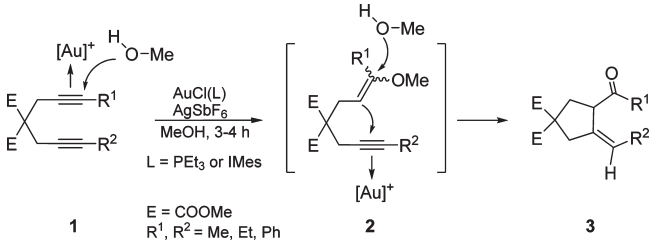


Investigations on gold-catalyzed tandem cyclization reactions of 1,6-diynes, tethered to nucleophilic functionalities such as amine, carboxylic acid, amide, and sulfonamide, are reported. The ability of such substrates to undergo tandem cyclization, triggered by internal nucleophiles, has been examined. Depending on the substrate, the catalytic system, and reaction conditions, different regioisomers of monocyclic and bridged bicyclic products were obtained.

Introduction

Gold-catalyzed cyclization reactions involving alkynes have emerged as an important and powerful tool for the formation of carbo- and heterocyclic compounds.[1] The strong alkynophilic character of cationic gold complexes allows these Lewis acids to selectively activate π-systems toward nucleophilic attack. Thus, a number of different intramolecular Au(I)- and Au(III)-catalyzed cyclizations of alkynes bearing proximate C, O, and N nucleophiles have provided a range of functionalized carbo- or heterocycles. For instance, gold-catalyzed cycloisomerizations of 1,6-enynes have been intensively investigated.[2] Interesting gold-catalyzed cyclization reactions involving indoles have recently been reported.[3] Cyclization reactions involving heteroatoms have been developed for alkynyl sulfoxides,[4] *in situ* generated enamine alkynes,[5] acetylenic acids for the formation of γ-lactones,[6] for *N*-Boc-protected alkynylamines,[7] *N* -propargylamides,[8] for *gem*-difluorohomopropargylamines to prepare 3-fluoropyrroles[9] or for the formation of tetracyclic indolines.[10] In all of these intramolecular cyclization reactions, the original triple bond is transformed into a double bond after nucleophilic attack.

SCHEME 1. Cyclization Reaction of Diynes in Methanol



Our group has recently developed different Au(I)-catalyzed cyclization reactions of symmetrically and unsymmetrically substituted 1,6-diynes **1**, triggered by an initial attack of methanol (Scheme 1).[11] We proposed the formation of an intermediate alkylenol ether **2**, acting as the nucleophile in

(1) (a) Skouta, R.; Li, C. J. *Tetrahedron* **2008**, *64*, 4917. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (c) Stephen, A.; Hashmi, K. *Chem. Rev.* **2007**, *107*, 3180. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Sohel, S. M. A.; Liu, R. S. *Chem. Soc. Rev.* **2009**, *38*, 2269. (f) Fuerstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

(2) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(3) (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358.

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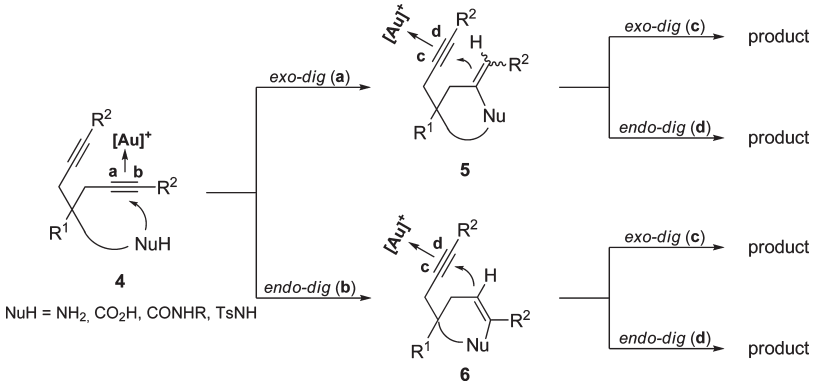
SCHEME 2. Envisaged Tandem Cyclization Reactions



the final cyclization step. The cyclization proceeded regio- and stereoselectively in a 5-*exo-dig* manner and provided different *Z*-cyclopentylidene derivatives **3**.

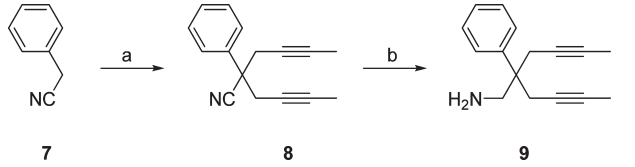
In the present investigation, we wanted to replace the external methanol nucleophile with internal O- and N-nucleophilic groups in order to trigger and enable tandem cyclization reactions (Scheme 2). In the initial reaction step the nucleophile could attack the activated alkyne moiety in an *exo*- (a) or an *endo-dig* manner (b) to provide two possible enyne intermediates **5** or **6**. Depending on whether N- or O-nucleophiles are involved, enamines, imines, enamides, or vinyl esters are formed in the first cyclization step. These alkene moieties, attached to a heteroatom, may then attack the remaining, gold-activated triple bond, to give *exo*- (c) or *endo-dig* cyclizations (d) to provide different bridged tandem reaction products.

We now report the results of a series of gold-catalyzed tandem cyclization reactions of various 1,6-diyne derivatives, connected to different internal nitrogen or oxygen nucleophilic groups. The aim of the investigation has been to identify the ability of such substrates to undergo tandem cyclization, triggered by internal nucleophiles. To study the regioselectivity arising from different cyclization processes, the effect of reaction conditions, including both gold-phosphine and gold-NHC catalysts and, in particular, the role of the counterion, provided by anion exchange with the appropriate silver salt additives, have been examined.

Results and Discussion

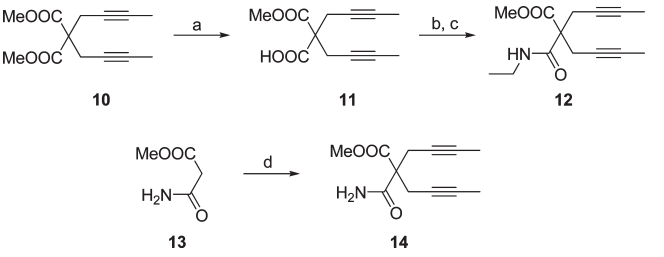
Preparation of Starting Materials. To investigate the envisaged tandem cyclization reactions, we synthesized a number of 1,6-diyne derivatives that included nucleophilic groups, such as amine **9**, carboxylic acid **11**, amides **12**, **14**, and **22**, and sulfonamides **15** and **19**. The amine **9** was prepared in a two-step procedure from benzyl cyanide (**7**) by bis-alkylation and subsequent nitrile reduction (Scheme 3).

SCHEME 3. Preparation of Amine 9[a]



[a]Conditions: (a) 1-bromo-2-butyne (2.2 equiv), NaH (2.2 equiv), THF, 17 h, 50 °C, 79%. (b) $LiAlH_4$ (2.0 equiv), Et_2O, 1 h, 0 °C and 4.5 h, rt, 86%.

SCHEME 4. Preparation of Bispropargylic Carboxylic Acid 11 and Amides 12 and 14[a]



[a]Conditions: (a) KOH (1.1 equiv), MeOH, 48 h, rt, 80%. (b) $C_2O_2Cl_2$ (1.25 equiv), cat. DMF, DCM, 1 h rt. (c) $EtNH_2 \cdot HCl$ (1.25 equiv), NEt_3 (2.5 equiv), DMAP (0.05 equiv), DCM, 17 h, rt, 80%. (d) 1-Bromo-2-butyne (2.2 equiv), NaH (2.2 equiv), THF, 23 h, rt, 83%.

The bispropargylic carboxylic acid **11** was obtained by monosaponification of diethylmalonate derivative **10** in basic methanolic medium in 80% yield.[12] Treatment of carboxylic acid **11** with oxalylchloride provided the acyl chloride, which was subsequently transformed into the secondary ethylamide **12** in 80% yield. Bis-alkylation of the monoamide malonate **13** provided diyne **14** in 83% yield (Scheme 4).

Tosylamide **15** was synthesized from amine **9** and TsCl in 74% yield. Tosylation of benzylamine **16** afforded sulfonamide **17**, which was further subjected to a standard Sonogashira reaction with the appropriate 1,6-diyne **18**[10] to give diyne **19** in 50% yield (Scheme 5).

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(8) (a) Verniest, G.; England, D.; De Kimpe, N.; Padwa, A. *Tetrahedron* **2010**, *66*, 1496. (b) Verniest, G.; Padwa, A. *Org. Lett.* **2008**, *10*, 4379.
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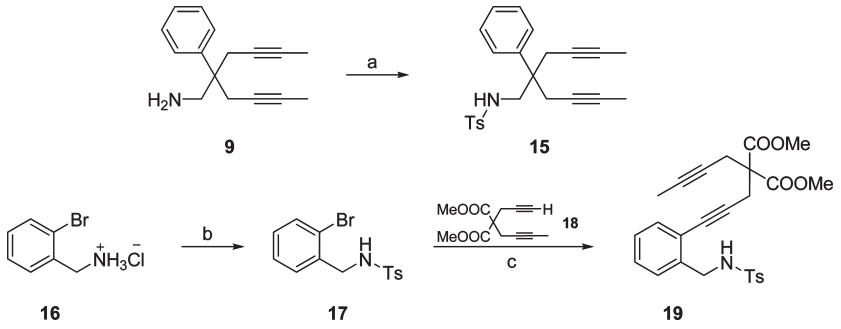
(10) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448.
(11) Sperger, C.; Fiksdahl, A. *Org. Lett.* **2009**, *11*, 2449.
(12) Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J. P.; Michelet, V. *ARKIVOK* **2007**, *5*, 67.

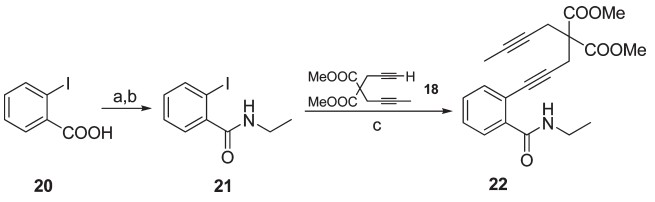
SCHEME 5. Preparation of Sulfonamides 15 and 19[a]



[a]Conditions: (a) TsCl (1.15 equiv), NEt_3 (1.5 equiv), DCM, 4 h, rt, 74%. (b) TsCl (1.1 equiv), NEt_3 (3.0 equiv), DCM, 19 h, rt, 95%. (c) 1,6-Diyne **18** (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CuI (0.1 equiv), PPh_3 (0.1 equiv), DMF/NEt_3 = 1:1, 21 h, 80 °C, 81%.

Arylamide diyne **22** was prepared in two steps from *o*-iodobenzoic acid (**20**). The iodoarylamide **21** was obtained in 85% yield by reaction of the acid chloride with ethylamine. Sonogashira cross-coupling of aryliodide **21** with 1,6-diyne **18** provided 1,6-diyne **22** in excellent yield (Scheme 6).

SCHEME 6. Preparation of Arylamide 22[a]



[a]Conditions: (a) $C_2O_2Cl_2$ (1.25 equiv), DCM, 4.5 h, rt. (b) $EtNH_2 \cdot HCl$ (1.5 equiv), NEt_3 (3 equiv), DCM, 17 h, rt, 85%. (c) 1,6-Diyne **18** (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), CuI (0.1 equiv), PPh_3 (0.1 equiv), THF/NEt_3 = 1:1, 19 h, rt, 98%.

Cyclization of 1,6-Diynes. In the following cyclization experiments gold-phosphine catalysts (**A**−**C**), the gold−NHC complex (**D**), and $AuCl_3$ were screened (Figure 1). The gold complexes **B**−**D** were used in combination with a silver additive to provide counterion exchange, while the commercially available catalyst **A** and $AuCl_3$ were used directly. The applied reaction conditions are specified in the respective tables (Tables 1−5). Most of the cyclization reactions created one or two new asymmetric centers.

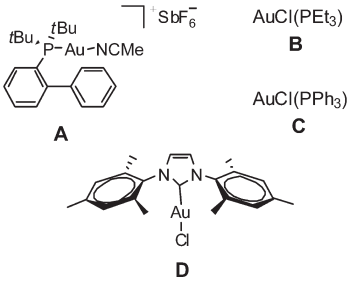
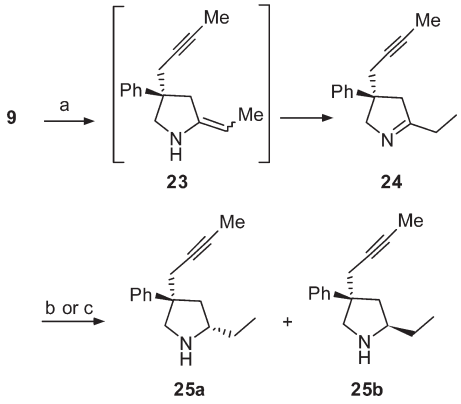


FIGURE 1. Applied gold catalysts.

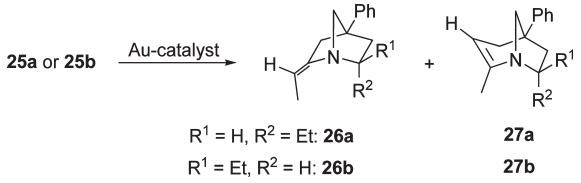
Cyclization of Amine 9. The $AuCl(PEt_3)$ and $AgSbF_6$ catalytic system was applied to the cyclization of primary amine **9** (Scheme 7). Within 2.5 h at room temperature, the starting material **9** was fully consumed, and the pyrrolidine derivative **23** was isolated in 94% yield. No subsequent reaction took place either with the intermediate enamine **23** or with the imine moiety in the isolated product **24**. An additional attempt to achieve

SCHEME 7. Formation of pyrrolidines 25a and 25b[a]



[a]Conditions: (a) $AuCl(PEt_3)$ (2.5 mol %), $AgSbF_6$ (2.5 mol %), Dioxane, 2.5 h, rt, 94%. (b) $NaBH_4$ (1.5 equiv), EtOH, 1.5 h, 0 °C and 15 h, rt, 77%. (c) $LiAlH_4$ (1.5 equiv), THF, 1 h, 0 °C and 1.5 h, rt, 95%.

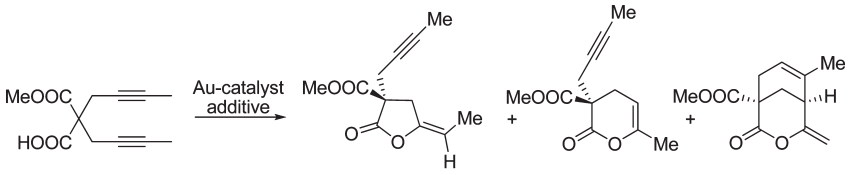
TABLE 1. Cyclization Reactions of Secondary Amines 25a and 25b[a]



						yield (%)	
entry	substrate	catalyst	additive[b]	time (h)	ratio (**26**/**27**)[c]	**26**	**27**
1	**25a**	$AuCl(PEt_3)$	$AgSbF_6$	2.5	33/67	23	43
2	**25a**	$AuCl(PEt_3)$	$AgNTf_2$	2.5	27/73	12	54
3	**25a**	**A**[d,e]		23	4/96		63
4	**25b**	$AuCl(PEt_3)$	$AgSbF_6$	2.5	53/47[f]	70[g]	
5	**25b**	**A**[e]		18	16/84[f]	d56[h]	

[a]Reactions were run at [**25**] = 500 mM in DCM at room temperature with 2.5 mol % catalyst loading. The reaction mixture was directly used for column chromatography. [b]2.5 mol %. [c]According to GC before column chromatography. [d]5.0 mol %. [e]See Figure 1. [f]According to ^1H NMR spectroscopy before column chromatography. [g]Isolated as a mixture **26b**/**27b** = 51:49. [h]Isolated as a mixture **26b**/**27b** = 10:90.

TABLE 2. Cyclization Reactions of Bispropargylic Carboxylic Acid 11[a]



11 28 29 30

					yield (%)		
entry	catalyst	additive[b]	time (h)	ratio (**28**/**29**/**30**)[c]	**28**	**29**	**30**
1	$AuCl(PEt_3)$	$AgSbF_6$	20	38/15/47	17		12
2	$AuCl(PEt_3)$	$AgNTf_2$	20	20/5/75			39
3	$AuCl(PEt_3)$	$AgBF_4$	21	53/29/18	[d]		
4	$AuCl(PEt_3)$	AgOTf	20	61/0/39	[d]		
5	$AuCl(PEt_3)$	$AgBPh_4$	20	90/10/0	[d]		
6	$AuCl(PPh_3)$	K_2CO_3	1	100/0/0	82		
7	$AuCl(PPh_3)$	$AgNTf_2$	20	23/7/70	[d]		
8	AuCl(IMes)[e,f]	K_2CO_3	1	100/0/0	81		
9	AuCl(IMes)	$AgSbF_6$	22	42/7/51	22		25
10	AuCl(IMes)	$AgNTf_2$	20	24/11/65	14		33
11	AuCl(IMes)	AgOTf	20	55/9/36	[d]		
12	AuCl(IMes)	$AgBPh_4$	18	85/15/0	83		
13	**A**[f]		22	55/9/36	[d]		
14	$AuCl_3$[g]		2	50/49/1	21	20	
15		$AgNTf_2$	20		[h]		

[a]Reactions were run at [**11**] = 500 mM in DCM at room temperature with 2.5 mol % catalyst loading. The reaction mixture was directly used for column chromatography. [b]2.5 mol %. [c]According to GC before column chromatography. [d]Not isolated. [e]IMes = 1,3-dimesitylimidazol-2-ylidene. [f]See Figure 1. [g]5 mol %. [h]No reaction.

cyclization of amine **9** with catalyst **A**, performed in toluene at 90 °C, only afforded a quantitative conversion to the imine **24**.

As the aim was to involve both triple bonds in a tandem cyclization, a reduction of the imine **24** to a secondary amine **25** would give a more flexible heterocyclic system that could allow a reaction with the remaining triple bond. The reduction of imine **24** was performed with either $NaBH_4$ to yield 77% of a mixture of both diastereomers **25a** and **25b** (diastereomeric ratio = 54:46 according to GC) or $LiAlH_4$ to provide 95% of a mixture of **25a** and **25b** (diastereomeric ratio = 48:52 according to GC). Stereoselective reductions of 2,3-dialkyl-3-chloro-1-pyrrolines with metal hydrides have been observed before.[13] The diastereomers **25a** and **25b** were separated by flash chromatography.

Gold-catalyzed cyclization of pyrrolidine **25a** gave the bridged products **26a** and **27a** by 5-*exo-dig* and 6-*endo-dig* processes, respectively. By applying $AuCl(PEt_3)$ as the gold catalyst precursor and either $AgSbF_6$ or $AgNTf_2$, an approximately 1:2 mixture of the bicyclic products **26a** and **27a** resulted, favoring the 6-*endo-dig* process (Table 1, entries 1 and 2). In contrast, when catalyst **A** was used, the azabicyclo derivative **27a** was almost exclusively formed, although 5 mol % catalyst loading and longer reaction times were required (Table 1, entry 3).

Comparable results were obtained for the other diastereomer **25b**, and an almost 1:1 mixture of azabicyclo products **26b** and **27b** was formed in the presence of $AuCl(PEt_3)$ and $AgSbF_6$ (Table 1, entry 4). Correspondingly, the reaction was shifted toward the 6-*endo-dig* cyclization when the gold complex **A** was used (Table 1, entry 5). However, a slightly reduced regioselectivity compared to the reaction of **25a** (Table 1, entry 3) was observed. According to NOESY experiments, all cyclization reactions selectively provided the *Z*-isomers of **26a** and **26b**.

Cyclization of Bispropargylic Carboxylic Acid 11. Potential tandem cyclization reactions, triggered by a carboxylic acid moiety, were also investigated (Table 2). When diyne **11** was treated with a number of different gold catalysts, three main reaction products, **28**, **29** and **30**, were formed in different ratios. Nucleophilic attack of the carboxylic acid in a 5-*exo-dig* manner provided the five-membered lactone derivative **28** selectively as the *E*-isomer. Once this dihydrofuranone derivative **28** was formed, no subsequent cyclization took place. In contrast, when the tetrahydropyranone **29** was formed in the initial cyclization step, a second reaction provided selectively the bridged product **30**. The alternative bridged bicyclic product, formed by a 5-*exo-dig* cyclization, could not be detected. The lack of propensity of **28** to undergo a second cyclization might be explained by a lower ring flexibility of the five-membered lactone **28** compared with the corresponding six-membered compound **29**, preventing a nucleophilic attack of the **28** ethylidene moiety.

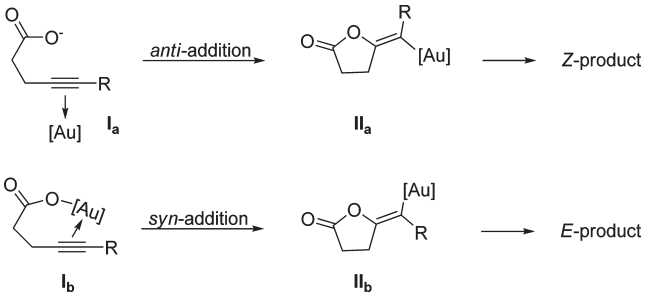
When the reaction was performed in the presence of either $AuCl(PEt_3)$ or AuCl(IMes) and $AgSbF_6$, all three main cyclic products were detected, slightly favoring the 6-*endo-dig* initial cyclization (Table 2, entries 1 and 9). By changing the counterion from SbF_6^- to NTf_2^- (bis(trifluoromethylsulfonyl)imide), the first cyclization step shifted toward a 6-*endo-dig* process and thus to the formation of higher amounts of tandem product **30** (Table 2, entries 2, 7, and 10). Alternative counterions, provided by $AgBF_4$ or AgOTf additives, afforded less effective catalytic systems for the formation of the tandem product **30** (Table 2, entries 3, 4, and 11). Catalyst **A** and $AuCl_3$ slightly favored the formation

(13) Aelterman, W.; De Kimpe, N.; Tyvorskii, V.; Kulinkovich, O. *J. Org. Chem.* **2001**, *66*, 53.

of the dihydrofuranone product **28** (Table 2, entries 13 and 14). An unexpected result was obtained by cyclization in the presence of $AgBPh_4$ and either $AuCl(PEt_3)$ or AuCl(IMes), since the 5-*exo-dig* cyclization was strongly favored, as shown by a ratio of approximately 9:1 (Table 2, entries 5 and 12).

The large, weakly nucleophilic BPh_4^- counterion shifted the reaction toward the formation of the dihydrofuranone derivative **28**. Pale et al. reported a regioselective 5-*exo-dig* cyclization of different 4-pentynoic acids in the presence of catalytic amounts of AuCl and K_2CO_3.[6b,c] To investigate the influence of K_2CO_3 on the regioselectivity, diyne **11** was treated with $AuCl(PPh_3)$ or AuCl(IMes) and K_2CO_3 (Table 2, entries 6 and 8). It is conceivable that the carboxylate anion, formed by carbonate deprotonation of the acidic moiety of substrate **11**, replaces the chlorine counterion of the gold complex and thereby generates an active gold species. As expected, the five-membered lactone **28** was obtained. However, the selective formation of the *E*-isomer was a surprising result as Pale et al. reported a 1:1 mixture of *Z*- and *E*-stereoisomers when *n*-butyl substituted 4-pentynoic acid was treated with AuCl in the presence of K_2CO_3, although phenyl or bromine substituted derivatives provided selectively the *Z*-isomers. The authors suggested the formation of two different intermediates $\mathbf{I_a}$ and $\mathbf{I_b}$ (Scheme 8). Depending on the gold coordination site, the nucleophilic addition of the carboxylate anion to intermediates $\mathbf{I_a}$ and $\mathbf{I_b}$ proceeds in an *anti* or *syn* mode to provide the respective vinylaurate intermediates $\mathbf{II_a}$ or $\mathbf{II_b}$ and, after protodeauration, the *Z*- and *E*-products, respectively.

SCHEME 8. Explanation for the Observed Regiochemistry



Whereas the *anti* addition is also reported for gold-catalyzed cyclization of *N* -propargylcarboxamides, [14] the *syn* mode was calculated for gold-catalyzed addition of alcohols to alkynes.[15] The *E*-stereochemistry of **28** is based on NOESY experiments as well as on chemical shift values of similar compounds. [16] Only traces of the respective *Z*-isomer **28** were detected according to ^{1}H NMR spectroscopy of the crude reaction mixtures.

Thus, our gold-catalyzed reaction conditions afford 5-*exo-dig* cyclizations always with complete stereoselectivity of the exocyclic double bond, as shown for *E*-isomers **28** (Table 2), **31** (Table 3), **38** (Scheme 9), and the previously reported *Z*-products **3**[11] (Scheme 1).

The ability of $AgNTf_2$ to catalyze one of the cyclization reactions was tested, but no reaction took place under such reaction conditions (Table 2, entry 15). According to the cyclization attempts with gold-phosphine or gold-NHC complexes (Table 2, entries 1−12), the regioselectivity of the first cyclization step is mainly dependent on the counterion. Thus, the weakly coordinating NTf_2^- anion showed a high tendency to shift the initial cyclization reaction toward the six-membered lactone **29** and further to the bridged product **30**. This trend decreased in the order $NTf_2^- > SbF_6^- > BF_4^- \approx OTf^- \gg BPh_4^- > COO^-$ (from **11** and K_2CO_3), thereby increasing the relative amount of product **28** formed by the 5-*exo-dig* process. Except for the BPh_4^- anion, these observations may be explained by increasing coordination tendency of the counterions. It has been reported that the BPh_4^- ion is prone to hydrolytic cleavage of one of the boron-phenyl bonds and is relatively strongly coordinating.[17]

Cyclization of Bispropargylic Amides 12 and 14. Similar tandem cyclization products were formed from propargylic amides by intramolecular *N*-nucleophilic ring closure. The diyne **12**, bearing a secondary amido group, was treated with a mixture of $AuCl(PPh_3)$ and $AgSbF_6$ in refluxing DCM, slow conversion having been observed at room temperature. Upon full consumption of the starting material **12**, three products were identified, a pyrrolidone derivative **31** as the single *E*-isomer and two major tandem cyclization products, **34** and **35** (Table 3, entry 1). The results show that no subsequent cyclization of the five-membered lactam **31** took place and are in accordance with the corresponding results for the carboxylic acid **11** discussed above (Table 2). The tandem cyclization products **34** and **35** would be formed from a six-membered lactam **32** by a 5-*exo-dig* and a 6-*endo-dig* cyclization, respectively. The putative lactam intermediate **32** was not observed. By changing the counterion from SbF_6^- to NTf_2^-, a comparable product ratio, but slightly lower conversion, was observed (Table 3, entry 2). An enamide moiety is formed in the first cyclization step. Such groups may possess latent nucleophilic character.

Only a few Pt(II)- and Ag(I)-catalyzed cycloisomerizations of enamides or enecarbamates, tethered to an electron-deficient alkyne, are reported in the literature.[18] It is noteworthy that the presence of 5 mol % NEt_3 in addition to $AuCl(PPh_3)$ and different silver salts strongly favored the 5-*exo-dig* monocyclization, providing lactam **31**. Only traces of tandem products **34** and **35** were detected (Table 3, entries 3−5). This behavior might be explained by deprotonation of the secondary amide moiety in **12**, generating a more reactive nucleophile. In contrast, applying 2.5 mol % of gold catalyst A and 2.5 mol % NEt_3, tandem cyclization was completely dominant. The starting material **12** was fully consumed within 6 h, providing an approximately 1:4 mixture of tandem products **34** and **35**. In contrast to the $AuCl(PPh_3)$-catalyzed reactions (Table 3, entries 1 and 2), it is evident that catalyst **A** mainly activated 6-*endo-dig* cyclizations (Table 3, entry 6).

By replacing the secondary amide **12** by the primary amide **14** and performing the reaction in the presence of catalyst **A**, one single tandem product **36** was isolated (Table 3, entry 7). This bicyclic compound was formed by two subsequent

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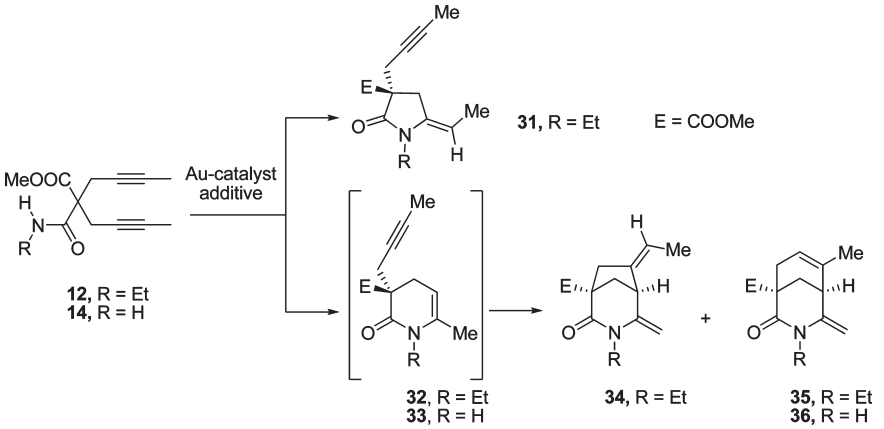
(17) Krossing, I.; Raabe, I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2066.
(18) (a) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023. (b) Harrison, T. J.; Patrick, O. B.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367.

TABLE 3. Cyclization Reactions of Bispropargylic Amides 12 and 14[a]



entry	substrate	catalyst	additive[b]	time (h)	ratio (**12**/**31**/**34**/**35**)[c]	yield (%)
1	**12**	$AuCl(PPh_3)$	$AgSbF_6$	18	1/14/66/19	[d]
2	**12**	$AuCl(PPh_3)$	$AgNTf_2$	18	24/0/61/15	[d]
3	**12**	$AuCl(PPh_3)$	$AgSbF_6$, NEt_3	18	9/82/1/8	**31** (59)
4	**12**	$AuCl(PPh_3)$	$AgNTf_2$, NEt_3	6	10/81/1/8	**31** (55)
5	**12**	$AuCl(PPh_3)$	AgOTf, NEt_3	20	39/55/2/4	**31**(35)
6	**12**	**A**[e]	NEt_3	6	0/0/18/82	(**34** + **35**) (88)[f]
7	**14**	**A**		4		**36** (32)
8	**14**	$AuCl(PPh_3)$	$AgNTf_2$	24		[g]
9	**14**	AuCl(IMes)[e]	$AgNTf_2$	24		**36** (6)
10	**14**		$AgNTf_2$	24		[h]

[a]Reactions were run at [**12**] or [**14**] = 500 mM in refluxing DCM for [**12**] and rt for [**14**] with 2.5−5.0 mol % catalyst loading. The reaction mixture was used directly for column chromatography. [b]2.5−5.0 mol %. [c]According to GC before column chromatography. [d]Not isolated. [e]See Figure 1. [f]Isolated as a mixture. For analytical purpose pure samples were obtained. [g]Low conversion. [h]No reaction.

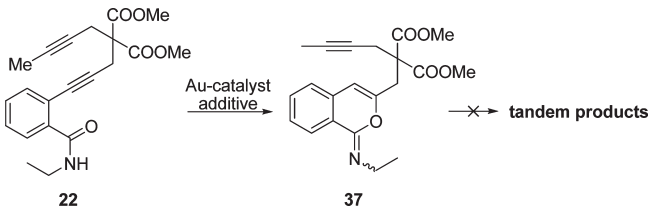
6-*endo-dig* cyclizations via intermediate **33**, in accordance with results above for substrate **12** and catalyst **A** (Table 3, entry 6). In addition, a mixture of different byproducts was formed, but the components could be neither separated nor characterized. In contrast to the reaction of the secondary amide **12**, the cyclization took place at room temperature within 4 h, probably due to the reduced steric hindrance of the primary amide moiety. Further cyclization attempts of **14** with $AuCl(PPh_3)$ or AuCl(IMes) in the presence of $AgNTf_2$ were less successful and showed only low conversion (Table 3, entries 8 and 9). Only $AgNTf_2$ as the catalyst showed no activity under the applied reaction conditions (Table 3, entry 10). The *E*- and *Z*-stereochemistry of **31** and **34**, respectively, was determined by NOESY experiments.

Cyclization of Arylamides 22. Different results were obtained by cyclization of the secondary arylamide **22**, tethered to a 1,6-diyne. On the basis of the results from the bispropargyl amide substrates **12** and **14**, we envisaged a nucleophilic attack of the amide nitrogen to provide isoindolin-1-one or isoquinolin-1-one derivatives by the initial cyclization. These cyclic intermediates were expected to undergo a subsequent cyclization with the remaining triple bond to provide the respective tandem bicyclic products. However, instead of the predicted transformations, an oxygen-nucleophilic attack took place. The reaction provided the imidate **37** as the single product by a regioselective 6-*endo-dig* cyclization. An experiment applying catalyst **A** in refluxing DCM, showed minor conversion after 18 h, according to ^1H NMR spectroscopy (Table 4, entry 1). As the addition of catalytic amounts of a base might increase the reactivity of the amide moiety by deprotonation, 5 mol % of NEt_3 was added to a reaction performed in DCE at 60 °C. Higher conversion was obtained and the six-membered imidate **37** was isolated in 27% yield (Table 4, entry 2).

Improved results were obtained by performing the reaction in toluene at 90 °C, providing full conversion of **22** in 21 h, and 59% yield of **37** was isolated (Table 4, entry 3). Replacing catalyst **A** (Table 4, entry 3) by $AuCl(PPh_3)$ and $AgNTf_2$ gave comparable results (Table 4, entry 5). Since the regioselectivity of the initial cyclization of amide **12** (Table 3) was dependent on whether NEt_3 was present, an additional experiment with amide **22** in the absence of base, was carried out (Table 4, entry 4). However, no other regioisomer was detected, and only one-third of the diyne **22** was converted into the imidate **37** after 20 h at 90 °C. An alternative cyclization attempt with $AuCl_3$ as the single catalyst gave no reaction after 23 h (Table 4, entry 6). However, by adding 15 mol % $AgNTf_2$, full conversion was observed (Table 4, entry 7). A similar transformation with different silver catalysts has recently been reported by Hong et al., synthesizing a number of different (1*H*)-isochromen-1-imine derivatives.[19] To investigate whether a silver salt may catalyze a tandem cyclization, an experiment was performed with only 10 mol % $AgNTf_2$ in the absence of any gold complex (Table 4, entry 8). Indeed, a silver-catalyzed cyclization of the diyne **22** was observed but provided only imidate **37** and no tandem product was formed. Nevertheless, a potential requirement of a silver salt additive for the cyclization of **22** can be excluded, since the reaction proceeded with catalyst **A** in the absence of any silver additive (Table 4, entries 2 and 3). Since hardly soluble AgCl is formed by exchanging the

(19) Guannan, L.; Yu, Z.; Deju, Y.; Dengyou, Z.; Xiao, D.; Hualiang, J.; Hong, L. *Adv. Synth. Catal.* **2009**, *351*, 2605.

TABLE 4. Cyclization Reactions of Arylamide 22[a]



22 37

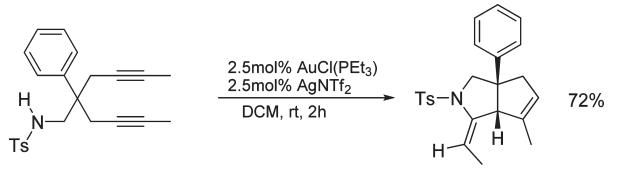
entry	catalyst	additive[b]	solvent	temp (°C)	time (h)	ratio **22**/**37**[c]	yield **37** (%)
1	**A**[d]		DCM	reflux	18	95/5	
2	**A**	NEt_3	DCE	60	24	60/40	27
3	**A**	NEt_3	toluene	90	20	0/100	59
4	**A**		toluene	90	20	66/34	[e]
5	$AuCl(PPh_3)$	$AgNTf_2/NEt_3$	toluene	90	20	0/100	57
6	$AuCl_3$		toluene	90	23	100/0	
7	$AuCl_3$	$AgNTf_2$[f]	toluene	90	22	0/100	48
8		$AgNTf_2$[g]	toluene	90	23	0/100	52

[a]Reactions were run at [**22**] = 250 mM with 5 mol % catalyst loading. The reaction mixture was directly used for column chromatography. [b]5 mol %. [c]According to ^{1}H NMR after workup. [d]See Figure 1. [e]Not isolated. [f]15 mol %. [g]10 mol %.

chlorine with a NTf_2^- counterion, the cyclizations in the presence of $AuCl(PPh_3)$, $AgNTf_2$, and NEt_3 (Table 4, entry 5) are likely to be catalyzed by a gold complex.

Cyclization of Sulfonamides 15 and 19. The present investigations also included 1,6-diyne substrates with an adjacent secondary sulfonamide functionality to act as the nucleophile and thus trigger tandem cyclization reactions. The diyne **15** was selectively converted into the tandem bicyclic product **38** (72%) as the single *E*-isomer within 2 h in the presence of 2.5 mol % $AuCl(PEt_3)$ and 2.5 mol % $AgNTf_2$ at room temperature (Scheme 9).

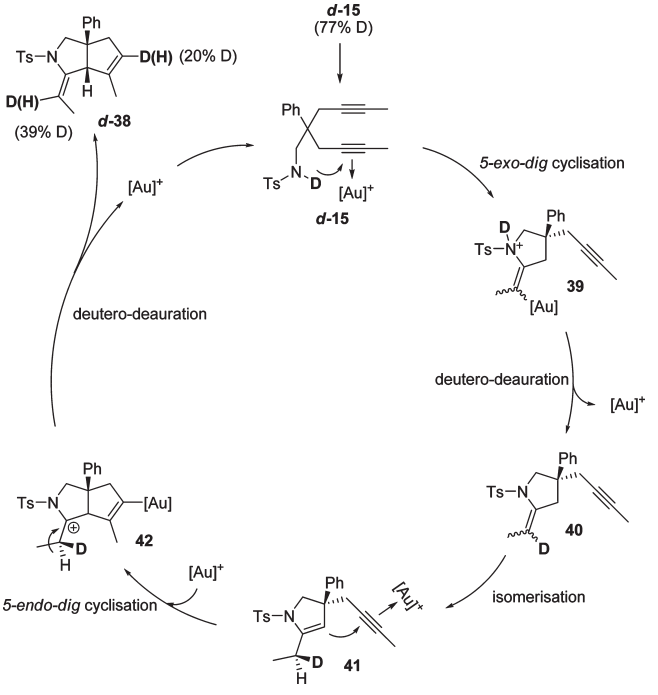
SCHEME 9. Cyclization of Sulfonamide 15



15 38

Based on an experiment with the *N*-deuterated diyne amide ***d*-15** (77% deuterium), prepared by proton abstraction with NaH and subsequent D_2O workup, the following reaction mechanism may be proposed (Scheme 10). One of the triple bonds in substrate ***d*-15** is activated by coordination to the active gold catalyst followed by a *5-exo-dig* attack of the sulfonamide moiety to give the cationic vinylaurate intermediate **39**. The pyrrolidine derivative **40** is formed by deutero-deauration (proto-deauration with deuterium) and regeneration of the active gold catalyst. To explain the structure of the final product ***d*-38**, we propose an isomerization of the exocyclic double bond in **40**, providing the more stable endocyclic enesulfonamide **41**. This isomerization step seems to be crucial for a successful second cyclization. The spatial alkene-alkyne proximity is not present in the previous five-membered imine **24** (Scheme 7), lactone **28** (Table 2), and lactam **31** (Table 3) products and may explain their lack of further cyclization. Subsequent activation of the remaining alkyne moiety followed by a nucleophilic attack of the enamide double bond, once more in a *5-exo-dig* manner, leads to the formation of a cationic gold intermediate **42**. Final deutero-deauration releases the product ***d*-38** and enables cyclization of the active gold catalyst. According to ^{1}H NMR spectroscopy, approximately 39% deuterium incorporation of the exocyclic alkene moiety and a 20% deuterium incorporation of the endocyclic double bond had taken place. The specific positions of both deuterium atoms can be rationalized by the two deutero-deauration steps in the proposed reaction mechanism.

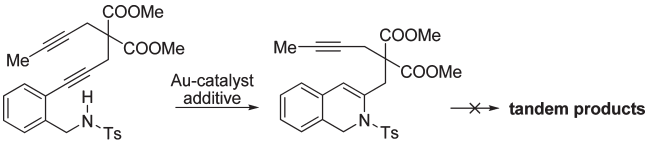
SCHEME 10. Proposed Mechanism for the Formation of 38



Gold-catalyzed tandem cyclization reaction of another bispropargyl sulfonamide **19** with a fundamentally different structure was studied. In contrast to substrate **15**, the diyne moiety of sulfonamide **19** is directly connected to an aryl system. In a cyclization performed with catalyst **A** in DCM, the starting material **19** was fully consumed after 23 h,

providing only the dihydroisoquinoline monocyclization product **43** in 72% yield (Table 5, entry 1). No second tandem cyclization, triggered by the sulfonyl enamide unit, occurred.

TABLE 5. Cyclization Reactions of Sulfonamide 19[a]



19 **43**

entry	catalyst	additive[b]	solvent	temp (°C)	time (h)	yield (%)
1	**A**[c]		DCM	rt	23	72
2	$AuCl(PPh_3)$	$AgNTf_2$	DCM	rt	24	[d]
3	$AuCl(PEt_3)$	$AgNTf_2$	DCM	rt	19	[d]
4	**A**		toluene	100	20	[e]

[a]Reactions were run at [**19**] = 500 mM with 5 mol % catalyst loading. The reaction mixture was directly used for column chromatography. [b]5 mol %. [c]See Figure 1. [d]Traces according to ^{1}H NMR. [e]36% conversion according to ^{1}H NMR.

In contrast to the initial cyclization product **41** (Scheme 10), the enamide double bond in **43** is conjugated to an aryl system that may reduce the reactivity of the alkene moiety, thus preventing a second cyclization. A conjugated alkene moiety is similarly present in isochromen imine **37**, obtained from arylamide **22** (Table 4), and may likewise explain the lack of a tandem reaction. As we observed a selective tandem transformation of bispropargyl sulfonamide **15** into the bicyclic product **38** in the presence of $AuCl(PEt_3)$ and $AgNTf_2$ (Scheme 9), two further sulfonamide (**19**) reactions were performed, using $AuCl(PPh_3)$ and $AuCl(PEt_3)$ with the NTf_2^- counterion (Table 5, entries 2 and 3). By applying similar reaction conditions as used for **15** (Scheme 9), only traces of product **43** were detected after 19 and 24 h, according to ^{1}H NMR spectroscopy. Thus, another attempt at tandem cyclization of **19** was performed in toluene at 100 °C with gold complex **A** (Table 5, entry 4). Rather than increasing the yield of the dihydroisoquinoline **43** or forming tandem cyclization products, only a reduced conversion of 36% into **43** was observed, according to ^{1}H NMR spectra of the crude reaction mixture.

Conclusion

The results from a series of tandem cyclization reactions of various 1,6-diyne substrates are reported. The reactions were triggered by internal O- and N-nucleophiles, such as amine, carboxylic acid, amide, and sulfonamide functionalities. Bicyclic bridged reaction products were obtained by successful tandem cyclizations of carboxylic acid **11**, secondary and primary amides **12** and **14**, and sulfonamide **15**. Tandem cyclization of amine **9** was obtained after reduction of the monocyclization imine product **24**. Arylamide substituted diynes **19** and **22** failed to undergo tandem cyclization, and only monocyclization products were formed. The regioselectivity of the reactions with carboxylic acid diyne **11** and amide diyne **12** was more closely investigated. The applied counterion turned out to be crucial for the formation of bicyclic products. All of the reported tandem reactions were successfully performed with the NTf_2^- and SbF_6^- counterions.

Experimental Section

General Experimental. All reactions were performed under argon atmosphere. Commercial grade reagents were used as received. AuCl(IMes) was prepared according to a literature procedure.[20] Dry solvents were collected from a solvent purification system. All reactions were monitored by GC and thin-layer chromatography (TLC) using silica gel 60 F254 (0.25 mm thickness). Flash chromatography was carried out using silica gel 60 (0.040−0.063 mm). High throughput flash purification (HPFP) was performed on prepacked cartridges. ^{1}H and ^{13}C NMR spectra were recorded using a 300 or 400 MHz spectrometer. Chemical shifts are reported in ppm (δ) 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 and are uncorrected. High resolution mass spectra (HRMS) were obtained using ESI ionization. IR spectra were obtained using a Smart Endurance reflection cell. Diynes **10** and **18** were prepared according to a literature procedure.[21]

Preparation of Starting Materials. 2-(But-2-ynyl)-2-phenyl-4-ynenitrile (8). To an ice-cold suspension of NaH (180 mg, 7.52 mmol, 2.5 equiv) in THF (30 mL) was added a solution of nitrile **8** (353 mg, 3.01 mmol) and 1-bromo-2-butyne (1.0 g, 7.52 mmol, 0.66 mL, 2.5 equiv) in THF (3 mL). The cooling bath was removed, and the suspension was heated in a 50 °C hot oil bath for 17 h. After the addition of water (40 mL) the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 15:1) to yield **8** (526 mg, 79%) as a colorless solid. R_f = 0.49 (*n*-hexane/EtOAc 4:1); mp 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (t, J = 2.5 Hz, 6 H, CH_3), 2.86 (dq, J = 16.6/2.5 Hz, 2 H, CH_2), 2.96 (dq, J = 16.6/2.5 Hz, 2 H, CH_2), 7.32−7.43 (m, 3 H, H_{arom}), 7.47−7.51 (m, 2 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (2 × CH_3), 29.9 (2 × CH_2), 46.9 (*C*CN), 72.8 (2 × C_{alkyne}), 80.6 (2 × C_{alkyne}), 121.6 (CN), 126.2 (2 × CH_{arom}), 128.3 (CH_{para}), 128.7 (2 × CH_{arom}), 137.3 (C_{arom}); IR (neat, cm^{-1}) 2925, 2359, 2244, 1448; HRMS (ESI) calcd for $C_{16}H_{15}NNa$ 244.1102, obsd 244.1100.

2-(But-2-ynyl)-2-phenylhex-4-yn-1-amine (9). To an ice-cold suspension of $LiAlH_4$ (151 mg, 3.98 mmol, 2.0 equiv) in Et_2O (5 mL) was added a solution of **8** (440 mg, 1.99 mmol) in Et_2O (5 mL). The gray suspension was stirred for 1 h at 0 °C and for an additional 4.5 h at room temperature. After cooling to 0 °C a NaOH solution (10 mL, 1 N) was added followed by the addition of water (20 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (DCM/methanol 97:3) to yield **9** (386 mg, 86%) as a colorless oil. R_f = 0.32 (DCM/methanol 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (bs, 2 H, NH_2), 1.73 (t, J = 2.4 Hz, 6 H, CH_3), 2.66 (q, J = 2.4 Hz, 4 H, CH_2), 3.06 (s, 2 H, CH_2NH_2), 7.19−7.27 (m, 1 H, H_{para}), 7.31−7.38 (m, 4 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (2 × CH_3), 26.4 (2 × CH_2), 46.2 (CH_2NH_2), 49.6 (PhC), 75.7 (2 × C_{alkyne}), 78.1 (C_{alkyne}), 126.4 (CH_{para}), 126.8 (2 × CH_{arom}), 128.3 (2 × CH_{arom}), 143.1 (C_{arom}); IR (neat, cm^{-1}) 2917, 2854, 761; HRMS (ESI) calcd for $C_{16}H_{20}N$ 226.1596, obsd 226.1595.

2-But-2-ynyl)-2-(methoxycarbonyl)hex-4-ynoic acid (11). The acid was prepared according to a procedure described by

(20) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677.

(21) Sperger, C.; Fiksdahl, A. *Org. Lett.* **2009**, *11*, 2449.

Michelet et al.[22] from diyne **10** (80 mg, 0.34 mmol) and KOH (20.9 mg, 0.37 mmol, 1.1 equiv) in methanol (500 μL). The acid **11** was obtained as a colorless solid (60.2 mg, 80%), mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (t, J = 2.6 Hz, 6 H, CH_3), 2.88−2.92 (m, 4 H, CH_2), 3.79 (s, 3 H, OCH_3), 10.55 (bs, 1 H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (2 × CH_3), 23.1 (2 × CH_2), 53.1 (2 × OCH_3), 57.1 (CO*C*CO), 72.8 (2 × C_{alkyne}), 79.3 (2 × C_{alkyne}), 169.6 (COOH), 174.7 (COOMe); IR (neat, cm^{-1}) 2958, 2920, 1748, 1710, 1434, 1202; HRMS (ESI) calcd for $C_{12}H_{15}O_4$ 223.0970, obsd 223.0969.

Methyl 2-(But-2-ynyl)-2-(ethylcarbamoyl)hex-4-ynoate (12). A solution of the acid **11** (150 mg, 0.675 mmol) in DCM (1.8 mL) and DMF (1 μL) was cooled to 0 °C, and oxalylchloride (107 mg, 0.844 mmol, 71.4 μL, 1.25 equiv) was added dropwise. After stirring for 10 min the cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature. The solvent and excess oxalylchloride were removed under reduced pressure, and the oily residue was dissolved in DCM (4.8 mL). After cooling again to 0 °C, NEt_3 (171 mg, 1.69 mmol, 235 μL, 2.5 equiv), DMAP (4.30 mg, 0.034 mmol, 5.0 mol %) and $EtNH_2 \cdot HCl$ (68.8 mg, 0.844 mmol, 1.25 equiv) were subsequently added. The reaction mixture was stirred for 5 min at 0 °C and for 17 h at room temperature before a HCl solution (20 mL, 0.5 N) was added. The aqueous layer was extracted with EtOAc (3 × 35 mL), and the combined organic layers were washed with a satd $NaHCO_3$ solution (20 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to yield **12** (134.3 mg, 80%) as a colorless solid, mp 113−114 °C; R_f = 0.47 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 1.75 (t, J = 2.6 Hz, 6 H, CH_3), 2.78 (dq, J = 16.7/2.6 Hz, 2 H, CH_2), 2.89 (dq, J = 16.7/2.6 Hz, 2 H, CH_2), 3.33 (qd, J = 7.4/5.7 Hz, 2 H, CH_2CH_3), 3.77 (s, 3 H, OCH_3), 6.60 (bs, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.6 (2 × CH_3), 14.6 (CH_2CH_3), 24.6 (2 × CH_2), 34.7 (CH_2CH_3), 52.8 (OCH_3), 57.1 (CO*C*CO), 73.8 (2 × C_{alkyne}), 78.9 (2 × C_{alkyne}), 168.2 (CONH), 172.2 (COOMe); IR (neat, cm^{-1}) 3323, 2923, 1740, 1635; HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ 250.1443, obsd 250.1443.

Methyl 2-(But-2-ynyl)-2-carbamoylhex-4-ynoate (14).[23] To an ice-cold suspension of NaH (90.2 mg, 3.76 mmol, 2.2 equiv) in THF (10 mL) was added a solution of methyl malonate monoamide (**13**) (200 mg, 1.71 mmol) and 1-bromo-2-butyne (500 mg, 3.76 mmol, 329 μL, 2.2 equiv) in THF (3 mL). The cooling bath was removed, and the suspension was stirred for 23 h at room temperature. After the addition of water (40 mL) the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 1:2) to yield **14** (312 mg, 83%) as a colorless solid. R_f = 0.29 (EtOAc); mp 133−134 °C (lit. 128−130 °C).

***N*-(2-(But-2-ynyl)-2-phenylhex-4-ynyl)-4-methylbenzenesulfonamide (15).** To a solution of the amine **9** (50 mg, 0.222 mmol) in DCM (3 mL) were successively added NEt_3 (33.7 mg, 0.333 mmol, 46.2 μL, 1.5 equiv), DMAP (1.36 mg, 0.01 mmol, 5 mol %), and TsCl (48.6 mg, 0.255 mmol, 1.15 equiv) at 0 °C. The cooling bath was removed, and stirring was continued for 4 h. The mixture was poured into a HCl solution (10 mL, 1 N), and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution (15 mL) and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to provide **15** (62.6 mg, 74%) as a colorless solid, mp 165−166 °C; R_f = 0.84 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (t, J = 2.5 Hz, 6 H, CH_3), 2.43 (s, 3 H, CH_3), 2.63 (q, J = 2.5 Hz, 4 H, CH_2), 3.30 (d, J = 6.6 Hz, 2 H, CH_2NH), 4.32 (t, J = 6.6 Hz, 1 H, NH), 7.20−7.34 (m, 7 H, H_{arom}), 7.67 (t, J = 8.4 Hz, 1 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (2 × CH_3), 21.5 (CH_3), 26.9 (2 × CH_2), 44.4 (CH_2NH), 50.3 (CO*C*CO), 74.8 (2 × C_{alkyne}), 79.0 (2 × C_{alkyne}), 126.5 (2 × CH_{arom}), 127.1 (CH_{arom}), 127.2 (2 × CH_{arom}), 128.6 (2 × CH_{arom}), 129.6 (2 × CH_{arom}), 136.5 (C_{arom}), 141.2 (C_{arom}), 143.4 (C_{arom}); IR (neat, cm^{-1}) 3274, 1315, 1160. HRMS (ESI) calcd for $C_{23}H_{26}NO_2S$ 380.1679, obsd 380.1685.

***N*-(2-Bromobenzyl)-4-methylbenzenesulfonamide (17).**[24] To a suspension of benzylamine hydrochloride **16** (300 mg, 1.35 mmol) in DCM (10 mL) were successively added NEt_3 (410 mg, 4.05 mmol, 565 μL, 3.0 equiv) and solid TsCl (283 mg, 1.49 mmol, 1.1 equiv). After 19 h at room temperature HCl (30 mL, 1 M) was added, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 4:1) to provide **17** (438 mg, 95%) as a colorless solid. The melting point (mp 72−73 °C, lit. 73.5 °C) and the ^{1}H NMR data are in accordance with the literature.

Dimethyl 2-(But-2-ynyl)-2-(3-(2-((4-methylphenylsulfonamido)-methyl)phenyl) Prop-2-ynyl)malonate (19). The reaction was performed with **17** (130 mg, 0.382 mmol), diyne **18** (102 mg, 0.458 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (13.4 mg, 0.019 mmol, 0.05 equiv), CuI (7.3 mg, 0.038 mmol, 0.1 equiv), and PPh_3 (10.0 mg, 0.038 mmol, 0.01 equiv) in a mixture of DMF/NEt_3 = 1:1 (2 mL) at 80 °C for 21 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 3:1) to provide **19** (149 mg, 81%) as a yellow oil. R_f = 0.41 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (t, J = 2.6 Hz, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.90 (q, J = 2.6 Hz, 2 H, CH_2), 3.16 (s, 2 H, CH_2), 3.78 (s, 6 H, OCH_3), 4.23 (d, J = 6.4 Hz, 2 H, CH_2NH), 5.41 (t, J = 6.4 Hz, 1 H, NH), 7.10−7.23 (m, 5 H, H_{arom}), 7.25−7.29 (m, 1 H, H_{arom}), 7.68 (d, J = 8.3 Hz, 2 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (CH_3), 21.4 (CH_3), 23.5 (CH_2CCCH_3), 24.0 ($CCCH_2$), 46.1 (CH_2NH), 53.2 (2 × OCH_3), 56.9 (CO*C*CO), 72.6 (C_{alkyne}), 79.7 (C_{alkyne}), 81.2 (C_{alkyne}), 89.2 (C_{alkyne}), 122.1 (C_{arom}), 127.0 (2 × CH_{arom}), 127.5 (CH_{arom}), 128.3 (CH_{arom}), 129.0 (CH_{arom}), 129.4 (2 × CH_{arom}), 132.6 (CH_{arom}), 137.7 (C_{arom}), 138.3 (C_{arom}), 142.9 (C_{arom}), 169.7 (2 × CO); IR (neat, cm^{-1}) 3294, 2954, 2923, 1735, 1435, 1156; HRMS (ESI) calcd for $C_{26}H_{28}NO_6S$ 482.1637, obsd 482.1646.

***N*-Ethyl-2-iodobenzamide 21.** The acid **20** (500 mg, 2.02 mmol) was suspended in DCM (5 mL) and DMF (2 μL). After the addition of oxalylchloride (320 mg, 2.52 mmol, 213 μL, 1.25 equiv), stirring was continued for 4.5 h at room temperature. The solvent and excess oxalylchloride were removed under reduced pressure, and the solid yellow residue was dissolved in DCM (15 mL). After cooling again to 0 °C, NEt_3 (613 mg, 6.06 mmol, 845 μL, 3.0 equiv) and $EtNH_2 \cdot HCl$ (247 mg, 3.03 mmol, 1.5 equiv) were subsequently added. The reaction mixture was stirred for 5 min at 0 °C and for 17 h at room temperature before a HCl solution (40 mL, 1 N) was added. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with a satd $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 2:1) to yield **21** (474 mg, 85%) as a colorless solid. The melting point (mp 117−118 °C, lit. 114−116 °C) and the ^{1}H NMR data are in accordance with the literature.[25]

Dimethyl 2-(But-2-ynyl)-2-(3-(2-(ethylcarbamoyl)phenyl)prop-2-ynyl) Malonate (22). The reaction was performed with **21** (103 mg, 0.375 mmol), diyne **18** (100 mg, 0.450 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (13.1 mg, 0.019 mmol, 0.05 equiv), CuI (7.1 mg,

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0.038 mmol, 0.1 equiv), and PPh_3 (9.8 mg, 0.038 mmol, 0.01 equiv) in a mixture of THF/NEt_3 = 1:1 (2.4 mL) at room temperature for 19 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 2:1 → 1:1) to provide **22** (135 mg, 98%) as a yellow oil. R_f = 0.23 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.77 (t, J = 2.6 Hz, 3 H, CH_3), 2.97 (q, J = 2.6 Hz, 2 H, CH_2), 3.25 (s, 2 H, CH_2), 3.50−3.60 (m, 2 H, CH_2CH_3), 3.78 (s, 6 H, OCH_3), 7.23 (bs, 1 H, NH), 7.34−7.46 (m, 3 H, H_{arom}), 7.99 (dd, J = 7.2/2.3 Hz, 1 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (CH_3), 14.8 (CH_2CH_3), 23.5 (CH_2CCCH_3), 24.0 (CH_2), 34.9 (CH_2CH_3), 53.1 (2 × OCH_3), 56.9 (COCCO), 72.6 (C_{alkyne}), 79.6 (C_{alkyne}), 82.1 (C_{alkyne}), 90.7 (C_{alkyne}), 119.2 (C_{arom}), 128.6 (CH_{arom}), 129.8 (CH_{arom}), 130.2 (CH_{arom}), 133.9 (CH_{arom}), 135.9 (C_{arom}), 166.1 (CONH), 169.4 (2 × CO); IR (neat, cm^{-1}) 3301, 2954, 1736, 1645, 1529, 1435, 1292; HRMS (ESI) calcd for $C_{21}H_{24}NO_5$ 370.1654, obsd 370.1667.

Cyclization Reactions. General Procedure. The gold catalyst and, if needed, a silver additive were placed in a Schlenk flask under an argon atmosphere, and a solution of the substrate in the given solvent was added. The reaction mixture was stirred at the appropriate temperature for the given time. If not stated otherwise, the reaction mixtures were used directly for flash chromatography.

3-(But-2-ynyl)-5-ethyl-3-phenyl-3,4-dihydro-2*H*-pyrrole (24). The title compound was prepared according to the general procedure from $AuCl(PEt_3)$ (7.82 mg, 22.3 μmol, 2.5 mol %), $AgSbF_6$ (7.62 mg, 22.2 μmol, 2.5 mol %), and **9** (200 mg, 0.888 mmol) in DCM or dioxane (1.8 mL). Flash chromatography (*n*-hexane/EtOAc 1:1) after 2.5 h at room temperature yielded **24** (187.8 mg, 94%) as a colorless oil. R_f = 0.20 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 1.72 (t, J = 2.5 Hz, 3 H, CH_3), 2.39 (q, J = 7.6 Hz, 2 H, CH_2CH_3), 2.42 (q, J = 2.5 Hz, 2 H, CH_2CC), 2.85 (dt, J = 17.1/2.0 Hz, 1 H, H-4), 2.97 (dt, J = 17.1/1.2 Hz, 1 H, H-4), 4.01 (dq, J = 15.2/2.0 Hz, 1 H, H-2), 4.19 (dq, J = 15.2/1.2 Hz, 1 H, H-2), 7.18−7.24 (m, 3 H, H_{arom}), 7.28−7.35 (m, 2 H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.5 (CH_3), 10.5 (CH_2CH_3), 27.2 (CH_2CH_3), 32.4 (CH_2CC), 48.9 (C-4), 50.0 (C-3), 71.6 (C-2), 76.1 (CH_2C), 77.8 (CCH_3), 126.2 (CH_{para}), 126.7 (2 × CH_{arom}), 128.2 (2 × CH_{arom}), 146.5 (C_{arom}), 178.6 (C-5); IR (neat, cm^{-1}) 2971, 2917, 1643; HRMS (ESI) calcd for $C_{16}H_{20}N$ 226.1596, obsd 226.1599.

(±)-4-(But-2-ynyl)-2-ethyl-phenylpyrrolidine (25a) and (±)-4-(But-2-ynyl)-2-ethyl-phenylpyrrolidine (25b). Method A. To an ice-cold solution of the imine **24** (137 mg, 0.608 mmol) in ethanol (2.8 mL) was added $NaBH_4$ (31.7 mg, 0.837 mmol, 1.5 equiv) in small portions. The dark brown solution was stirred for 1.5 h at 0 °C and an additional 15 h at room temperature. After the addition of a satd $NaHCO_3$ solution (20 mL), the aqueous layer was extracted with DCM (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (DCM/methanol 9:1) to yield a mixture of both diastereomers **25a** and **25b** (97.2 mg, 77%) as a colorless oil. The mixture was further purified by using a VersaFlash purification system (23 × 110 mm, 23 g SiO_2, DCM/methanol 97:3) to yield **25a** (45.5 mg, 36%) as a colorless oil and **25b** (34.4 mg, 27%) as a colorless oil.

Method B. $LiAlH_4$ (83.9 mg, 2.21 mmol, 1.5 equiv) was suspended in THF (5 mL) and cooled to 0 °C. Imine **24** (332 mg, 1.47 mmol) in THF (5 mL) was then added dropwise, and the brown solution was stirred for 1 h at 0 °C before the cooling bath was removed. After an additional 1.5 h at room temperature a Na_2SO_4 solution (25 mL, 1 M) was added, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness providing a mixture of both diastereomers **25a** and **25b** as a yellow oil (335 mg, 95%). The diastereomers were separated by two HPFP (DCM/methanol/*i*PrOH 95:4:4) to provide **25a** (141.5 mg, 42%), **25b** (87.6 mg, 26%), and a mixture of both diastereomers (40.5 mg, 12%). **25a**: R_f = 0.15 (DCM/methanol 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.51−1.78 (m, 2 H, CH_2CH_3), 1.74 (t, J = 2.6 Hz, 3 H, CH_3), 1.83 (dd, J = 13.6/9.0 Hz, 1 H, H-3), 2.40 (dd, J = 13.6/7.5 Hz, 1 H, H-3), 2.53 (q, J = 2.6 Hz, 2 H, CH_2), 3.08−3.21 (m, 1 H, H-2), 3.31 (d, J = 11.5 Hz, 1 H, H-5), 3.44 (d, J = 11.5 Hz, 1 H, H-5), 4.49 (bs, 1 H, NH), 7.19−7.26 (m, 1 H, H_{arom}), 7.27−7.38 (m, 4 H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4 (CH_3), 11.6 (CH_2CH_3), 28.8 (CH_2CH_3), 32.6 (CH_2), 43.2 (C-3), 50.7 (C-4), 56.8 (C-5), 61.1 (C-2), 76.3 (C_{alkyne}), 77.8 (C_{alkyne}), 126.3 (2 × CH_{arom}), 126.5 (CH_{para}), 128.2 (2 × CH_{arom}), 146.1 (C_{arom}); IR (neat, cm^{-1}) 2958, 2872, 1445. HRMS (ESI) calcd for $C_{16}H_{22}N$ 228.1752, obsd 228.1748. **25b**: R_f = 0.15 (DCM/methanol 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.35−1.60 (m, 2 H, CH_2CH_3), 1.67 (dd, J = 13.2/9.0 Hz, 1 H, H-3), 1.72 (t, J = 2.6 Hz, 3 H, CH_3), 2.31 (bs, 1 H, NH), 2.42 (dd, J = 13.2/6.8 Hz, 1 H, H-3), 2.47 (q, J = 2.6 Hz, 2 H, CH_2), 3.20−3.38 (m, 1 H, H-2), 3.21 (d, J = 10.9 Hz, 1 H, H-5), 3.33 (d, J = 10.9 Hz, 1 H, H-5), 7.17−7.36 (m, 5 H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.5 (CH_3), 11.6 (CH_2CH_3), 30.1 (CH_2CH_3), 31.3 (CH_2), 43.5 (C-3), 51.4 (C-4), 56.6 (C-5), 59.7 (C-2), 76.5 (C_{alkyne}), 77.7 (C_{alkyne}), 126.1 (CH_{para}), 126.9 (2 × CH_{arom}), 128.0 (2 × CH_{arom}), 147.0 (C_{arom}); IR (neat, cm^{-1}) 2957, 2917, 2857, 1445. HRMS (ESI) calcd for $C_{16}H_{22}N$ 228.1752, obsd 228.1751.

(*Z*)-(±)-2-Ethyl-6-ethylidene-4-phenyl-1-azabicyclo[2.2.1]heptane (26a) and (±)-7-Ethyl-2-methyl-5-phenyl-1-azabicyclo[3.2.1]oct-2-ene (27a). Representative Procedure. (Table 1, entry 1) The title compounds were prepared according to the general procedure from $AuCl(PEt_3)$ (1.54 mg, 4.4 μmol, 2.5 mol %), $AgSbF_6$ (1.51 mg, 4.4 μmol, 2.5 mol %), and **25a** (40 mg, 0.176 mmol) in DCM (c = 500 mM). Flash chromatography (DCM/ethanol 96:4) after 2.5 h at room temperature provided **26a** (9.2 mg, 23%) as a yellow oil and **27a** (17.1 mg, 43%) as a colorless oil. **26a**: R_f = 0.61 (DCM/methanol 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.18 (ddd, J = 11.8/6.0/2.2 Hz, 1 H, CH_2, H-3), 1.28−1.44 (m, 1 H, CH_2CH_3), 1.62−1.80 (m, 1 H, CH_2CH_3), 1.75 (dt, J = 6.8/1.9 Hz, 3 H, CH_3), 2.08 (ddd, J = 11.8/8.3/3.1 Hz, 1 H, H-3), 2.13−2.21 (m, 1 H, H-5), 2.44−2.51 (m, 1H, H-5), 2.81 (dd, J = 9.0/2.2 Hz, 1 H, H-7), 2.97 (dd, J = 9.0/3.1 Hz, 1 H, H-7), 3.18−3.31 (m, 1 H, H-2), 5.14 (qt, J = 6.8/2.0 Hz, 1 H, CH), 7.17−7.37 (m, 5 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (CH_2CH_3), 13.4 (CH_3), 26.1 (CH_2CH_3), 43.3 (C-3), 45.1 (C-5), 54.0 (C-4), 65.2 (C-7), 67.9 (C-2), 113.4 (CH), 126.3 (CH_{para}), 126.6 (2 × CH_{arom}), 128.4 (2 × CH_{arom}), 142.7 (C_{arom}), 146.2 (C-6); IR (neat, cm^{-1}) 3027, 2959, 2932, 1497, 1446; HRMS (ESI) calcd for $C_{16}H_{22}N$ 228.1752, obsd 228.1751. **27a**: R_f = 0.55 (DCM/methanol 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.39−1.56 (m, 1 H, CH_2CH_3), 1.61 (dd, J = 12.4/8.3 Hz, 1 H, CH_2, H-3), 1.81−1.83 (m, 3 H, CH_3), 1.81−1.97 (m, 1 H, CH_2CH_3), 2.02−2.12 (m, 1 H, H-5), 2.27 (ddd, J = 12.4/8.3/1.9 Hz, 1 H, H-3), 2.34−2.44 (m, 1 H, H-5), 3.15 (d, J = 10.5 Hz, 1 H, H-8), 3.23 (dd, J = 10.5/1.9 Hz, 1 H, H-8), 3.24−3.37 (m, 1 H, H-2), 5.24−5.28 (m, 1 H, CH), 7.20 (tt, J = 6.8/2.2 Hz, 1 H, H_{para}), 7.24−7.37 (m, 4 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3 (CH_2CH_3), 24.3 (CH_3), 25.6 (CH_2CH_3), 44.6 (C-5), 45.0 (C-4), 45.7 (C-3), 62.7 (C-8), 72.3 (C-2), 114.7 (CH), 125.9 (CH_{para}), 126.1 (2 × CH_{arom}), 128.3 (2 × CH_{arom}), 146.7 (C-6), 148.1 (C_{arom}); IR (neat, cm^{-1}) 3024, 2959, 2875, 1495, 1445; HRMS (ESI) calcd for $C_{16}H_{22}N$ 228.1752, obsd 228.1751.

(*Z*)-(±)-2-Ethyl-6-ethylidene-4-phenyl-1-azabicyclo[2.2.1]heptane (26b) and (±)-7-Ethyl-2-methyl-5-phenyl-1-azabicyclo[3.2.1]oct-2-ene (27b). Representative Procedure. (Table 1, entry 5) The title compounds were prepared according to the general procedure from catalyst **A** (5.95 mg, 7.7 μmol, 5.0 mol %) and **25b**

(35 mg, 0.154 mmol) in DCM (c = 500 mM) for 18 h. Flash chromatography (DCM/ethanol 96:4) provided a mixture of **26b** and **27b** (19.5 mg, 56%, **26b**/**27b** 10:90) as a pale yellow oil. **26b** and **27b**: R_f = 0.67 (DCM/methanol 4:1). As it was not possible to separate **26b** and **27b**, detailed analytical data could not be obtained. (See ^{1}H NMR and NOESY spectra of mixture).

(*E*)-(±)-Methyl 3-(But-2-ynyl)-5-ethylidene-2-oxotetrahydro-3-carboxylate (28), Methyl 3-(But-2-ynyl)-6-methyl-2-oxo-3,4-dihydro-2*H*-pyran-3-carboxylate (29), and (±)-Methyl 6-Ethylidene-4-methylene-2-oxo-3-oxabicyclo[3.2.1]octane-1-carboxylate (30). Representative Procedure I. (Table 2, entry 10) The title compounds were prepared according to the general procedure from AuCl(IMes) (2.42 mg, 4.5 μmol, 2.0 mol %), $AgNTf_2$ (1.75 mg, 4.5 μmol, 2.0 mol %) and **11** (50 mg, 0.225 mmol) in DCM (c = 500 mM) for 18 h. Flash chromatography (n-hexane/EtOAc 12:1) provided **28** (7.1 mg, 14%) as a colorless oil and **30** (16.3 mg, 33%) as a colorless oil.

Representative Procedure II. (Table 2, entry 14) The title compounds were prepared according to the general procedure from $AuCl_3$ (2.05 mg, 6.8 μmol, 5.0 mol %) and **11** (30 mg, 0.135 mmol) in DCM (c = 500 mM) for 2 h. The crude reaction mixture was purified using a VersaFlash purification system (23 × 110 mm, 23 g SiO_2, n-hexane/EtOAc 12:1) to yield **28** (6.3 mg, 21%) as a colorless oil and **29** (6.0 mg, 20%) as a colorless oil.

28: R_f = 0.56 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (dt, J = 6.8/1.9 Hz, 3 H, CH_3), 1.75 (t, J = 2.6 Hz, 3 H, CCH_3), 2.80−2.85 (m, 2 H, CH_2C), 3.09−3.18 (m, 1 H, H-4), 3.18−3.27 (m, 1 H, H-4), 3.78 (s, 3 H, OCH_3), 4.70 (qt, J = 6.8/1.9 Hz, 1 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.4 (CH_3), 10.4 (CH_3), 24.3 (CH_2), 34.6 (C-4), 53.4 (C-3), 54.6 (OCH_3), 72.4 (C_{alkyne}), 79.7 (C_{alkyne}), 99.9 (CH), 145.4 (C-5), 169.0 (CO), 171.9 (CO); IR (neat, cm^{-1}) 2954, 1738, 1716, 1435, 1198. HRMS (ESI) calcd for $C_{12}H_{15}O_4$ 223.0970, obsd 223.0967. **29**: R_f = 0.52 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (t, J = 2.6 Hz, 3 H, CH_3), 1.86−1.89 (m, 3 H, CH_3), 2.56−2.67 (m, 1 H, H-4), 2.69−2.81 (m, 2 H, CH_2, H-4 + CH_2CC), 2.86 (dq, J = 16.6/2.6 Hz, 1 H, CH_2CC), 3.76 (s, 3 H, OCH_3), 4.98−5.04 (m, 1 H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6 (CH_3), 18.4 (CH_3), 24.8 (CH_2), 27.5 (C-4), 52.2 (OCH_3), 53.2 (C-3), 73.1 (C_{alkyne}), 79.3 (C_{alkyne}), 99.1 (C-5), 149.8 (C-6), 166.8 (CO), 170.0 (CO); IR (neat, cm^{-1}) 2955, 2923, 1796, 1772, 1737, 1716, 1435, 1146; HRMS (ESI) calcd for $C_{12}H_{15}O_4$ 223.0970, obsd 223.0969. **30**: R_f = 0.51 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74−1.78 (m, 3 H, CH_3), 1.98 (dd, J = 12.4/3.5 Hz, 1 H, H-9), 2.47 (dd, J = 12.4/2.3 Hz, 1 H, H-9), 2.53−2.65 (m, 1 H, H-8), 2.74−2.85 (m, 1 H, H-8), 2.97 (dd, J = 3.5/2.3 Hz, 1 H, H-5), 3.78 (s, 3 H, OCH_3), 4.36 (d, J = 1.6 Hz, 1 H, CCH_2), 4.64 (d, J = 1.6 Hz, 1 H, CCH_2), 5.53−5.59 (m, 1 H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 30.2 (C-9), 34.7 (C-8), 38.7 (C-5), 50.2 (C-1), 53.0 (OCH_3), 92.7 (CH_2), 121.1 (C-7), 132.6 (C-6), 155.9 (C-4), 168.4 (CO), 170.9 (CO); IR (neat, cm^{-1}) 2954, 1741, 1658, 1271, 1225, 1054; HRMS (ESI) calcd for $C_{12}H_{15}O_4$ 223.0970, obsd 223.0967.

(*E*)-Methyl 3-(But-2-ynyl)-1-ethyl-5-ethylidene-2-oxopyrrolidine-3-carboxylate (31), (*Z*)-Methyl 3-Ethyl-6-ethylidene-4-methylene-2-oxo-3-azabicyclo[3.2.1]octane-1-carboxylate (34), and Methyl 3-Ethyl-6-methyl-4-methylene-2-oxo-3-azabicyclo[3.3.1]non-6-ene-1-carboxylate (35). Representative Procedure I. (Table 3, entry 6) The title compounds were prepared according to the general procedure from AuCl(PPh_3) (3.72 mg, 8.0 μmol, 5.0 mol %), $AgNTf_2$ (3.11 mg, 8.0 μmol, 5.0 mol %), NEt_3 (0.81 mg, 8.0 μmol, 1.12 μL, 5.0 mol %), and **12** (40 mg, 0.160 mmol) in refluxing DCM (c = 500 mM) for 6 h. Flash chromatography (n-hexane/EtOAc 4:1) yielded **31** (21.8 mg, 55%) as a colorless oil.

Representative Procedure II. (Table 3, entry 6) The title compounds were prepared according to the general procedure from catalyst **A** (2.32 mg, 3.0 μmol, 2.5 mol %), NEt_3 (0.30 mg, 3.0 μmol, 0.42 μL, 5.0 mol %), and **12** (30 mg, 0.120 mmol) in refluxing DCM (c = 500 mM) for 6 h. Flash chromatography (n-hexane/EtOAc 4:1) provided a mixture of **34** and **35** (26.3 mg, 88%, **34**/**35** 18:82) as a colorless oil. A pure sample of **35** was obtained by HPFP (23 × 110 mm, 23 g SiO_2, n-hexane/EtOAc 10:1).

31: R_f = 0.26 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.68 (dt, J = 6.9/1.1 Hz, 3 H, CH_3), 1.70 (t, J = 2.6 Hz, 3 H, CH_3), 2.76−2.80 (m, 2 H, CH_2), 2.79−2.89 (m, 1 H, H-4), 3.04−3.13 (m, 1 H, H-4), 3.39−3.52 (m, 1 H, CH_2CH_3), 3.57−3.70 (m, 1 H, CH_2CH_3), 3.74 (s, 3 H, OCH_3), 4.78 (qt, J = 6.8/2.3 Hz, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (CH_3), 11.7 (CH_2CH_3), 11.9 (CH_3), 24.7 (CH_2), 31.9 (C-4), 35.2 (CH_2CH_3), 53.0 (C-3), 54.0 (OCH_3), 73.5 (C_{alkyne}), 78.3 (C_{alkyne}), 95.0 (CH), 136.2 (C-5), 171.2 (CO), 171.5 (CO); IR (neat, cm^{-1}) 2954, 1744, 1707, 1677, 1417, 1250; HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ 250.1443, obsd 250.1440. **34**: R_f = 0.35 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J = 6.8 Hz, 3 H, CH_2CH_3), 1.66−1.73 (m, 3 H, CH_3), 1.94 (dd, J = 11.5/4.9 Hz, 1 H, H-8), 2.36 (dd, J = 11.5/1.9 Hz, 1 H, H-8), 2.70−2.79 (m, 1 H, H-7), 2.84−2.95 (m, 1 H, H-7), 2.57−3.75 (m, 3 H, CH_2CH_3 + H-5), 3.78 (s, 3 H, OCH_3), 4.19 (s, 2 H, CCH_2), 5.43 (qm, J = 6.8 Hz, 1 H, CH). As a pure sample of **34** could not be obtained only the ^{1}H NMR datas are given. **35**: R_f = 0.35 (n-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.70−1.73 (m, 3 H, CH_3), 1.90 (dd, J = 12.1/3.4 Hz, 1 H, H-9), 2.42−2.47 (m, 1 H, H-9), 2.50−2.59 (m, 1 H, H-7), 2.66−2.74 (m, 1 H, H-7), 2.86−2.90 (m, 1 H, H-5), 3.72 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.75 (s, 3 H, OCH_3), 4.30 (d, J = 1.1 Hz, 1 H, CCH_2), 4.32 (d, J = 1.1 Hz, 1 H, CCH_2), 5.44−5.49 (m, 1 H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_2CH_3), 21.0 (CH_3), 31.0 (C-9), 33.7 (C-8), 37.5 (CH_2CH_3), 41.9 (C-4), 50.8 (OCH_3), 52.5 (C-1), 91.0 (CH_2), 120.8 (C-7), 133.4 (C-6), 144.8 (C-4), 169.1 (CON), 172.7 (CO); IR (neat, cm^{-1}) 2956, 1739, 1673, 1620, 1230; HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ 250.1443, obsd 250.1436.

(±)-Methyl 6-Methyl-4-methylene-2-oxo-3-azabicyclo[3.3.1]-non-6-ene-1-carboxylate (36). Representative Procedure. (Table 3, entry 7) The title compound was prepared according to the general procedure from catalyst **A** (8.73 mg, 11.3 μmol, 5 mol %) and **14** (50 mg, 0.226 mmol) in DCM (c = 500 mM) for 4 h at room temperature. Flash chromatography (n-hexane/EtOAc 1:1) provided **36** (16.2 mg, 32%) as a colorless solid. R_f = 0.24 (n-hexane/EtOAc 1:1); mp 123−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72−1.75 (m, 3 H, CH_3), 1.94 (dd, J = 12.6/3.4 Hz, 1 H, H-9), 2.41−2.48 (m, 1 H, H-9), 2.48−2.59 (m, 1 H, H-8), 2.71−2.82 (m, 1 H, H-8), 2.83−2.89 (m, 1 H, H-5), 3.76 (s, 3 H, OCH_3), 4.19 (s, 1 H, CCH_2), 4.23 (s, 1 H, CCH_2), 5.44−5.50 (m, 1 H, H-7), 7.69 (s, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 30.6 (C-9), 33.0 (C-8), 39.4 (C-5), 49.6 (OCH_3), 52.6 (C-1), 90.8 (CH_2), 120.5 (C-7), 133.2 (C-6), 142.7 (C-4), 170.5 (CONH), 172.2 (CO); IR (neat, cm^{-1}) 3180, 1739, 1655, 1234; HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ 222.1130, obsd 222.1123.

Dimethyl 2-(But-2-ynyl)-2-((1-(ethylimino)-1*H*-isochromen-3-yl)methyl)malonate (37). Representative Procedure. (Table 4, entry 3) The title compound was prepared according to the general procedure from catalyst **A** (3.14 mg, 4.1 μmol, 5 mol %) and **22** (30 mg, 0.08 mmol) in toluene (c = 250 mM) at 90 °C for 20 h. Flash chromatography (n-hexane/EtOAc 4:1) provided **37** (17.7 mg, 59%) as a colorless oil. R_f = 0.35 (n-hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.80 (t, J = 2.6 Hz, 3 H, CH_3), 2.86 (q, J = 2.6 Hz, 2 H, CH_2), 3.20 (s, 2 H, CH_2), 3.45 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 3.76 (s, 6 H, OCH_3), 5.99 (s, 1 H, CH), 7.11 (dd, J = 7.9/1.1 Hz, 1 H, H_{arom}), 7.25−7.32 (m, 1 H, H_{arom}), 7.38−7.44 (m, 1 H, H_{arom}), 8.03−8.13 (m, 1 H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.5

(CH_3), 16.0 (CH_2CH_3), 23.4 (CH_2CCCH_3), 36.1 (CH_2), 40.6 (CH_2CH_3), 53.0 ($2 \times OCH_3$), 56.6 (COCCO), 73.2 (C_{alkyne}), 79.5 (C_{alkyne}), 105.0 (CH), 123.9 (C_{arom}), 124.8 (CH_{arom}), 126.5 (CH_{arom}), 127.8 (CH_{arom}), 131.4 (CH_{arom}), 132.4 (C_{arom}), 149.7 (OCCH), 151.0 (NCO), 170.0 ($2 \times CO$); IR (neat, cm^{-1}) 2955, 1736, 1671, 1650, 1435; HRMS (ESI) calcd for $C_{21}H_{24}NO_5$ 370.1654, obsd 370.1659.

(±)-(*E*)-1-Ethylidene-6-methyl-3a-phenyl-2-tosyl-1,2,3,3a,4,6a-hexahydrocyclo Penta[*c*]pyrrole (38). The title compound was prepared according to the general procedure from sulfonamide **15** (25.0 mg, 0.066 mmol), $AuCl(PEt_3)$ (0.60 mg, 1.7 μmol, 0.025 equiv), and $AgNTf_2$ (0.63 mg, 1.7 μmol, 0.025 equiv) in DCM (136 μL) for 2 h at room temperature. Flash chromatography (*n*-hexane/EtOAc 4:1) provided **38** (18 mg, 72%) as a colorless oil that solidified upon standing. R_f = 0.60 (*n*-hexane/EtOAc 1:1); mp 109−111 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27−1.31 (m, 3 H, CCH_3), 1.76 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 2.40 (s, 3 H, CH_3), 2.61−2.67 (m, 2 H, CH_2CH), 3.65 (d, J = 9.8 Hz, 1 H, NCH_2), 3.86 (bs, 1 H, CH), 4.00 (d, J = 9.8 Hz, 1 H, NCH_2), 5.18−5.24 (m, 1 H, $CHCH_2CH$), 5.85 (qd, J = 7.2/1.1 Hz, 1 H, CH), 7.11−7.28 (m, 7 H, H_{arom}), 7.59 (d, J = 8.3 Hz, 2 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3), 14.7 (CH_3), 21.5 (CH_3), 42.5 (CH_2CH), 53.0 (PhC), 59.2 (CH), 63.6 (NCH_2), 103.2 (CH), 123.8 (CH), 125.9 ($2 \times CH_{arom}$), 126.3 (CH_{arom}), 127.5 ($2 \times CH_{arom}$), 128.6 ($2 \times CH_{arom}$), 129.1 ($2 \times CH_{arom}$), 134.8 (C), 138.9 (C), 140.7 (C), 143.5 (C), 145.5 (C); IR (neat, cm^{-1}) 2914, 2859, 1336, 1159; HRMS (ESI) calcd for $C_{23}H_{26}NO_2S$ 380.1684, obsd 380.1688.

Dimethyl 2-(But-2-ynyl)-2-((2-tosyl-1,2-dihydroisoquinolin-3-yl)methyl) Malonate (43). The title compound was prepared according to the general procedure from catalyst **A** (4.01 mg, 5.2 μmol, 5 mol %) and **19** (50 mg, 0.104 mmol) in DCM (c = 500 mM) for 23 h at room temperature. Flash chromatography (*n*-hexane/EtOAc 4:1) provided **43** (35.9 mg, 72%) as a colorless solid. R_f = 0.53 (*n*-hexane/EtOAc 1:1); mp 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J = 2.6 Hz, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.77 (q, J = 2.6 Hz, 2 H, CH_2), 3.56 (s, 2 H, CH_2), 3.83 (s, 6 H, OCH_3), 4.54 (s, 2 H, CH_2N), 6.39 (s, 1 H, CH), 6.63 (d, J = 7.5 Hz, 1 H, H_{arom}), 6.80 (d, J = 8.1 Hz, 2 H, H_{arom}), 6.86 (d, J = 7.5 Hz, 1 H, H_{arom}), 6.89−6.96 (m, 1 H, H_{arom}), 6.97−7.04 (m, 1 H, H_{arom}), 7.30 (d, J = 8.1 Hz, 1 H, H_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.5 (CH_3), 21.2 (CH_3), 23.0 (CH_2CCCH_3), 38.5 (CH_2), 50.3 (CH_2N), 52.9 ($2 \times OCH_3$), 56.7 (COCCO), 73.4 (C_{alkyne}), 79.4 (C_{alkyne}), 124.6 (CH_{arom}), 125.0 (CH), 125.2 (CH_{arom}), 126.9 (CH_{arom}), 127.4 ($2 \times CH_{arom}$), 127.8 (CH_{arom}), 128.2 ($2 \times CH_{arom}$), 129.9 (C), 130.3 (C), 134.1 (C), 135.7 (C), 143.1 (C), 170.5 ($2 \times CO$); IR (neat, cm^{-1}) 2953, 1730, 1343, 1156; HRMS (ESI) calcd for $C_{26}H_{28}NO_6S$ 482.1637, obsd 482.1642.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.