Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 1741

Unexpected regio- and chemoselectivity of cationic gold-catalyzed cycloisomerizations of propargylureas: access to tetrasubstituted 3,4-dihydropyrimidin-2(1*H*)-ones†

Olga P. Pereshivko,[a] Vsevolod A. Peshkov,*‡[a] Anatoly A. Peshkov,[a] Jeroen Jacobs,[b] Luc Van Meervelt[b] and Erik V. Van der Eycken*[a]

Received 9th November 2013,
Accepted 8th January 2014

DOI: 10.1039/c3ob42221f

www.rsc.org/obc

Cationic gold-catalyzed cycloisomerizations of propargylureas, derived *in situ* from secondary propargylamines and aryl or alkyl isocyanates, have been studied. The reaction outcome was found to be different from what was previously observed for the tosyl isocyanate-derived ureas in terms of both regio- and chemoselectivity. As a result, the current protocol offers efficient access to the 3,4-dihydropyrimidin-2(1*H*)-one core through the 6-*endo*-dig *N*-cyclization.

Processes involving the addition of secondary propargylamines to various heteroallenes and subsequent transition metal-catalyzed or electrophile-mediated cyclosomerizations have recently emerged as a convenient and general strategy for the synthesis of a number of important small heterocycles.[1,2] Successful examples include the application of carbon dioxide (CO_2),[3] *N*-sulfonyl ketenimine[4] as well as various carbodiimides[5] and isocyanates[6] as the heteroallene component. The preparation of the required secondary propargylamines in many cases is achieved through transition metal-catalyzed coupling of an amine, an aldehyde and an alkyne, known as the A^3-coupling reaction, which at the same time serves the purpose of the final scaffold diversification.[7,8]

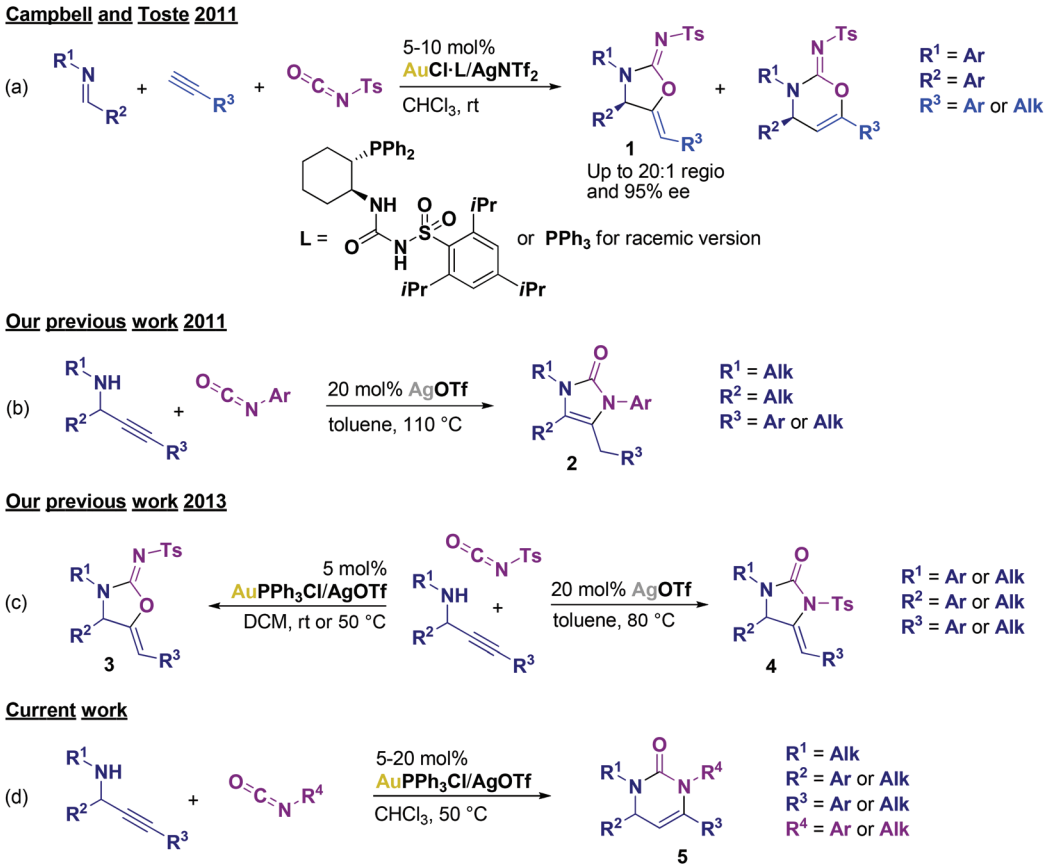
In 2011, Campbell and Toste described a cationic Au(I)-catalyzed three-component reaction of an imine, an alkyne, and a tosyl isocyanate for the enantioselective synthesis of oxazolidin-2-imines **1** (Scheme 1a).[9] In their process Au(I)-catalyzed addition of an alkyne to an imine was followed by the acylation of the generated propargylamine with tosyl isocyanate and subsequent Au(I)-catalyzed *O*-cyclizomerization into **1**. Simultaneously we have established an efficient protocol for the synthesis of tetrasubstituted imidazol-2-ones **2** with the key step being a Ag(I)-catalyzed *N*-cycloisomerization of a propargylurea, produced *in situ* by the acylation of A^3-coupling-derived secondary *N*-alkylpropargylamine with aryl isocyanate (Scheme 1b).[10] Intrigued by the difference in chemoselectivity of the above processes we decided to perform a comparative study of transition metal-catalyzed cycloisomerizations of propargylureas derived *in situ* from secondary propargylamines and tosyl isocyanate resulting in the establishment of two selective protocols for both *O*- and *N*-cyclizations. The application of cationic Au(I) catalysis generally gave rise to oxazolidin-2-imines **3** as major products while the application of AgOTf selectively provided the corresponding imidazolidin-2-ones **4** (Scheme 1c).[11] Remarkably, cationic Au(I)-catalyzed cycloisomerization of propargylureas derived from aryl or alkyl isocyanates did not follow the above trend. Both chemo- and regioselectivity were altered compared to what was observed for the tosyl isocyanate derived ureas, resulting in the formation of tetrasubstituted 3,4-dihydropyrimidin-2(1*H*)-ones **5** (Scheme 1d).[12] Notably, the same selectivity was recently documented by Looper and coworkers for the cationic Rh(II)-catalyzed cycloisomerizations of preformed propargylureas.[13] Herein we present a detailed investigation on our cationic Au(I)-catalyzed procedure.[14]

We have chosen cycloisomerization of urea **8a**, derived *in situ* from propargylamine **6a** and phenyl isocyanate (**7a**), as a model reaction for the optimization survey (Table 1). Initially we found that the reaction catalyzed by 5 mol% of $AuPPh_3Cl$/AgOTf, being conducted for 23 hours at rt in $CDCl_3$, produced 3,4-dihydropyrimidin-2(1*H*)-one **5a** in a low yield of 18% apart from 76% of uncyclized urea **8a** (Table 1, entry 1). To our great satisfaction the cycloisomerization rate could be dramatically

[a]*Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium. E-mail: vapeshkov@gmail.com, erik.vandereycken@chem.kuleuven.be*
[b]*Biomolecular Architecture, Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium*

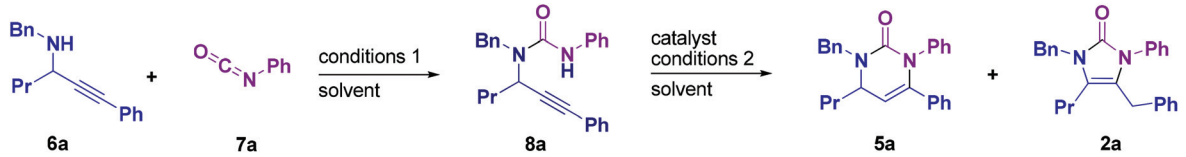
†Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for **2l,m,q**, **5a–s**, **8d,h,k** and **9r–t** as well as crystallographic data for **2a** and **5a**. CCDC 966797 and 966798. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42221f

‡Present address: Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260, USA.



Scheme 1 Processes involving cationic Au(I) or Ag(I)-catalyzed cycloisomerizations of *in situ* generated propargylureas.

Table 1 Optimization of the reaction parameters of cationic gold-catalyzed cycloisomerization of phenyl isocyanate-derived propargylurea **8a**[a]



					Yields[b]		
Entry	Solvent	Conditions 1	Catalyst	Conditions 2	**5a**	**2a**	Uncyclized **8a**
1	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	23 h, 25 °C	18	—	76
2	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	23 h, 50 °C	84	5	—
3	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	15 h, 50 °C	89[c]	6	—
4	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	5 h, 50 °C	46	—	51
5	CD_2Cl_2	5 min, rt	5 mol% $AuPPh_3Cl/AgOTf$	15 h, 50 °C	82	10	4
6	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgNTf_2$	15 h, 50 °C	87	6	2
7	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgSbF_6$	15 h, 50 °C	61	2	35
8	$CDCl_3$	5 min, rt	5 mol% [Au(JohnPhos)(MeCN)]SbF_6	15 h, 50 °C	87	3	—
9	$CDCl_3$	5 min, rt	5 mol% $AuPPh_3Cl/AgBF_4$	15 h, 50 °C	58	3	30
10	$CDCl_3$	5 min, rt	5 mol% (IPr)AuCl/AgOTf	15 h, 50 °C	88	5	—
11	$CDCl_3$	5 min, rt	5 mol% $AuCl_3$	15 h, 50 °C	29	2	57
12	$CDCl_3$	5 min, rt	10 mol% TfOH	15 h, 50 °C	—	—	84
13[d]	Toluene	1 h, 110 °C	20 mol% AgOTf	2 h, 110 °C	—	72[e]	—

[a] Reactions were carried out on a 0.1 mmol scale in 0.4 mL of dry solvent. After completion of the indicated time an internal standard (3,4,5-trimethoxybenzaldehyde) was added and the resulting mixture was analyzed by ^{1}H NMR. [b] Yields are determined by ^{1}H NMR using 3,4,5-trimethoxybenzaldehyde as an internal standard. [c] This value corresponds to both NMR and isolated yields from 0.1 mmol and 0.2 mmol scale reactions in $CDCl_3$ and $CHCl_3$, respectively. [d] Taken from ref. 10. [e] Isolated yield from a 0.33 mmol scale reaction conducted in 2.5 mL of dry toluene.

improved by elevating the reaction temperature up to 50 °C, delivering **5a** in a good yield of 84% along with some minor amounts of imidazol-2-one **2a** (Table 1, entry 2). Further we found that the reaction time could be shortened to 15 hours without any loss in the reaction rate providing even slightly improved yield of **5a** (Table 1, entry 3). However, further reduction to 5 hours gave incomplete conversion of **8a** (Table 1, entry 4). Switching to CD_2Cl_2 as the solvent gave a somewhat poorer result in terms of regioselectivity and general cycloisomerization rate (Table 1, entry 5). Changing the counterion by using other silver(I) salts, or the use of a preformed [Au(JohnPhos)(MeCN)]SbF_6 complex, as well as the application of *N*-heterocyclic carbene instead of phosphine ligands, all resulted in either diminished or comparable yield of the desired product (Table 1, entries 6–10). The $AuCl_3$-catalyzed reaction gave a very poor cycloisomerization rate while remaining 6-*endo*-dig selective (Table 1, entry 11). Catalytic amount of a strong Brønsted acid did not facilitate cycloisomerization at all (Table 1, entry 12). The AgOTf-catalyzed reaction selectively producing imidazol-2-one **2a** and documented by us previously[10] is also listed here for comparison (Table 1, entry 13).

Next we performed an X-ray crystallographic analysis of both the observed cycloisomerization products. The resulting ORTEP representations of 3,4-dihydropyrimidin-2(1*H*)-one **5a** and imidazol-2-one **2a** are shown in Fig. 1.[15]

Having completed the optimization study and structural assignment of the representative products we moved to evaluation of the scope and limitations of the process (Table 2). First we reacted propargylamine **6a** with various aromatic isocyanates **7a,b,c**. In all cases the *in situ* formed ureas **8a,b,c** could be successfully cyclized into the expected 3,4-dihydropyrimidin-2(1*H*)-ones **5a,b,c** in high yields ranging from 89% to 93% (Table 2, entries 1–3). The formation of minor amounts of imidazol-2-ones **2a,b,c** was also detected but their yields did not exceed 6%. The reaction of **6a** with aliphatic benzyl isocyanate **7d** under the standard conditions gave only 43% yield of the desired product **5d** along with 49% of uncyclized urea **8d** (Table 2, entry 4). To our delight the cycloisomerization could be driven to completion through increasing the reaction time and the catalyst loading allowing the isolation of 3,4-dihydropyrimidin-2(1*H*)-one **5d** in an excellent yield of 95% as a single reaction product (Table 2, entry 5). We further successfully applied these modified conditions to the reactions of **6a** with a few other aliphatic isocyanates **7e,f,g**. In all cases 3,4-dihydropyrimidin-2(1*H*)-ones **5e,f,g** were produced in very high yields as the only reaction products (Table 2, entries 6–8). An attempt to cyclize propargylurea **8h**, derived from secondary cyclopentyl isocyanate **7h**, was fairly unsuccessful considering that the reaction catalyzed by 20 mol% of $AuPPh_3Cl$/AgOTf at 50 °C for 22 hours provided only 19% of the desired 3,4-dihydropyrimidin-2(1*H*)-one **5h** (Table 2, entry 9).

Next we evaluated several propargylamines **6b–g** in combination with various aromatic and aliphatic isocyanates **7a,c,d,i** (Table 2, entries 10–21). In most cases the *in situ* formed propargylureas **8i–p** could be efficiently cyclized into the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones **5i–p** following the tendencies established for the **6a**-derived ureas **8a–g** (Table 2, entries 10–18). However, for the ureas **8q–s** derived from propargylamines **6f,g**, bearing either aromatic R^2 or aliphatic R^3 substituent, imidazolidin-2-ones **9q–s**, bearing an exocyclic double-bond, were formed, in addition to the 3,4-dihydropyrimidin-2(1*H*)-ones **5q–s** and imidazol-2-ones **2q–s** (Table 2, entries 19–21). The imidazolidin-2-one **9q** obtained in a mixture with an unidentified contaminant slowly isomerizes into imidazol-2-one **2q** while impurity remains intact (Scheme 2a).[16] In contrast imidazolidin-2-ones **9r,s** do not undergo a similar double bond migration. Instead they were found to be in equilibrium with 3,4-dihydropyrimidin-2(1*H*)-ones **5r,s** at the same time showing a considerable decomposition rate during long term storage (Scheme 2b).[16]

Interestingly, in the case of terminal propargylurea **8t** the 6-*endo*-dig pathway was not realized and, thus, imidazol-2-one **2t** appeared to be a major cycloisomerization product for both cationic Au and AgOTf-catalyzed reactions (Table 3). Additionally, the cationic Au-catalyzed process produced a small amount of imidazolidin-2-one **9t** (Table 3, entry 1).

In our previous comparative study on cationic Au and Ag-catalyzed cycloisomerizations of tosyl isocyanate-derived propargylureas (Scheme 1c) we appealed to Pearson's concept of hard and soft acids and bases (HSAB) in order to rationalize the observed *O- vs. N*-selectivity. Comparing the current cationic Au-catalyzed cycloisomerization process of aryl or alkyl isocyanate-derived propargylureas (Scheme 1d) with the complementary AgOTf-catalyzed procedure (Scheme 1b) it is unclear why both processes provide only *N*-cyclized products. However, the reason for the different regioselectivity seems to lie in the

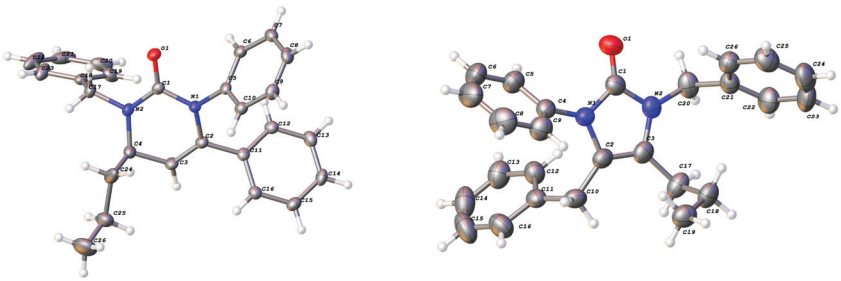
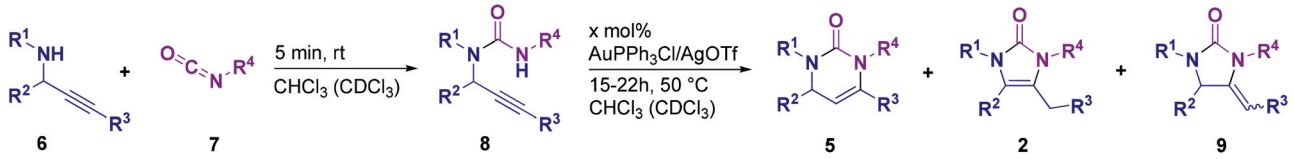


Fig. 1 X-ray crystallographic structures of 3,4-dihydropyrimidin-2(1*H*)-one **5a** (left) and imidazol-2-one **2a** (right), showing thermal ellipsoids at the 50% probability level and the atom labeling scheme.

Table 2 Scope and limitations of cationic Au-catalyzed cycloisomerization of aryl or alkyl isocyanate-derived propargylureas **8**[a]



6 7 8 5 2 9

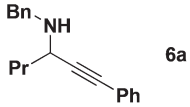
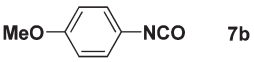
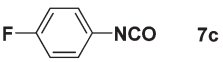
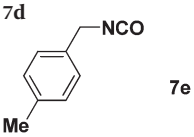
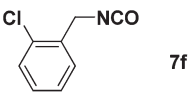
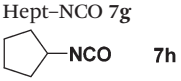
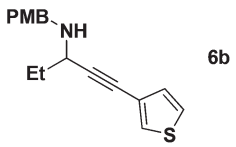
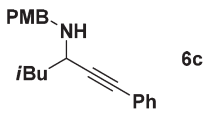
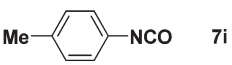
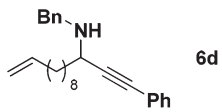
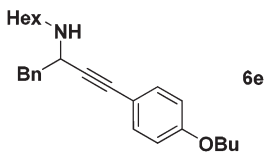
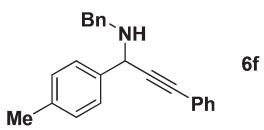
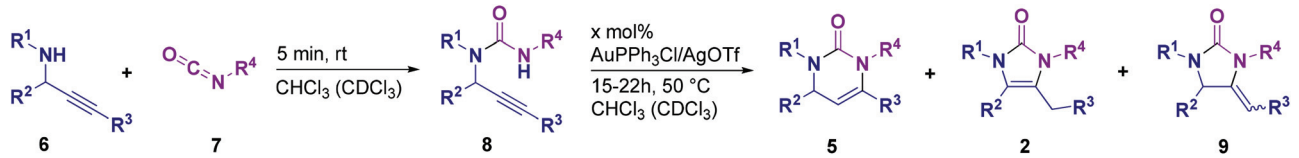
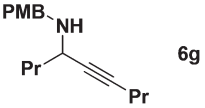
Entry	*x*	Time	Propargylamine **6**	Isocyanate **7**	Products code	Yields[b] **5**	**2**	**9**	Uncyclized **8**
1	5	15	 **6a**	Ph–NCO **7a**	**a**	89	6[c]	—	—
2	5	15	**6a**	 **7b**	**b**	92	5[c]	—	—
3	5	15	**6a**	 **7c**	**c**	93	6[c]	—	—
4	5	15	**6a**	Bn–NCO **7d**	**d**	43	—	—	49
5	15	16.5	**6a**	**7d**	**d**	95	—	—	—
6	15	16.5	**6a**	 **7e**	**e**	95	—	—	—
7	15	16.5	**6a**	 **7f**	**f**	93	—	—	—
8	15	16.5	**6a**	Hept–NCO **7g**	**g**	88	—	—	—
9	20	22	**6a**	 **7h**	**h**	19	—	—	61
10	5	15	 **6b**	**7a**	**i**	80	—	—	—
11	5	15	**6b**	**7c**	**g**	91	2[c]	—	—
12	5	15	**6b**	**7d**	**k**	37	—	—	56
13	15	18.5	**6b**	**7d**	**k**	92	—	—	—
14	5	15	 **6c**	**7a**	**l**	89	7	—	—
15	5	15	**6c**	 **7i**	**m**	88	6	—	—
16	15	16	**6c**	**7d**	**n**	94	—	—	—
17	5	15	 **6d**	**7a**	**o**	90	6[c]	—	—
18	5	15	 **6e**	**7d**	**p**	84	—	—	—
19	15	16.5	 **6f**	**7a**	**q**	46 (49[c])	6 (10[c])	9[c]	—

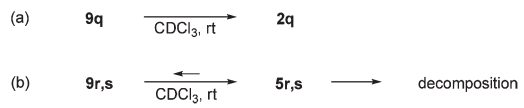
Table 2 *(Contd.)*



6 7 8 5 2 9

Entry	x	Time	Propargylamine 6	Isocyanate 7	Products code	Yields[b] 5	2	9	Uncyclized 8
20	5	15	 6g	7c	r	44	24	22	—
21	5	15	6g	7i	s	46	23	20	—

[a] Reactions were carried out on a 0.15–0.45 mmol scale in dry $CHCl_3$ (0.25 M). [b] Isolated yields. [c] Yields determined by ^1H NMR from the corresponding 0.1 mmol scale reaction in $CDCl_3$ using 3,4,5-trimethoxybenzaldehyde as an internal standard.



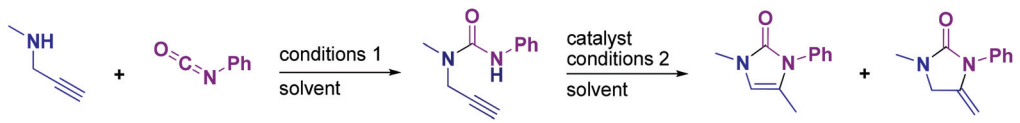
Scheme 2 Transformations of imidazolidin-2-ones **9q–s** and 3,4-dihydropyrimidin-2(1*H*)-ones **5r,s** observed upon storage of their NMR samples.

area of thermodynamic/kinetic control. Thus, an *endo*-pathway prevailing in the current cationic Au-catalyzed process operating at a mild temperature of 50 °C within 15–22 hours appears to be thermodynamically favorable. This is also in agreement with the shift of equilibrium in Scheme 2b to the *endo*-cyclized 3,4-dihydropyrimidin-2(1*H*)-ones **5r,s**. The AgOTf-catalyzed *exo*-cyclization followed by double bond migration as we previously described proceeds in a shorter time and at the same time requires higher temperature (110 °C) and catalyst loading and therefore could be regarded as kinetically favored. Noteworthy, preliminary results of Niehaus and Krause suggest that cationic Au-catalysis at a high temperature of 100 °C also promotes *exo*-cyclization/double bond migration sequence[17] in contrast to our *endo*-cyclization observed at 50 °C. This demonstrates that for the cycloisomerization of aryl isocyanate-derived propargylureas the thermodynamic/kinetic factors might be more important than the catalyst nature.

Conclusions

In conclusion, we have developed a novel cationic Au-catalyzed protocol for the 6-*endo*-dig *N*-cycloisomerization of propargylureas, derived *in situ* from secondary propargylamines and aryl or alkyl isocyanates, leading to 3,4-dihydropyrimidin-2(1*H*)-ones. This study complements our previous advances in the field in terms of substrate scope, reaction outcome and Ag *versus* Au catalysis comparisons. The 4-dihydropyrimidin-2(1*H*)-one scaffold is an important pharmacophore[18] and thus novel methodologies to access this core are highly desirable.

Table 3 Cycloisomerization of terminal propargylurea **8t**



6h 7a 8t 2t 9t

Entry	Solvent	Conditions 1	Catalyst	Conditions 2	Yields[a] 2t	9t
1[b]	$CHCl_3$	5 min, rt	5 mol% $AuPPh_3Cl$/AgOTf	3 h, 60 °C	81	18
2[c,d]	MeCN	5 min, 0–5 °C	10 mol% AgOTf	2 h, 80 °C	94	—

[a] Isolated yields. [b] Reaction was carried out on a 0.5 mmol scale in 1.5 mL of dry $CHCl_3$. [c] Taken from ref. 10. [d] Reaction was carried out on a 1 mmol scale in 2.5 mL of dry MeCN.

Therefore our current protocol might be regarded as an interesting alternative to Looper's Rh(II)-catalyzed procedure[13] and as a welcome addition to the classical Biginelli reaction.[19]

Experimental section

General information

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively using a Bruker Avance instrument. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. High-resolution EI mass spectra were recorded on a Kratos MS50TC system with a resolution of 10 000. The ion source temperature was 150–250 °C, as required. High-resolution ESI mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL min^{-1} and spectra were obtained in positive ionization mode with a resolution of 15 000 (FWHM) using leucine enkephalin as lock mass. Infrared (IR) spectra were recorded neat on a Bruker ALPHA FT-IR spectrometer, and wavelengths are reported in cm^{-1}.

Synthesis of starting propargylamines

Propargylamines **6a,c,f**[8c] and **6b,d,g**[10] were synthesized as described previously.

***N*-(4-(4-Butoxyphenyl)-1-phenylbut-3-yn-2-yl)hexan-1-amine (6e).** Copper bromide (56 mg, 0.39 mmol), toluene (2 mL), hexylamine (228 mg, 2.25 mmol), phenylacetaldehyde (180 mg, 1.5 mmol) and 1-butoxy-4-ethynylbenzene (523 mg, 3 mmol) were consecutively loaded to a screw cap vial equipped with a magnetic stirring bar. The mixture was degassed and flushed with argon. The reaction vessel was heated with stirring for 4 h at 100 °C. The resulting reaction mixture was cooled to ambient temperature and subjected to silicagel column chromatography with (EtOAc–heptane, 1 : 9) to afford **6e** (300 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.15 (m, 7H), 6.80 (d, J = 8.6 Hz, 2H), 3.94 (t, J = 6.5 Hz, 2H), 3.87–3.79 (m, 1H), 3.11–2.83 (m, 3H), 2.71–2.59 (m, 1H), 1.82–1.69 (m, 2H), 1.56–1.40 (m, 4H), 1.36–1.19 (m, 6H), 0.97 (t, J = 7.3 Hz, 3H), 0.91–0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 138.0, 132.9, 129.8, 128.3, 126.6, 115.3, 114.4, 88.9, 84.4, 67.7, 52.1, 47.6, 42.4, 31.8, 31.3, 30.0, 27.1, 22.7, 19.3, 14.1, 13.9; HRMS (ESI, $[M + H]^+$) for $C_{26}H_{36}NO$ calcd 378.2791, found 378.2787.

General procedure for the $AuPPh_3Cl$/AgOTf-catalyzed cycloisomerization of propargylureas derived from aryl or alkyl isocyanate (Table 2)

Propargylamine **6** (0.4 mmol) was dissolved in dry $CHCl_3$ (1.6 mL) followed by addition of isocyanate **7** (0.48 mmol). After stirring at rt for about 5 min, AgOTf (5–20 mol%) and $AuPPh_3Cl$ (5–20 mol%) were added.[20] The reaction mixture was stirred at 50 °C for 15–22 h[20] in a sealed screw cap vial under an air atmosphere. The resulting mixture was directly subjected to silicagel column chromatography to give the desired cycloisomerization products. For entries 1–3, 5–8, 10, 11, 13, and 16–18, elution with 8% EtOAc in heptane yielded pure 3,4-dihydropyrimidin-2(1*H*)-ones **5a–g,i–k,n–p**. For entries 4, 9 and 12 gradient elution with 8→30% EtOAc in heptane first provided 3,4-dihydropyrimidin-2(1*H*)-ones **5d,h,k** followed by propargylureas **8d,h,k**. For entries 14 and 15 gradient elution with 8→30% EtOAc in heptane first provided 3,4-dihydropyrimidin-2(1*H*)-ones **5l,m** followed by imidazol-2-ones **2l,m**. For entry 19 gradient elution with 8→30% EtOAc in heptane first provided 3,4-dihydropyrimidin-2(1*H*)-one **5q**, then imidazolidin-2-one **9q** contaminated with an unidentified impurity, and finally imidazol-2-one **2q**. For entries 20 and 21 gradient elution with 8→30% EtOAc in heptane first provided 3,4-dihydropyrimidin-2(1*H*)-ones **5r,s** followed by imidazolidin-2-ones **9r,s** and imidazol-2-ones **2r,s**.

3-Benzyl-1,6-diphenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.20 (m, 7H), 7.20–7.07 (m, 7H), 7.07–6.96 (m, 1H), 5.30–5.19 (m, 2H), 4.15 (d, J = 15.4 Hz, 1H), 3.98–3.88 (m, 1H), 1.83–1.40 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.9, 141.1, 139.8, 137.7, 135.9, 128.6, 128.5, 127.9, 127.84, 127.77, 127.3, 125.9, 102.9, 53.9, 49.2, 36.6, 17.6, 14.2; IR (ATR): ν = 3202, 1565 (C═O), 1386, 1259, 1104, 1070, 761, 697; HRMS (ESI, $[M + H]^+$) for $C_{26}H_{27}N_2O$ calcd 383.2118, found 383.2112.

3-Benzyl-1-(4-methoxyphenyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.22 (m, 5H), 7.21–7.04 (m, 7H), 6.74–6.61 (m, 2H), 5.23 (d, J = 15.2 Hz, 1H), 5.16 (d, J = 5.9 Hz, 1H), 4.16 (d, J = 15.2 Hz, 1H), 3.98–3.87 (m, 1H), 3.68 (s, 3H), 1.82–1.40 (m, 4H), 0.95 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 155.2, 141.2, 137.8, 136.0, 132.7, 129.6, 128.6, 128.1, 128.0, 127.8, 127.7, 127.3, 113.3, 106.1, 55.3, 53.9, 49.2, 36.6, 17.5, 14.2; IR (ATR): ν = 2930, 1654 (C═O), 1509, 1444, 1358, 1240, 1170, 1030, 910, 829, 726, 696, 555; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{29}N_2O_2$ calcd 413.2224, found 413.2217.

3-Benzyl-1-(4-fluorophenyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.26 (m, 5H), 7.24–7.08 (m, 7H), 6.90–6.77 (m, 2H), 5.29–5.16 (m, 2H), 4.15 (d, J = 15.3 Hz, 1H), 3.99–3.87 (m, 1H), 1.80–1.40 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 158.9, 154.9, 140.9, 137.6, 135.73, 135.69, 135.65, 130.1, 130.0, 128.6, 128.02, 127.96, 127.9, 127.4, 115.0, 114.7, 106.7, 53.9, 49.2. 36.6, 17.5, 14.2; IR (ATR): ν = 2960, 1661 (C═O), 1507, 1447, 1217, 1153, 831, 750, 697, 529; HRMS (ESI, $[M + H]^+$) for $C_{26}H_{26}FN_2O$ calcd 401.2024, found 401.2022.

1,3-Dibenzyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.11 (m, 13H), 7.04–6.95 (m, 2H), 5.29 (d, J = 15.4 Hz, 1H), 5.17 (d, J = 15.1 Hz, 1H), 4.86 (d, J = 6.0 Hz, 1H), 4.31 (d, J = 15.1 Hz, 1H), 4.01 (d, J = 15.4 Hz, 1H), 3.82–3.70 (m, 1H), 1.47–1.30 (m, 2H), 1.29–1.07 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.8, 140.8, 138.7, 137.8, 135.6, 128.5, 128.4, 128.2, 128.04, 128.01, 127.7, 127.2, 126.9, 105.5, 53.9, 48.9, 47.6, 36.4, 17.5, 14.1; IR (ATR): ν = 2958, 1650 (C═O), 1447,

1228, 751, 696; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{29}N_2O$ calcd 397.2274, found 397.2269.

3-Benzyl-1-(4-methylbenzyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.19 (m, 10H), 7.00 (d, J = 7.8 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 5.30 (d, J = 15.4 Hz, 1H), 5.14 (d, J = 15.1 Hz, 1H), 4.87 (d, J = 6.0 Hz, 1H), 4.26 (d, J = 15.1 Hz, 1H), 4.00 (d, J = 15.4 Hz, 1H), 3.81–3.69 (m, 1H), 2.28 (s, 3H), 1.47–1.07 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.9, 140.9, 137.9, 136.4, 135.8, 135.7, 128.7, 128.5, 128.42, 128.38, 128.3, 128.0, 127.7, 127.2, 105.5, 53.8, 48.9, 47.4, 36.4, 21.1, 17.5, 14.1; IR (ATR): ν = 2957, 1653 (C═O), 1447, 753, 698, 477; HRMS (ESI, $[M + H]^+$) for $C_{28}H_{31}N_2O$ calcd 411.2431, found 411.2428.

3-Benzyl-1-(2-chlorobenzyl)-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5f). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.00 (m, 14H), 5.29 (d, J = 15.4 Hz, 1H), 5.07 (d, J = 16.0 Hz, 4.86 (d, J = 5.8 Hz, 1H) 4.53 (d, J = 16.0 Hz, 1H), 4.05 (d, J = 15.4 Hz, 1H), 3.90–3.77 (m, 1H), 1.73–1.25 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.5, 141.3, 137.8, 136.4, 135.5, 132.9, 129.8, 129.2, 128.5, 128.44, 128.37, 128.2, 128.0, 127.7, 127.2, 126.4, 104.6, 54.0, 48.9, 45.9, 36.3, 17.8, 14.1; IR (ATR): ν = 2959, 1656 (C═O), 1443, 1039, 748, 697; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{28}ClN_2O$ calcd 431.1885, found 431.1880.

3-Benzyl-1-heptyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.14 (m, 10H), 5.27 (d, J = 15.4 Hz, 1H), 4.84 (d, J = 6.1 Hz, 1H), 4.06 (d, J = 15.4 Hz, 1H), 4.03–3.89 (m, 1H), 3.84–3.72 (m, 1H), 3.17–3.01 (m, 1H), 1.74–1.00 (m, 14H), 0.93 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.8, 141.1, 138.1, 135.9, 128.5, 128.3, 128.2, 127.7, 127.2, 104.8, 53.8, 48.9, 44.1, 36.3, 31.7, 29.3, 28.8, 26.6, 22.5, 17.7, 14.2, 14.1; IR (ATR): ν = 2927, 1660 (C═O), 1448, 698; HRMS (ESI, $[M + H]^+$) for $C_{27}H_{37}N_2O$ calcd 405.2900, found 405.2892.

3-Benzyl-1-cyclopentyl-6-phenyl-4-propyl-3,4-dihydropyrimidin-2(1*H*)-one (5h). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.19 (m, 10H), 5.25 (d, J = 15.5 Hz, 1H), 4.89 (d, J = 6.5 Hz, 1H), 4.03 (d, J = 15.5 Hz, 1H), 3.74–3.51 (m, 2H), 2.52–2.32 (m, 1H), 2.13–1.17 (m, 11H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.6, 143.2, 138.0, 137.0, 128.5, 128.3, 127.9, 127.7, 127.1, 105.3, 60.0, 53.2, 48.4, 36.1, 31.1, 29.8, 25.7, 25.1, 17.8, 14.2; IR (ATR): ν = 2925, 1650 (C═O), 1447, 1383, 1352, 1249, 730, 698; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{31}N_2O$ calcd 375.2431, found 375.2428.

4-Ethyl-3-(4-methoxybenzyl)-1-phenyl-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (5i). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, J = 8.1 Hz, 2H), 7.28–7.16 (m, 4H), 7.15–7.06 (m, 1H), 7.04–6.93 (m, 2H), 6.88 (d, J = 8.1 Hz, 2H), 6.77–6.68 (m, 1H), 5.28–5.10 (m, 2H), 4.07 (d, J = 15.1 Hz, 1H), 3.96–3.85 (m, 1H), 3.80 (s, 3H), 1.87–1.68 (m, 1H), 1.67–1.50 (m, 1H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 154.7, 139.8, 136.8, 136.4, 129.6, 129.4, 128.5, 128.1, 127.2, 126.2, 124.8, 123.7, 114.0, 105.0, 55.3, 54.5, 48.4, 26.8, 8.4; IR (ATR): ν = 2929, 1653 (C═O), 1511, 1441, 1242, 1173, 1031, 729, 696; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{25}N_2O_2S$ calcd 405.1631, found 405.1630.

4-Ethyl-1-(4-fluorophenyl)-3-(4-methoxybenzyl)-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (5j). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, J = 8.1 Hz, 2H), 7.24–7.14 (m, 2H), 7.07–7.00 (m, 1H), 7.00–6.95 (m, 1H), 6.95–6.82 (m, 4H), 6.74–6.65 (m, 1H), 5.25–5.09 (m, 2H), 4.07 (d, J = 15.1 Hz, 1H), 3.97–3.86 (m, 1H), 3.80 (s, 3H), 1.87–1.68 (m, 1H), 1.67–1.49 (m, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.4, 159.1, 159.0, 154.6, 136.6, 136.3, 135.73, 135.68, 130.1, 130.0, 129.45, 129.40, 127.2, 125.1, 123.8, 115.1, 114.8, 114.0, 104.9, 55.3, 54.5, 48.5, 26.8, 8.3; IR (ATR): ν = 2931, 1652 (C═O), 1506, 1450, 1240, 1174, 1032, 729; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{24}FN_2O_2S$ calcd 423.1537, found 423.1530.

1-Benzyl-4-ethyl-3-(4-methoxybenzyl)-6-(thiophen-3-yl)-3,4-dihydropyrimidin-2(1*H*)-one (5k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.15 (m, 6H), 7.14–7.07 (m, 1H), 7.07–6.98 (m, 2H), 6.98–6.91 (m, 1H), 6.87 (d, J = 8.4 Hz, 2H), 5.23 (d, J = 15.1 Hz, 1H), 5.10 (d, J = 15.4 Hz, 1H), 4.85 (d, J = 5.7 Hz, 1H), 4.39 (d, J = 15.4 Hz, 1H), 3.96 (d, J = 15.1 Hz, 1H), 3.85–3.71 (m, 4H), 1.61–1.37 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 155.4, 139.0, 136.5, 136.0, 129.7, 129.2, 128.1, 127.8, 127.5, 126.8, 125.6, 124.5, 113.9, 104.1, 55.3, 54.7, 48.1, 47.7, 26.8, 8.4; IR (ATR): ν = 2927, 1645 (C═O), 1511, 1450, 1243, 1174, 1030, 695, 510; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{27}N_2O_2S$ calcd 419.1788, found 419.1782.

4-Isobutyl-3-(4-methoxybenzyl)-1,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one (5l). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.22 (m, 4H), 7.21–7.07 (m, 7H), 7.07–6.97 (m, 1H), 6.88 (d, J = 8.1 Hz, 2H), 5.36 (d, J = 6.5 Hz, 1H), 5.16 (d, J = 15.0 Hz, 1H), 4.06 (d, J = 15.0 Hz, 1H), 3.91–3.73 (m, 4H), 1.94–1.75 (m, 1H), 1.75–1.61 (m, 1H), 1.61–1.47 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 155.0, 140.9, 139.8, 135.8, 129.6, 129.4, 128.2, 128.0, 127.91, 127.86, 127.8, 125.8, 114.0, 108.0, 55.3, 52.0, 48.8, 44.1, 24.6, 24.0, 22.1; IR (ATR): ν = 2955, 1664 (C═O), 1511, 1446, 1243, 1173, 1031, 909, 756, 729, 695, 570; HRMS (ESI, $[M + H]^+$) for $C_{28}H_{31}N_2O_2$ calcd 427.2380, found 427.2375.

4-Isobutyl-3-(4-methoxybenzyl)-6-phenyl-1-*p*-tolyl-3,4-dihydropyrimidin-2(1*H*)-one (5m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 7.8 Hz, 2H), 7.22–7.04 (m, 7H), 6.95 (d, J = 7.3 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 5.32 (d, J = 5.5 Hz, 1H), 5.14 (d, J = 15.1 Hz, 1H), 4.06 (d, J = 15.1 Hz, 1H), 3.90–3.69 (m, 4H), 2.18 (s, 3H), 1.92–1.73 (m, 1H), 1.73–1.60 (m, 1H), 1.60–1.45 (m, 1H), 0.97 (d, J = 5.8 Hz, 3H), 0.90 (d, J = 5.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 155.1, 140.9, 137.2, 135.9, 135.4, 129.7, 129.4, 128.6, 128.0, 127.9, 127.8, 127.7, 113.9, 107.6, 55.2, 52.0, 48.8, 44.1, 24.5, 24.0, 22.1, 20.9; IR (ATR): ν = 2955, 1663 (C═O), 1510, 1446, 1242, 1173, 1032, 909, 817, 754, 729, 697, 516; HRMS (ESI, $[M + H]^+$) for $C_{29}H_{33}N_2O_2$ calcd 441.2537, found 441.2528.

1-Benzyl-4-isobutyl-3-(4-methoxybenzyl)-6-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (5n). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.29 (m, 3H), 7.29–7.13 (m, 7H), 7.05–6.95 (m, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.24 (d, J = 15.1 Hz, 1H), 5.20 (d, J = 15.0 Hz, 1H), 4.98 (d, J = 6.4 Hz, 1H) 4.25 (d, J = 15.1 Hz, 1H), 3.91 (d, J = 15.0 Hz, 1H), 3.77 (s, 3H), 3.73–3.63 (m, 1H), 1.71–1.49 (m, 1H), 1.40–1.13 (m, 2H), 0.80 (d, J = 6.6 Hz, 3H),

0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 156.1, 140.7, 138.8, 135.6, 129.8, 129.2, 128.43, 128.35, 128.3, 128.11, 128.06, 127.0, 113.9, 106.3, 55.2, 51.8, 48.4, 47.6, 43.6, 24.2, 23.8, 21.9; IR (ATR): ν = 2925, 1656 (C═O), 1511, 1447, 1244, 1174, 1030, 820, 752, 698, 584, 512; HRMS (ESI, $[M + H]^+$) for $C_{29}H_{33}N_2O_2$ calcd 441.2537, found 441.2532.

3-Benzyl-4-(dec-9-enyl)-1,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one (5o). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.20 (m, 7H), 7.20–7.06 (m, 7H), 7.06–6.97 (m, 1H), 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.29–5.16 (m, 2H), 5.06–4.88 (m, 2H), 4.16 (d, J = 15.3 Hz, 1H), 3.98–3.86 (m, 1H), 2.11–1.98 (m, 2H), 1.84–1.13 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.0, 141.2, 139.8, 139.2, 137.8, 135.9, 128.6, 128.5, 128.0, 127.9, 127.8, 127.4, 125.9, 114.2, 107.0, 54.1, 49.3, 34.4, 33.8, 29.6, 29.5, 29.4, 29.1, 29.0, 24.3; IR (ATR): ν = 2925, 1662 (C═O), 1494, 1446, 756, 695; HRMS (ESI, $[M + H]^+$) for $C_{33}H_{39}N_2O$ calcd 479.3057, found 479.3052.

1,4-Dibenzyl-6-(4-butoxyphenyl)-3-hexyl-3,4-dihydropyrimidin-2(1*H*)-one (5p). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.12 (m, 6H), 7.08 (d, J = 8.6 Hz, 2H), 7.05–6.95 (m, 4H), 6.82 (d, J = 8.6 Hz, 2H), 5.09 (d, J = 15.1 Hz, 1H), 4.73 (d, J = 6.2 Hz, 1H), 4.24 (d, J = 15.1 Hz, 1H), 4.01–3.83 (m, 4H), 2.80–2.64 (m, 2H), 2.46 (dd, J = 12.8, 8.5 Hz, 1H), 1.85–1.68 (m, 2H), 1.66–1.40 (m, 4H), 1.38–1.19 (m, 6H), 0.98 (t, J = 7.3 Hz, 3H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3, 155.5, 140.8, 139.1, 137.3, 129.6, 129.5, 128.3, 128.2, 128.0, 127.7, 126.9, 126.4, 114.2, 104.2, 67.7, 56.6, 47.5, 46.9, 41.9, 31.6, 31.3, 28.1, 26.5, 22.6, 19.2, 14.0, 13.9; IR (ATR): ν = 2928, 1660 (C═O), 1603, 1510, 1453, 1247, 1172, 698; HRMS (ESI, $[M + H]^+$) for $C_{34}H_{43}N_2O_2$ calcd 511.3319, found 511.3314.

3-Benzyl-1,6-diphenyl-4-*p*-tolyl-3,4-dihydropyrimidin-2(1*H*)-one (5q). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.14 (m, 13H), 7.14–7.00 (m, 6H), 5.44 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 5.8 Hz, 1H), 4.92 (d, J = 5.8 Hz, 1H), 3.65 (d, J = 15.2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.4, 139.8, 139.3, 138.5, 137.9, 137.0, 135.8, 129.8, 128.9, 128.6, 128.3, 128.1, 128.0, 127.8, 127.7, 127.4, 126.6, 126.2, 106.8, 58.4, 48.4, 21.2; IR (ATR): ν = 1656 (C═O), 1494, 1445, 1234, 750, 694, 524; HRMS (ESI, $[M + H]^+$) for $C_{30}H_{27}N_2O$ calcd 431.2118, found 431.2115.

1-(4-Fluorophenyl)-3-(4-methoxybenzyl)-4,6-dipropyl-3,4-dihydropyrimidin-2(1*H*)-one (5r). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.15 (m, 4H), 7.12–7.00 (m, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.12 (d, J = 15.0 Hz, 1H), 4.73 (d, J = 5.6 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H), 3.85–3.70 (m, 4H), 1.87–1.55 (m, 3H), 1.52–1.18 (m, 5H), 0.91 (t, J = 7.0 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.2, 159.9, 158.9, 154.8, 139.0, 134.8, 134.7, 131.4, 131.3, 129.8, 129.3, 115.6, 115.3, 113.9, 100.9, 55.3, 53.4, 48.0, 36.4, 34.1, 20.3, 17.1, 14.2, 13.5; IR (ATR): ν = 2958, 1650 (C═O), 1507, 1451, 1215, 1173, 1034, 833, 749, 537; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{30}FN_2O_2$ calcd 397.2286, found 397.2277.

3-(4-Methoxybenzyl)-4,6-dipropyl-1-*p*-tolyl-3,4-dihydropyrimidin-2(1*H*)-one (5s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.12 (d, J = 15.1 Hz, 1H), 4.70 (d, J = 5.7 Hz, 1H), 3.99 (d, J = 15.1 Hz, 1H), 3.83–3.73 (m, 4H), 2.36 (s, 3H), 1.89–1.54 (m, 3H), 1.50–1.17 (m, 5H), 0.91 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.8, 155.0, 139.3, 137.0, 136.2, 130.1, 129.5, 129.3, 129.2, 113.8, 100.4, 55.3, 53.4, 48.0, 36.4, 34.1, 21.2, 20.4, 17.1, 14.2, 13.5; IR (ATR): ν = 2928, 1653 (C═O), 1511, 1450, 1240, 1173, 1034, 817, 748; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{33}N_2O_2$ calcd 393.2537, found 393.2529.

4-Benzyl-5-isobutyl-1-(4-methoxybenzyl)-3-phenyl-1*H*-imidazol-2(3*H*)-one (2l). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.17 (m, 5H), 7.17–7.03 (m, 5H), 6.88 (d, J = 8.6 Hz, 2H), 6.85–6.77 (m, 2H), 4.90 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 2.23 (d, J = 7.4 Hz, 2H), 1.81–1.63 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.6, 138.2, 135.3, 130.1, 128.8, 128.3, 128.2, 128.0, 127.8, 127.5, 126.2, 119.8, 117.7, 114.0, 55.3, 44.4, 32.6, 29.5, 28.6, 22.3; IR (ATR): ν = 2923, 1676 (C═O), 1513, 1406, 1245, 1175, 1030, 807, 758, 694, 506; HRMS (EI, $[M]^+$) for $C_{28}H_{30}N_2O_2$ calcd 426.2307, found 426.2323.

4-Benzyl-5-isobutyl-1-(4-methoxybenzyl)-3-*p*-tolyl-1*H*-imidazol-2(3*H*)-one (2m). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 8.6 Hz, 2H), 7.17–7.09 (m, 3H), 7.07 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 6.91–6.80 (m, 4H), 4.89 (s, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.31 (s, 3H), 2.20 (d, J = 7.4 Hz, 2H), 1.82–1.61 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.7, 138.4, 137.4, 132.6, 130.1, 129.5, 128.23, 128.22, 127.8, 126.2, 119.6, 117.8, 114.0, 55.3, 44.4, 32.6, 29.4, 28.6, 22.3, 21.1; IR (ATR): ν = 2924, 1688 (C═O), 1512, 1405, 1245, 1175, 1031, 815, 702, 545, 510; HRMS (EI, $[M]^+$) for $C_{29}H_{32}N_2O_2$ calcd 440.2464, found 440.2469.

1,4-Dibenzyl-3-phenyl-5-*p*-tolyl-1*H*-imidazol-2(3*H*)-one (2q). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–6.99 (m, 17H), 6.77–6.65 (m, 2H), 4.85 (s, 2H), 3.65 (s, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5, 138.5, 138.3, 137.9, 135.1, 130.3, 129.4, 128.9, 128.4, 128.1, 128.0, 127.9, 127.7, 127.2, 126.1, 125.9, 122.3, 118.8, 45.4, 29.7, 21.3; IR (ATR): ν = 2922, 1669 (C═O), 1496, 1401, 822, 693, 519; HRMS (ESI, $[M + H]^+$) for $C_{30}H_{27}N_2O$ calcd 431.2118, found 431.2115.

The spectroscopic characterization data for imidazol-2-ones **2a,r,s** are documented by us previously.[10]

4-Butylidene-3-(4-fluorophenyl)-1-(4-methoxybenzyl)-5-propylimidazolidin-2-one (9r). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.5 Hz, 2H), 7.20–7.04 (m, 4H), 6.86 (d, J = 8.5 Hz, 2H), 5.20 (d, J = 14.9 Hz, 1H), 4.21 (dt, J = 7.5, 1.2 Hz, 1H), 3.91 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H), 3.37–3.25 (m, 1H), 2.78 (dd, J = 14.3, 2.0 Hz, 1H), 2.33 (dd, J = 14.3, 4.3 Hz, 1H), 2.00–1.80 (m, 2H), 1.68–1.45 (m, 2H), 1.45–1.17 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.1, 159.9, 158.9, 153.3, 136.2, 136.1, 135.5, 131.3, 131.2, 130.4, 129.4, 116.3, 116.0, 113.9, 110.6, 55.3, 51.5, 49.2, 33.7, 27.1, 20.1, 19.5, 15.0, 14.1; IR (ATR): ν = 2930, 1641 (C═O), 1508, 1451, 1237, 1174, 1033, 830, 753, 532; HRMS (ESI, $[M + H]^+$) for $C_{24}H_{30}FN_2O_2$ calcd 397.2286, found 397.2282.

4-Butylidene-1-(4-methoxybenzyl)-5-propyl-3-*p*-tolylimidazolidin-2-one (9s). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.21 (d, J = 14.9 Hz, 1H), 4.25 (dt,

J = 7.5, 1.7 Hz, 1H), 3.91 (d, J = 14.9 Hz, 1H), 3.8 (s, 3H), 3.36–3.22 (m, 1H), 2.77 (dd, J = 14.3, 2.3 Hz, 1H), 2.41–2.26 (m, 4H), 1.98–1.80 (m, 2H), 1.66–1.14 (m, 4H), 0.93 (t, J = 7.3 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 153.4, 137.6, 136.8, 135.5, 130.6, 129.9, 129.5, 129.3, 113.9, 110.3, 55.3, 51.5, 49.2, 33.7, 27.1, 21.2, 20.1, 19.5, 15.1, 14.1; IR (ATR): ν = 2925, 1642 (C=O), 1511, 1451, 1241, 1173, 1034, 814, 740, 592, 529; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{33}N_2O_2$ calcd 393.2537, found 393.2530.

1,3-Dibenzyl-1-(1-phenylhex-1-yn-3-yl)urea (8d). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.14 (m, 13H), 7.06–6.93 (m, 2H), 5.52 (t, J = 7.6 Hz, 1H), 4.81–4.64 (m, 2H), 4.50–4.24 (m, 3H), 1.78 (q, J = 7.6 Hz, 2H), 1.68–1.39 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.6, 139.2, 138.0, 131.5, 128.9, 128.4, 128.19, 128.15, 127.6, 127.1, 127.0, 126.8, 122.8, 88.3, 84.7, 48.6, 47.8, 44.8, 37.0, 19.6, 13.7; HRMS (EI, $[M]^+$) for $C_{27}H_{28}N_2O$ calcd 396.2202, found 396.2214.

1-Benzyl-3-cyclopentyl-1-(1-phenylhex-1-yn-3-yl)urea (8h). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.14 (m, 10H), 5.51 (t, J = 7.5 Hz, 1H), 4.67 (d, J = 17.0 Hz, 1H), 4.43–4.20 (m, 2H), 4.12–3.96 (m, 1H), 1.90–0.88 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.4, 138.4, 131.5, 128.9, 128.2, 128.1, 127.6, 126.7, 122.9, 88.6, 84.5, 52.5, 48.3, 47.8, 37.0, 33.32, 33.28, 23.3, 23.2, 19.6, 13.7; HRMS (ESI, $[M + H]^+$) for $C_{25}H_{31}N_2O$ calcd 375.2431, found 375.2429.

3-Benzyl-1-(4-methoxybenzyl)-1-(1-(thiophen-3-yl)pent-1-yn-3-yl)urea (8k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.14 (m, 7H), 7.06–6.91 (m, 3H), 6.85 (d, J = 8.2 Hz, 2H), 5.40 (t, J = 7.5 Hz, 1H), 4.80–4.70 (m, 1H), 4.64 (d, J = 16.9 Hz, 1H), 4.43–4.24 (m, 3H), 3.79 (s, 3H), 1.89–1.69 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 157.7, 139.2, 129.84, 129.79, 128.6, 128.4, 128.0, 127.1, 127.0, 125.2, 121.7, 114.3, 87.8, 79.8, 55.3, 50.2, 47.2, 44.8, 28.1, 10.9; HRMS (EI, $[M]^+$) for $C_{25}H_{26}N_2O_2S$ calcd 418.1715, found 418.1727.

$AuPPh_3Cl$/AgOTf-catalyzed cycloisomerization of terminal propargylurea 8t

Propargylamine **6h** (35 mg, 0.5 mmol) was dissolved in dry $CHCl_3$ (1.5 mL) followed by addition of isocyanate **7a** (66 mg, 0.55 mmol). After stirring at rt for about 5 min, AgOTf (6.4 mg, 0.025 mmol) and $AuPPh_3Cl$ (12.4 mg, 0.025 mmol) were added. The reaction mixture was stirred at 60 °C for 3 h in a sealed screw cap vial under an air atmosphere. The resulting mixture was directly subjected to silicagel column chromatography. Elution with (EtOAc–heptane, 1 : 1) provided imidazolidin-2-one **9t** (17 mg, 18%). Subsequent elution with (MeOH–CH_2Cl_2, 1 : 9) provided imidazol-2-one **2t** (76 mg, 81%).

1-Methyl-4-methylene-3-phenylimidazolidin-2-one (9t). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.19 (m, 2H), 7.11–6.94 (m, 3H), 4.67 (q, J = 2.6 Hz, 1H), 4.24 (q, J = 2.2 Hz, 1H), 4.18–4.07 (m, 2H), 3.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.3, 150.6, 146.8, 128.5, 123.5, 122.4, 85.5, 50.5, 31.7; HRMS (EI, $[M]^+$) for $C_{11}H_{12}N_2O$ calcd 188.0950, found 188.0957.

Acknowledgements

Support was provided by the Fund for Scientific Research (FWO), Flanders and by the Research Fund of the University of Leuven (KU Leuven). V.A.P. and A.A.P. are grateful to the EMECW (Triple I) for obtaining doctoral scholarships. J.J. and L.V.M. thank the Hercules Foundation for supporting the purchase of the single crystal diffractometer through the project AKUL/09/0035. The authors thank Ir. B. Demarsin and Prof. J. Rozenski for valuable help with EI and ESI HRMS respectively. ESI HRMS was made possible by the support of the Hercules Foundation (grant 20100225-7).

References

1 For a short overview, see: O. P. Pereshivko, Ph.D. Thesis, University of Leuven (KU Leuven), 2013.
2 For a focused review on the synthesis of heterocycles from propargylic precursors, see: W. Jia-Jie, Y. Zhu and Z.-P. Zhan, *Asian J. Org. Chem.*, 2012, **1**, 108–129.
3 (*a*) W.-J. Yoo and C.-J. Li, *Adv. Synth. Catal.*, 2008, **350**, 1503–1506; (*b*) J. Zhao, H. Huang, C. Qi and H. Jiang, *Eur. J. Org. Chem.*, 2012, 5665–5667; (*c*) H. Feng, D. S. Ermolat'ev, G. Song and E. V. Van der Eycken, *Adv. Synth. Catal.*, 2012, **354**, 505–509; (*d*) M. Yoshida, T. Mizuguchi and K. Shishido, *Chem.–Eur. J.*, 2012, **18**, 15578–15581.
4 Z. Jiang, P. Lu and Y. Wang, *Org. Lett.*, 2012, **14**, 6266–6269.
5 (*a*) D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2010, **49**, 9465–9468; (*b*) O. P. Pereshivko, V. A. Peshkov, D. S. Ermolat'ev, S. Van Hove, K. Van Hecke, L. Van Meervelt and E. V. Van der Eycken, *Synthesis*, 2011, 1587–1594; (*c*) M. J. Gainer, N. R. Bennett, Y. Takahashi and R. E. Looper, *Angew. Chem., Int. Ed.*, 2011, **50**, 684–687; (*d*) Y. Wang, H. Shen and Z. Xie, *Synlett*, 2011, 969–973.
6 C. Madaan, S. Saraf, G. Priyadarshani, P. P. Reddy, S. K. Guchhait, A. C. Kunwar and B. Sridhar, *Synlett*, 2012, 1955–1959.
7 For recent reviews on A^3-coupling, see: (*a*) V. A. Peshkov, O. P. Pereshivko and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2012, **41**, 3790–3807; (*b*) W.-J. Yoo, L. Zhao and C.-J. Li, *Aldrichimica Acta*, 2011, **44**, 43–51.
8 For the synthesis of secondary propargylamines *via* A^3-coupling, see: (*a*) C.-J. Li and C. Wei, *Chem. Commun.*, 2002, 268–269; (*b*) C. Wei, J. T. Mague and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5749–5754; (*c*) J. B. Bariwal, D. S. Ermolat'ev and E. V. Van der Eycken, *Chem.–Eur. J.*, 2010, **16**, 3281–3284; (*d*) O. P. Pereshivko, V. A. Peshkov and E. V. Van der Eycken, *Org. Lett.*, 2010, **12**, 2638–2641; (*e*) C. E. Meyet, C. J. Pierce and C. H. Larsen, *Org. Lett.*, 2012, **14**, 964–967.
9 M. J. Campbell and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1369–1378.

10 V. A. Peshkov, O. P. Pereshivko, S. Sharma, T. Meganathan, V. S. Parmar, D. S. Ermolat'ev and E. V. Van der Eycken, *J. Org. Chem.*, 2011, **76**, 5867–5872.
11 O. P. Pereshivko, V. A. Peshkov, J. Jacobs, L. Van Meervelt and E. V. Van der Eycken, *Adv. Synth. Catal.*, 2013, **355**, 781–789.
12 For a closely related example of Au/Ag-catalyzed chemoselective 6-*endo*-dig *N*- and *O*-cycloisomerizations of the enyne–urea system for the synthesis of annulated indoles, see: S. Gupta, D. Koley, K. Ravikumar and B. Kundu, *J. Org. Chem.*, 2013, **78**, 8624–8633.
13 M. Yang, S. J. Odelberg, Z. Tong, D. Y. Li and R. E. Looper, *Tetrahedron*, 2013, **69**, 5744–5750.
14 For reviews on Au catalysis, see: (*a*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351–3378; (*b*) H. Huang, Y. Zhou and H. Liu, *Beilstein J. Org. Chem.*, 2011, **7**, 897–936; (*c*) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885–3903; (*d*) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266–3325; (*e*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239–3265; (*f*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211; (*g*) A. S. K. Hashmi and M. Rudolph, *Chem. Commun.*, 2011, **47**, 6536–6544; (*h*) A. S. K. Hashmi and M. Bührle, *Aldrichimica Acta*, 2010, **43**, 27–33; (*i*) F. López and J. L. Mascareñas, *Beilstein J. Org. Chem.*, 2011, **7**, 1075–1094.
15 CCDC-966797 and CCDC-966798 contain the supplementary crystallographic data for this paper.
16 See ESI† for more details.
17 M. Niehaus and N. Krause, *unpublished results* (http://www.ccb.tu-dortmund.de/fb03/en/Fields_of_research/OC/Krause/Research_Interests/Niehaus.pdf).
18 C. O. Kappe, *Eur. J. Med. Chem.*, 2000, **35**, 1043–1052.
19 (*a*) P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360–413; (*b*) C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879–888; (*c*) J.-P. Wan and Y. Liu, *Synthesis*, 2010, 3943–3953; (*d*) Suresh and J. S. Sandhu, *ARKIVOC*, 2012, **i**, 66–133.
20 See Table 2 for exact catalyst loading and reaction time.

